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

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EU Vigilance Ltd. Office

Editorial – IDMP – a chance for pharmaceutical business?

This edition contains many useful articles and links about pharmacovigilance in Europe including a main focus on IDMP from different views.

For the pharmaceutical industry there will be a particular challenge in 2016-17. The European Medicines Agency (EMA) is in the process of implementing the standards developed by the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP).

These are a set of common global standards for data elements, formats and terminologies for the unique identification of and the exchange of information on medicines. Following a phased implementation process, pharmaceutical companies will be required to submit data on medicines to EMA in accordance with these formats and terminologies.

IDMP results of the former XEVMPD standard. Other (not only EU) agencies such as the US FDA and SwissMedic have also announced that IDMP implementation will become mandatory. Pharmaceutical companies, which in the revenue-generating markets continue to sell your products must be up to 01.07.2016 "IDMP-compliant". This presents a special challenge for both sides. The subsequent integration of sustainable IDMP into the basic processes and procedures of a company will require efficient change management for the whole organization. IDMP will be a feature throughout the lifecycle of a drug in the market. It plays an important role for the pharmacovigilance department as well as for regulatory affairs manager. EU Vigilance Ltd. has been following this topic from the beginning arising from our expertise with XEVMPD. We are prepared!

We hope that you will enjoy this edition and you will continue reading 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

by

www.euvigilance.eu

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Further information about EU Vigilance Ltd. and it´s work is available on our website:

http://www.euvigilance.eu

In particular, you may be interested in these links:

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News in Europe

Introduction: One dead in clinical trial

Sadly, news from Rennes in France where a First-in-Man clinical trial has gone horribly wrong. One volunteer has died, and four have been hospitalised. Limited information is available at present. Questions at this time include: What was the drug product under test? Why were, apparently, six volunteers given the new dose regime at the same time rather than the new regime being evaluated in a single volunteer, and only in further subjects after safety has been demonstrated? Could the adverse effects have been evaluated in further non-clinical studies? What was the role of the ANSM in all this, noting that it is only about 5 years since the French agency reinvented itself (previously AFFSAPS) after the "Mediator" scandal? Read more on page 8.

European Commission: The 'Blue Guide' on the implementation of EU product rules 2014

The Guide to the implementation of directives based on the New Approach and the Global Approach (the "Blue Guide") was published in 2000. Since then, it has become one of the main reference documents explaining how to implement the legislation based on the New Approach, now covered by the New Legislative Framework.
Much of the 2000 edition of the "Blue Guide" is still valid but it requires updating to cover new developments and to ensure the broadest possible common understanding on implementation of the New Legislative Framework (NLF) for the marketing of products. It is also necessary to take account of the changes introduced by the Lisbon Treaty (in force since 1st December 2009) with regard to the legal references and terminology applicable to EU-related documents, procedures, etc.

This new version of the Guide will therefore build on the past edition, but include new chapters, for example on the obligations of economic operators or accreditation, or completely revised chapters such as those on standardization or market surveillance. The Guide has also been given a new title reflecting the fact that the New Legislative Framework is likely to be used, at least in part, by all types of Union harmonization legislation and not only by the so-called "New Approach" directives.

Implementation of "the blue guide" has to be supported by clear and appropriate communication with stakeholders at International, European and National level.

EU Vigilance Ltd. can assist you with all necessary information and services concerning the implementation of EU product rules 2014. The whole "Blue Guide" can be read here.

News of EMA

Directorate General for Health & Consumers

Human Medicines:

The European Medicines Agency (EMA) published on 12th January 2016 its

"Highlights of 2015", which included an overview of its 2015 key recommendations in relation to the marketing authorizations of new medicines and the safety monitoring of authorized medicines.

2015 was an important year for public health in the European Union (EU). Therapeutic innovations that have the potential to make a difference to people's lives were seen in particular for the treatment of certain cancers, cardiovascular diseases, and in the areas of hematology (diseases of the blood) and neurology (disorders of the nervous system).

In 2015, EMA recommended 93 medicines for marketing authorization. This included recommendations for 39 new active substances.

New important safety advice was issued for a number of medicines on the market in the EU.

The document can be found here.

PRAC: Strategy on measuring the impact of pharmacovigilance activities

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC), at its 11-14 January 2016 meeting, adopted a 'Strategy on measuring the impact of pharmacovigilance activities'. The new strategy details how to gather data and knowledge on the concrete effect of measures and processes meant to ensure the safe use of medicines for patients in the European Union.

