New EU Pharmacovigilance Legislation

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New EU Pharmacovigilance Legislation

Dec 2010 Publication in the Official Journal of the EU
Jan 2011 Entry into force

**Directive 2010/84/EU**
- Amends, as regards pharmacovigilance, Directive 2001/83/EC
- Applies to MRP/DCP/national products
- is in parts referred to for CP products
- Transposition deadline for Member States and application as from 21 July 2012

**Regulation (EU) No 1235/2010**
- Amends, as regards pharmacovigilance, Reg. (EC) 726/2004 and Reg. 1394/2007 on ATMPs
- Applies to CP products and advanced therapy medicinal products
- Provisions shall apply from 2 July 2012
Amended legal Proposal on Information to Patients & Pharmacovigilance

- Adopted by COM on 11 October 2011
  - Amendment of 2008 Legal proposal by COM on Info to Patients
  - Includes additional measures for PV following Mediator crisis


- Discussions will now start in Parliament and Council
  (expected time: 1 – 3 years before final adoption, publication and entry into force)
Status quo

• **European Commission** launched a **consultation** on implementing provision on 08 September for submission of comments **by 07 November 2011**

• **EMA** plans to consult on draft guidelines **during 2011**

• **Stakeholder Fora**
  – Supplement public consultations on implementation
  – Goal: start stakeholder dialogue and identify key priorities
    • **1st Stakeholder Forum** - 15 April 2011 (EMA)
    • **2nd Stakeholder Forum** - 17 June 2011 (EMA)
    • **3rd Stakeholder Forum** – Oct 2011 (COM)
PV-Definitions - **System**

Pharmacovigilance (PV) System

**MAH**
Marketing Authorisation Holder

*Quality-System*
to fulfil tasks and responsibilities according to PV legislation
incl.
Risk Management System (RMS)
for each product

→ Oversight by EU QPPV

**Member State & EMA**

*Quality-System*
to fulfil tasks and responsibilities according to PV legislation

**PSMF**
detailed description of PV-System
to be included in application

→ will replace DDPS
**PV-Definitions – Product**

**Risk Management System RMS**

(part of PV System)

- per product
- set of pharmacovigilance activities & interventions
- designed to identify, characterise, prevent, or minimise risks
- assessment of effectiveness of interventions

**Risk Management Plan – RMP**

= Detailed description of RMS
⇒ covers whole lifecycle of a product
⇒ global reference doc !?
- to be included in applications for MA
- part of CTD
- electronic submission
- Publication: web portal
RMP — *Content* - currently for consultation (1)

- Identify or characterise the safety profile
- Describe how safety profile will be assessed and monitored
- Document measures in place for risk minimisation and the assessment of those interventions

- 1 RMP for products with same API from the same MAH
- If RMP has previously been submitted, there should be an update
RMP – **Format** - currently for consultation (2)

**Part I** Product(s) Overview

**Part II** Safety Specification

  - Module I Epidemiology of indications and target population
  - Module II Non-clinical part of safety specification
  - Module III Clinical trial exposure
  - Module IV Population not studied in clinical trials*
  - Module V Post authorisation experience
  - Module VI Identified and potential risks
  - Module VII Additional EU requirements for safety specification
  - Module VIII Summary of safety concerns

**Part III** Pharmacovigilance Plan

**Part IV** Plans for studies on effectiveness and long term efficacy*

**Part V** Risk minimisation measures – including plans to assess the effectiveness of these measures

**Part VI** Summary of the RMP *(will be made public)*

**Part VII** Annexes
Key aspects of new legislation

**Strengthening**

- **Pharmacovigilance system**: changes, incl.
  - introduction of **pharmacovigilance system master files (PSMF)**
  - inspections

- **Risk management plans (RMPs)**: new definition, format, content

- **Periodic safety update reports (PSURs)**:
  - electronic submission
  - changes to the content, incl. ongoing benefit/risk assessment
  - repository

