New EU Pharmacovigilance Legislation Innovative Industry's perspective on implementation 1st year experience

7th stakeholders forum

27 September 2013, European Medicines Agency (EMA)

EFPIA - EBE - VE – EuropaBio – AIPES –Europharm SMC - AESGP

Innovative Industry Aims

- Industry Aims have not changed
  - Protection of public health
  - Robust and efficient pharmacovigilance system
  - Transparency which adds value for stakeholders
  - Simplification of processes and systems which facilitates a focus on public health vs non value added bureaucracy

General Challenges
Where do we stand since the 6th stakeholder forum?

- Massive changes in multiple processes going beyond pharmacovigilance
  - Important processes reengineered by Industry:
    - Periodic reports, RMP, signal management, Non-interventional study monitoring, PSMF
    - Involvement of non-PV functions (Medical, Regulatory, Marketing)
    - Extensive education and training for PV and non PV functions
    - New skill sets required e.g. lay summary for RMP
    - IT System investments (e.g. x-EVMPD)
- Enormous corpus of new regulatory guidance: no simplification!
  - Inconsistencies and overlap between finalised modules
  - Missing pieces, module updates awaited (announced schedule not respected)
- Different speed of adoption/harmonisation across the Member States
  - Transposition of Directive not fully achieved in all 28 Member States (4 missing as of August 2013)
- Impact beyond EEA: regression in international harmonisation
  - Perceived increased bureaucratic burden with no contribution towards promoting global patient safety.

Specific challenges

- Follow-up from previous Stakeholders forum
  - Individual Case Safety Reports (ICSRs)
  - PSURs/PBRERs
  - Risk Management Plans (RMPs)
  - PRAC
- Other concerns
  - Practical issues arising from detailed implementing regulatory guidance
  - Interpretation of Art 23 of directive 2010/84/EU
- Not brought up today:
  - PV fees (under discussion with the EU commission, council, parliament)
  - Art 57(2) of regulation 726/2004 (xEVMPD): separate working group established to address this topic
- Specific points by SMEs

Specific challenges - ICSR reporting

Follow-up on proposals at 6th stakeholder forum

- Final updated GVP Module VI update still awaited to address industry's main concerns:
  - Non serious case collection in non-interventional studies
    - EMA Proposed amendment to GVP VI in June 2013
  - Reporting from PSP and Market Research
    - Workshop organised by EMA on 7 June 2013
    - EFPIA will submit an updated position paper
- Diversion of resources away from true added value activities
- Impediment to the development of observational research

Specific challenges - ICSR reporting

Follow-up on proposals at 6th stakeholder forum

- Off-label use without AE
  - Industry made the following proposals:
    - Confirm in GVP Module VI that there is no requirement to actively solicit
    - Collect only if become aware through existing processes
  - Align expectation of inspectors and assessors
- Inconsistent requirements across MSs
  - In July 2013, EMA published the 7th (!) Revision to the reporting requirements applicable to ICSRs
  - Refer to CMDh for resolution

Specific challenges - ICSR reporting

Traceability of biological products

- New EU PV Legislation recognises the importance of traceability of biologicals for effective pharmacovigilance (art 102e DIR 2010/84/EU)
- In Europe, the lack of a distinguishable INN using the unique identifier weakens the robustness of the system to ensure traceability from prescription onward, taking into account:
  - Current prescribing practices in a number of countries
  - Incomplete recording of data in patient dossier
  - Implementation of Serialisation and IDMP initiatives will take time and are only part of the solution
- Industry Proposal: Distinguishable INN using the unique identifier helps ensure global traceability.
  - It supports the EVMPD database
  - It provides back-up in the event automated systems break down

Specific challenges: PBRER/PSUR

Follow-up on proposals at 6th stakeholder forum

- International harmonisation on-going with ICH E2C(R2) IWG
  - Final revised GVP Module VII still awaited
  - EMA opened to align the PBRER submission planning to IBD instead of EURD through update requests per product.
  - PBRER format generally accepted outside EEA, however not the periodicity, and frequent additional requests.
- Difficulties at the level of national CAs (NAPs)
  - Assessors still asking more than what is expected based on the new legislation
  - No formal acknowledgment that no PSUR required per EURD list
  - No timelines for assessment
- Lack of clarity with the parallel maintenance of the Worksharing / synchronisation processes and lists
- Industry proposal
  - Discussion forum with EMA/NCAs (including inspectors) to share experiences/ best practices with first submissions/ assessments