Measuring the impact of such activities is crucial in order to know whether the measures taken to minimise the risks of a medicine have been effective. Measuring the impact of pharmacovigilance activities also allows regulators to determine which activities are most successful and so helps to promote best practice and improve pharmacovigilance.

The new strategy adopted by the PRAC builds on existing activities in the Member States and the Agency and relies on a collaborative approach with stakeholders.

Information on all topics discussed by the PRAC is available in the agenda for the meeting. A record of the discussions will be provided in the minutes of this meeting, which will be published following the next PRAC meeting, held from 8-11 February. See more information and the draft agenda here:

A number of changes to EU GVP guidelines have been issued, including the adoption of a revision of the Module on PV audits:

- Guideline on good pharmacovigilamce practices (GVP): Module III – Post authorization safety studies (rev 2). See more here.
- Guideline on good pharmacovigilance practices (GVP): Module III addendum I – Requirements for transmission on non-interventional post-authorisation safety studies (rev 2). See more here .
- Guideline on good pharmacovigilance practices (GVP): Module IV – Pharmacovigilance audits (Rev 1) See more here.

Other EMA news:

EMA's medical literature monitoring enters into full operation.

Extended service will improve safety monitoring of medicines and simplify pharmacovigilance activities for companies

The European Medicines Agency (EMA) starts its full medical literature monitoring service on 1 September 2015.

A total of 400 active substance groups (300 chemical active substance groups and 100 herbal active substance groups) will now be monitored by EMA. The service will benefit over 4,000 companies. The list of active substance groups and a reference to the journals covered by EMA's medical literature monitoring service are available on the monitoring of medical literature page. Companies are advised to consult the list to check whether their products are covered by the service.

The implementation of EMA's full service follows a launch phase which began on 1 July 2015 and which included the 50 most common chemical active substance groups. Read more here.

Monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agencies (Questions and Answers)

This Questions and Answers (Q&A) document addresses a first set of frequently asked questions from marketing authorisation holders in preparation of the implementation of the monitoring of medical literature and entry of adverse reaction reports into EudraVigilance by the Agency in line with Article 27 of Regulation (EC) 726/2014.
This Q&A document will be regularly updated based on further questions received. All questions and answers are subject to evaluation and agreement by the pharmacovigilance governance.
Read more here.

New functionalities in support of the medical literature monitoring service User manual:
EV ICHISCR Export Manager, MLM EVWEB & tracking spreadsheets

Article 27 of Regulation (EC) No 726/2004 sets out the provisions for the monitoring of medical literature and the entry of relevant information into the EudraVigilance (EV) database by the European Medicines Agency. A detailed guide (EMA/161530/2014) further defines the scope of the activities and the applicable business processes.
The medical literature monitoring (MLM) service covers a range of active substances including herbal active substances as well as designated medical literature based on the use of literature reference databases.
The outcome of the screening results is published on a daily basis as " MLM Search Results "at a dedicated area of the EudraVigilance website.
MAHs can access and download the ICSRs from EudraVigilance or a dedicated area of the EudraVigilance website via the ICSR export tool in line with the applicable formats and standards as outlined in Article 25 and 26 of the Commission Implementing Regulation (EC) No 520/2010. A list of ICSRs entered in EudraVigilance is published daily as "MLM ICSRs".
https://eudravigilance.ema.europa.eu/human/restricted/PublicView/list2.asp
Read the whole document here.

Guido Rasi takes office as head of EMA.

Professor Rasi was nominated as Executive Director for a five-year mandate by the Management Board of the Agency on 1 October 2015. He was appointed following

his statement to the European Parliament's Committee on Environment, Public Health and Food Safety (ENVI) on 13 October 2015.

"I am very happy to be back at the helm of the Agency," said Professor Rasi on his first day in office. "We are currently undergoing the most significant transformation of the system of medicine development and authorisation that I have seen during my 35-year career in public health, either as a doctor, a researcher or a regulator. It is exciting and challenging to be leading the Agency during this time." Read more here.