- **Pharmacovigilance Risk Assessment Committee (PRAC)**:
  - new committee at EMA
  - to provide recommendations to CHMP and CMDh

- **Safety signal detection**: legal basis for EMA and national agencies

- **Urgent union procedure**: revision

- **Post-authorisation safety and efficacy studies (PASS/PAES)**:
  strengthened legal basis for request
New legal proposal (11 October 2011): *Additional strengthening for PV*

- New public list of medicinal products subject to additional monitoring
  - Include all medicinal products authorised subject to conditions
  - Full transparency and publication (all products and not case-by-case)

- Voluntary withdrawal by MAH
  - Measures have to avoid safety issues not being addressed in the EU
  - Clarification of information obligations for MAH

- Implementation of an automatic procedure at European level
  - in the case of specific serious safety issues with nationally authorised products
  - Objective: to ensure that the matter is assessed and addressed in all Member States where the medicinal product is authorised.
Periodic Safety Update Reports – PSURs - Content currently for consultation

- 1 PSUR for all medicinal products containing same API authorised to one MAH
- Scientific evaluation of benefit-risk balance
- Cumulative data – no detailed listing of individual cases
  (except case narratives where relevant)
- Estimation of population exposed, volume of sales and prescriptions
Periodic Safety Update Reports — PSURs — Format (1) currently for consultation

- Signature by person responsible for PV
- Executive Summary
  1. Introduction
  2. Worldwide marketing approval status
  3. Actions taken in reporting period for safety reasons
  4. Changes to reference safety information
  5. Estimated exposure
  6. Data in summary tabulations
  7. Summaries of significant findings from clinical trials in reporting period
  8. Findings from non-interventional studies
  9. Other clinical trial/ study information
  10. Non-clinical data
Periodic Safety Update Reports – PSURs – Format (2) currently for consultation

- Executive Summary ctd
  11. Literature
  12. Other periodic reports
  13. Lack of efficacy in controlled clinical trials
  14. Late breaking information
  15. Overview of signals ongoing and closed
  16. Signal and risk evaluation
  17. Benefit evaluation
  18. Integrated Benefit-risk analysis for approved indications
  19. Conclusions and actions
  20. Region-specific information
  21. Appendices to PSUR
Key aspects of new legislation

**Efficiency**

- **Internationally agreed terminology, formats and standards**
  for the performance of pharmacovigilance activities
  - MedRA
  - ICH (M2, E2B)
  - European Pharmacopoeia Commission
  - ISO/EN (IDMP)

- **Adverse drug reactions**
  - definition & sources
  - reporting (timelines, Eudravigilance only)

- **Eudravigilance**
  - single database
  - full access to authorities (COM, EMA, MS)
  - limited access to MAH, healthcare professionals & public
Key aspects of new legislation

Transparency

• **Products subject to additional monitoring:**
  - Statement & black symbol in label
  - Publication of list

• **Off-label use:** collection and reporting in Eudravigilance

• **Public hearing by PRAC:** Process & rules

• **Web Portals:**
  • **National:**
    Assessment reports, SPCs, PIL, RMPs, medicinal products,
    ADR reporting
  • **EU:**
    Committee members, meeting minutes & agendas, RMPs, medicinal products, results of PASS (PAES?), urgent union procedure, public hearings...
EU web portal - Implementation

• **July 2011**: EMA guidance on electronic submission of information
• **2 July 2012**:
  – **By Deadline**: MAHs to **submit electronically to EMA** information on all medicinal products authorized in the EU/EEA
  – **After deadline**: MAHs have to **inform EMA of any new or amended MA** granted in the EU/EEA
• **21 July 2012**: National Agencies set up **web-portals** linked to EMA

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EMAToEMA

• Electronic submission
  • Info on any new/amended MA

Web-portals of national Agencies linked to EMA
**Implementing measures by the European Commission**
for consultation by 7 November 2011