Specific challenges: RMPs

Follow-up on proposals at 6th stakeholder forum

- Under GVP module V, there is an increased requirement to produce RMPs for products on the market for >10 years.
- GVP focuses on peri-approval period and limited feedback has been received on EU-RMPs submitted so far. Thus, expectations for older products are unclear.
- The workload for MAHs and regulators is not insignificant & the value to patient safety is minimal when there are no risk minimisation measures other than routine.
- For established non-prescription products, an appropriate benefit-risk ratio has already been demonstrated for use without intervention of healthcare professional
- Industry proposal
  - To target a concise document, length & structure dictated by relevant content only
  - AESGP and EFPIA are working on a joint proposal to be submitted to EMA to make EU-RMP more aligned to the stage of the product in the life cycle (similar to abridged EU-RMP for generics)

Specific challenges: PRAC

- A continuous dialogue between the key stakeholders of the benefit-risk management process (NCA, EMA/PRAC and MAH) is required:
  - to ensure that the public is provided with factual, consistent and understandable information in a timely manner on the benefit-risk of medicinal products
  - to continuously evaluate and improve benefit/risk processes
- MAHs need to be involved in B/R discussions as early as possible as experts on the totality of the information for a product and primary interface with patients and HCPs
- The good intention to be transparent should not lead to the situation that unconfirmed information confuses HCPs or the public
- Sometimes PRAC and CHMP requests do not exactly match
- Regulators outside the EU are asking for information based on the published PRAC agenda, sometime before the MAH have had time to assess the request and data
- The signal management process by the EU CAs requires more clarity
- Industry proposal
  - Develop opportunities for on-going dialogue Industry/regulators

Other Specific Challenge: Article 23 (1/2)

Article 23 of DIR 2010/84/EU amended by DIR 2012/26/EU of 25 Oct 2012

- "[..] the MAH shall forthwith inform the NCA of any prohibition or restriction imposed by the competent authorities **of any country** in which the medicinal product is marketed and of **any other new information which might influence the evaluation of the benefits and risks** of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the **use of the medicinal product where such use is outside the terms of the marketing authorisation**"

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Other Specific Challenge: Article 23 (2/2)

- EMA announcement on June 6
  - CAPs: obligation in force but current product-specific reported from MAHs to EMA PTL considered sufficient and should apply
  - NCAs: EMA will work with NCAs on a process before implementation date (end Oct)
- Application of these provisions already enforced in France (art 12 of the national law)
- Industry has developed various processes, however submissions to the EMA on hold awaiting further regulatory guidance
- Industry proposal
  - Workshop to discuss the best way to apply this article

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Other Specific Challenges

Detailed implementing regulatory guidance

- Products subject to additional monitoring
  - Monthly post-PRAC review of published list on EMA website, with no indication of what is new
  - Industry Proposal: clear communication of changes, MAHs to be directly notified
- Labeling (QRD) template revisions
  - 3 revisions in a few months of the MS contacts for AE reporting
  - Industry Proposal: MS to be encouraged to fix consistent and minimal contact information so that there is no inconsistency between circulating printed labels and Agency website.

SMEs concerns

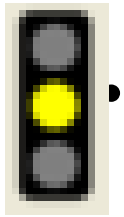
- Small companies are in general also those with the oldest products on the market (also the cheapest, and considered safe by experience) and with more limited resources.
- Impact of the new PV legislation to be considered specifically for European Pharma SMEs in terms of:
  - Competitiveness, compared to US SMEs
  - Public health, if the burden induced by the legislation leads the SME to close and withdraw these “old” products.
- SME plea is to have such an impact analysis on their business before final decisions are taken regarding the new PV fees
- Specific concerns
  - PSURs: Need to completely replace the worksharing process by the EURD list, to decrease the burden of national submissions
  - PASS: Resource burden on SME for operationalisation
  - No dialogue with National CAs to clarify the signal management process
  - General Training on GVP at National Level

Where are Industry expectations?

- Better protection of the public health
  - Focus on benefit/risk balance with PBRER concept spread worldwide
  - Improved surveillance of the use of medicinal products, with more focus on signals rather than ICSRs
  - Big step toward harmonised pharmacovigilance processes and product evaluation throughout EU

- Robust and efficient PV system
  - Clear within the industry, oversight improved through PSMF and reinforcement of QPPV role

- Transparency which adds value for stakeholders
  - Communication from regulators to MAH to be anticipated prior to public announcements
  - Proportionality to the risks and prioritisation not obvious within the massive amount of PRAC activities (specially for mature products)



- Simplification of processes and systems
  - Better predictability of changes in implementing regulatory guidance

General Industry Proposal

- Industry would welcome a continuous dialogue with EMA/NCAs to optimise the PV processes within the EU, for example:
  - quarterly meetings to review progress
  - establishment of a regular forum to review progress as occurred with the paediatrics provisions
  - Specific topic workshops as occurred for PSP/MR