EudraVigilance

eXtended Medicinal Product Dictionary (XEVMPD) – Updates

- **EudraVigilance Access Policy**
- **Regulatory information – Green light for reliance on Article 57 database for key pharmacovigilance information on medicines for human use in Europe**

Implementation of ISO IDMP Standards:

As mentioned in the editorial of this issue, the European Medicines Agency (EMA) is in the process of implementing the standards developed by the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP). These are a set of common global standards for data elements, formats and terminologies for the unique identification of and the exchange of information on medicines. Following a phased implementation process, pharmaceutical companies will be required to submit data on medicines to EMA in accordance with these formats and terminologies. The approach to the implementation of the ISO IDMP standards is based on the EMA **master data management roadmap.** Implementation will be structured in three main phases: preparation, transition and maintenance.

In the preparation phase, EMA will establish the necessary technical services to support the submission of organisation and referential data. EMA will develop and release a set of controlled vocabularies (for pharmaceutical forms, routes of administration, etc.) and an organisation dictionary. Meanwhile, EMA will continue to work closely with partners in the EU regulatory network and the pharmaceutical industry to develop guidance to define the implementation aspects and requirements of the ISO IDMP standards and terminologies in the EU (EU IDMP implementation guides) for the submission of data on substances and products. Read the whole report here.

Please also consider in the report of Topra (Regulatory Rappateur) : *IDMP: An opportunity for information integration across the pharmaceutical value chain***.** We give an abstract at page 8.

CMDh

Report from the CMDh meeting held on 14-16 December 2015

CMDh discussed several topic during this meeting. See here an overview about the topic and results:

- Mandatory use of electronic Application Form (eAF) from January 2016
- Pharmacovigilance: CMDh positions following PSUSA procedure for only nationally authorized products

- Revision of the CMDh working document – Information to be submitted by the member state of the European reference medicinal products
- Revision of the Questions and Answers an QP declaration
- Regulation (EC) No 1234/2008 on variations
- CMDh Strategy to 2020
- Pilots for merging and splitting of MRP/DCPs
- CMDh/EMA Working Party on Paediatric Regulation
- EU Work-sharing Articles 56 & 46 of the Paediatric Regulation – Pubic Assessment Reports
- Change in the Presidency of the Council of the European Union
- See the whole report here.

News of national authorities in Europe

Ireland

The HPRA in November 2015 – regulatory news: The HPRA called on all organisations with automated external defibrillators (AEDs) to urgently check that the recommended safety and maintenance updates on their device have been undertaken. The HPRA is issuing this advice as it has identified some 940 defibrillators in Ireland, incorporating five particular models, where a corrective action remains outstanding. Updates to these AEDs are needed immediately to ensure that the devices will work as necessary in a life-saving situation. In addition, the HPRA warns that weather temperatures will affect a defibrillator's performance and all AED devices should be stored correctly and regularly checked during the winter months ahead. The HPRA's AED information leaflet also provides advice on selecting and purchasing an AED for use in a community setting as well as recommendations for maintaining the device after it has been purchased. See the whole report here.

New Chief Executive of the HPRA

It was announced on the 14th Jan 2016 that Ms Lorraine Nolan has been appointed as the new Chief Executive of the HPRA, and takes up office with immediate effect. She previously held the position of Director of Human Products Authorisation with the HPRA where she oversaw the evaluation and authorisation of medicines and medical devices for the Irish market. Ms Nolan has extensive experience of the public health sector, the health product sector and the regulatory landscape. She will be responsible for the management of the HPRA whilst leading the organisation nationally and internationally in its ambition to protect and enhance human and animal health. See here.

Denmark:

New Danish Medicines Agency has new website

On 4th of January the Danish Medicines Agency launched their new website, where you can read about and subscribe to news about licensing and supervision of medicines, side effects, reimbursement, pharmacies and medical devise. Background: In October 2015, the former Danish Health and Medicines Authorities was split into three separate agencies: The Danish Medicines Agency, the

Danish Health Authority and the Danish Patient Safety Authority. Until today, the three agencies shared the same website. But with today's launch of our new website, you can subscribe to news from the Danish Medicines Agency within seven categories.

France

One dead and 5 hospitalized in French clinical trial

A volunteer for a phase I trial of a novel compound, BIA 10-2474, from a Portugese company Bial-Portela & Ca. SA, has died, while five others were hospitalised with identical neurological symptoms at the University Hospital Centre of Rennes in France. The compound is designed to target pain relief, and was being tested in a first-in-man trial conducted by Biotrial Research SAS, in Rennes, France.