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<td>a)</td>
<td>Content &amp; maintenance of the <strong>pharmacovigilance system master file</strong> by MAH</td>
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<td>b)</td>
<td>Minimum requirements for the <strong>quality system</strong> for the performance of pharmacovigilance activities (NCAs and MAH)</td>
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<td>c)</td>
<td>Use of internationally agreed <strong>terminology, formats</strong> and standards for the performance of pharmacovigilance activities</td>
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<td>d)</td>
<td>Minimum requirements for the monitoring of data included in the <strong>Eudravigilance database</strong> to determine whether there are new risks or whether risks have changed</td>
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<td>e)</td>
<td>Format and content of <strong>electronic transmission of suspected adverse reactions</strong> by Member States and MAHs</td>
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<td>f)</td>
<td>Format and content of <strong>electronic PSURs and RMPs</strong></td>
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<td>g)</td>
<td>Format of <strong>protocols, abstracts and final study reports of the PASS</strong></td>
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**Not included in current consultation:**

Delegated acts (=implementing legislation) to determine situations in which **PAES** may be required and for additional supplementing measures
Guidelines by **EMA** to be expected on

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<td>• <strong>Good Pharmacovigilance Practice</strong> for competent authorities and MAH</td>
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<td>• <strong>Repository</strong> for PSURs</td>
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<td>• Rules for organisation and conduct of <strong>public hearings</strong></td>
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<td>• <strong>Scientific guidance on PAES</strong></td>
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<td>• Specifications for <strong>web-portal</strong></td>
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<td>• Specifications for <strong>Eudravigilance database</strong>, incl. Guide on conduct of literature monitoring and entry of information into Eudravigilance</td>
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Impact on Company Procedures

**Transparency, PV-Concepts, RMS/ RMP**

1. **Transparency**
   
   i. Dealing with public hearings
   
   ii. Rules for internal document writing

2. **PV-System/ PSMF**
   
   i. PV-System: Review responsibilities and ensure internal audits
   
   ii. PSMF: to be in place for products to be authorised ≥ July 2012

3. **Risk Management System (RMS) within Roche**
   
   i. RMS to be in place
      
      for new products to be authorised ≥ July 2012
      
      for products authorised before July 2012: at renewal or latest by July 2015
   
   ii. RMP
      
      - implement template
      
      - ensure compliance and follow-up
Impact on Company Procedures

Risk-Benefit, PASS and PAES

4. **PSUR Benefit-Risk Assessment**
   i. Revised benefit-risk description in PSUR
   ii. Cumulative data replaces detailed listing of individual case reports
   iii. Compliance with submission and frequency dates ≥ July 2012

5. **Post-Authorisation Safety Studies – PASS**
   i. Consider PASS may be required for products authorized ≥ July 2012
   ii. Consider PRAC/NCAs review timeline of PASS protocol in project planning
   iii. Ensure PASS protocols have realistic timelines to avoid penalties

6. **Post Authorisation Efficacy Studies - PAES**
   i. Explore opportunities for PAES with GPS for relative effectiveness
   ii. Design realistic efficacy endpoints and timelines for PAES, as failure could lead to
      • Suspension or revocation of the MA if the view is taken that the product lacks therapeutic efficacy
      • Implications on future costs for drug development and reimbursement
Impact on Company Procedures

Other

7. Eudravigilance:
   i. Ensure electronic submissions of ADRs \(\Rightarrow\) 6 months after announcement
   ii. Ensure retrieval of case reports out of Eudravigilance

8. Signal detection:
   i. Signal reporting to EMA and national competent authorities
   ii. Response to publication of signals by PRAC/EMA

9. New Terminology & Standards
   i. Compliance with new terminology and formats
   ii. Adapt procedures and IT systems

10. Labelling
    i. Additional monitoring: Statement and black symbol: SmPC and package leaflet
    ii. Health care professional/ patient ADR reporting:
        - Review Core Company Data Sheet
        - Implement in product information for submissions > July 2012
We Innovate Healthcare