Biotrial submitted the trial to the ANSM on April 30, 2015. On June 26, 2015, it received approval of protocols and authorisation to conduct the clinical trial. Initially single doses were tested. On Jan 10, the first of the six men taking multiple doses was hospitalized, and the others followed progressively, according to a chronology of events presented by the French Minister of Health, Marisol Touraine, during a press conference on 15th January.

Biotrial halted the study on Jan. 11.

The test compound was being developed for "the treatment of different medical conditions from anxiety to Parkinson's disease, but also for the treatment of chronic pain of sclerosis, cancer, hypertension or the treatment of obesity."

See here the report.

Other interesting news

Effectiveness evaluated

With the revised EU pharmacovigilance legislation, early access schemes and increasing number of conditional marketing authorizations, the requirements for post-approval safety (PAS) and efficacy studies (PAES) has never been greater. However, while there have been inroads for harmonization of clinical trial requirements throughout Europe, there are still wide differences in requirements for non-interventional or real-world observational studies. Here we look at some of the requirements and challenges evaluating the e effectiveness of risk management materials in PAS studies. This article from Richard Huckle is published in Regulatory Rapporteur – Vol 13, No1, January 2016.

ICH revisions for benefit – risk assessment

The assessment of a medicinal product which measures its benefits/efficacy and risks/safety is a core concept of regulatory decision-making both for sponsors and regulators.
Benefit–risk assessment has been an important topic in the industry over the past decade. The globally accepted standard for the documentation of bene- t–risk that lies within the International Conference on Harmonization (ICH) common technical document (CTD) was issued in 2002 and has not kept
pace with the progress made in this area. Under current ICH Guideline, M4E (R1), sponsors are expected to include their conclusions on benefits and risks in the Clinical Overview of Module 2 of the CTD (Section 2.5.6). There is general guidance provided in M4E (R1) regarding the expected content of this Section, but no further structure is suggested that could aid industry in structuring their benefit – risk assessment.

We do know that the US FDA and European Medicines Agency have developed structured approaches that are currently being implemented within their organizations and although they have adopted different approaches, there are elements that can be harmonized and included in the CTD structure to provide applicants guidance in how to format and present this important information. This article from Nancy Pire-Snerkanich is published in Regulatory Rapporteur – Vol 13, No1, January 2016.

IDMP: An opportunity for information integration across the pharmaceutical value chain

The need for end-to-end visibility of regulatory information has been the driver for implementing integrated regulatory information management (RIM) solutions within the pharmaceutical industry. The European Medicine Agency's identification of medicinal products (IDMP) requires even greater integration across multiple functions and systems such as regulatory, labelling, safety, manufacturing, supply chain, clinical and quality. In addition to meeting the EMA's compliance requirements, it is believed that IDMP is coming at a time when there is need for end-to-end information integration across the pharmaceutical value chain.

This paper describes how an enterprise architecture (EA) approach is best suited to integrate multiple systems together across multiple functions. It discusses the relevance of three EA constructs, namely, master data management (MDM) for managing a single source of truth around product data, information services bus for the purposes of integration and a data warehouse to manage integrated data for aggregated reporting. This article from This article from V. "Bala" Balasubramanian is published in Regulatory Rapporteur – Vol 13, No1, January 2016.

Interesting publications

- Voda A Perkins & Monique Garrett (2015): *Actively working across international borders.* Regulatory Rapporteur, Vol. 12, No 12. See full publication.
- Julie Warner & Anne-Maria van Nederkassel (2015): *Managing procedures for the marketplace.* Regulatory Rapporteur, Vol. 13 No. 1. See full publication.
- Ian Schofield (2015): *EMA Widens Stakeholder Access to EU Adverse Reaction Reports.* SCRIP Regulatory Affairs. See full publication.
- Vibha Sharma (2015): *EMA To Open Up Article 57 Pharmacovigilance Database to Simplify Regulatory Changes*. SCRIP Regulatory Affairs. See full publication.

List of used websites in this edition

- www.ansa.it
- www.ansm.sante.fr
- www.bfarm.de
- www.hma.eu/cmdh.html
- www.ema.europa.eu
- www.europa.eu
- www.eudravigilance.ema.europa.eu
- www.euvigilance.eu
- www.hpra.ie
- www.ich.org
- www.mhra.gov.uk
- www.laegemiddelstyrelsen.dk
- www.onlinelibrary.wiley.com
- www.reuters.com
- www.topra.org