Implementation of the Pharmacovigilance legislation: Building on two years of operation

8th Stakeholders forum – 15 September 2014

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Head of Pharmacovigilance Department
In this presentation

Pharmacovigilance legislation - Building on two-years of operation:

- Key messages
- Reminders: objectives, constraints, priorities
- What has been delivered in 2013-2014
- Looking forward
- Conclusions
Pharmacovigilance legislation: Building on two years of operation - Key messages

Two-years of operation delivered:

- Proactive planning of studies and risk minimisation
- Increased patient reporting of ADRs
- Signals managed through PRAC
- Benefit risk assessment delivered through referrals and periodic safety updates
- Increased transparency
- EU coordination of safety messages

Now focus on:

- Continued delivery for public health
- Process improvement to increase effectiveness and efficiency,
  - Based on experience
  - Based on better scientific methods
  - Based on delivering IT systems and business change
- Enhanced stakeholder engagement
- Demonstrating impact
Reminders: objectives, constraints, priorities

Objectives: Promote and protect public health by reducing burden of Adverse Drug Reactions and optimising the use of medicines:

1. Clear roles and responsibilities
2. Science based and risk proportionate
3. Increased proactivity
4. Reduced duplication and increased efficiency
5. Integrate benefit and risk
6. Ensure robust EU decision-making
7. Strengthen the EU Network
8. Engage patients and healthcare professionals
9. Increase transparency
10. Provide better information on medicines
Reminders: objectives, constraints, priorities

**Challenges:**

- Major resource constraints
- Size of change
- Number of stakeholders impacted
Reminders: objectives, constraints, priorities

Criteria for prioritisation:

- Firstly, public health activities
- Secondly, transparency and communication activities
- Thirdly, simplification activities (primarily for pharmaceutical industry)
What has been delivered in 2013-2014

- Pharmacovigilance Risk Assessment Committee continued full operation
- New business processes operating
- Audits of the National Competent Authorities pharmacovigilance systems
- Audits of the European Medicines Agency’s pharmacovigilance systems
- More and better guidance
- Process improvements
Good pharmacovigilance Practice (GVP)- Developments since October 2013

<table>
<thead>
<tr>
<th>I PhV and QS</th>
<th>XI Participation</th>
<th>Consult on Public Hearings</th>
</tr>
</thead>
<tbody>
<tr>
<td>II PSMF</td>
<td>XII Continuous PhV</td>
<td>Drafting Out:2015</td>
</tr>
<tr>
<td>III Inspections</td>
<td>Rev 1 published</td>
<td>XIV International</td>
</tr>
<tr>
<td>VI Audits</td>
<td>XV Communication</td>
<td></td>
</tr>
<tr>
<td>V RMP</td>
<td>XVI RMM</td>
<td>Published</td>
</tr>
<tr>
<td>VI ICSR</td>
<td>Rev 2 published</td>
<td>P.I Vaccines</td>
</tr>
<tr>
<td></td>
<td>Published today</td>
<td></td>
</tr>
<tr>
<td>VII PSUR</td>
<td>Rev 1 published</td>
<td>P.II Biologicals</td>
</tr>
<tr>
<td>VIII PASS</td>
<td>Rev 1 in preparation</td>
<td>P.III Pregnancy</td>
</tr>
<tr>
<td>IX Signals</td>
<td>Rev planned</td>
<td>P.IV Geriatrics</td>
</tr>
<tr>
<td>X Add Monitoring</td>
<td></td>
<td>Annex I Definitions</td>
</tr>
</tbody>
</table>
Guidance: Next steps

Look out for the following revisions:

• GVP Module V – Risk management systems
• GVP Module VI – Management and reporting of adverse reactions to medicinal products
• GVP Module VIII – Post-Authorisation Safety Studies
• GVP Module IX – Signal management
• ENCePP methods guide

Look out for the new modules:

• GVP Module XII – Continuous Pharmacovigilance
• GVP Product /Population-Specific Considerations II: Biologicals, pregnancy, geriatrics
• Good practice guides on medication errors
• Good practice guide on educational materials
• Efficacy studies scientific guidance
2013 – 2014: business processes
Risk management plans - submitted with applications for new medicines and when issues with medicines on the market: to plan studies and risk minimisation

<table>
<thead>
<tr>
<th>RMP in the context of:</th>
<th>July 2012 - June 2013</th>
<th>July 2013 - June 2014</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial application</td>
<td>101</td>
<td>120</td>
<td>221</td>
</tr>
<tr>
<td>Type II variation</td>
<td>70</td>
<td>194</td>
<td>264</td>
</tr>
<tr>
<td>PSUR</td>
<td>91</td>
<td>112</td>
<td>203</td>
</tr>
<tr>
<td>Renewal</td>
<td>18</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>Stand alone RMP</td>
<td>51</td>
<td>34</td>
<td>85</td>
</tr>
</tbody>
</table>

The new legislation has delivered unprecedented proactivity in pharmacovigilance.
Periodic Safety Update Reports – benefit risk assessments for authorised medicines

Outcomes of PSURs at PRAC in 2012-2014

PSURs = Periodic Safety Update Reports
PSURs: Observations and next steps

• Procedure for CAPs now well established with a proportion of PSUR procedures leading directly to MA variation

• Efficiency gains since no need for follow-up variation and health gains through rapid update of product information

• Mixed single assessments for CAPs and NAPs provides insight into upcoming NAPs only PSUSAs and areas for clarification:
  - For pharmaceutical industry:
    ➢ Need to clearly list NAPs covered by a PSUR on level of national authorisation
  - For regulators:
    ➢ requests for additional information to be more clearly phrased and tailored to the affected products

• New dedicated service for PSURs established in the procedural department with a dedicated mailbox for pre-submission queries PSURquery@ema.europa.eu
Post-Authorisation Safety Studies fill knowledge gaps: protocols and results at PRAC 2012 to June 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Imposed Protocols</th>
<th>Non-imposed Protocols</th>
<th>PASS Results on Imposed Protocols</th>
<th>PASS Results on non-Imposed Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to June 2014</td>
<td>25</td>
<td>48</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>2013</td>
<td>41</td>
<td>50</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2012</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
So:

- Increase in protocols reviewed
- Increase in results assessed
- Increase in studies registered
Post authorisation efficacy studies

- PAES scientific guidance: in preparation, public consultation Q1 2015, publish Q3 2015
Spontaneous reporting in EEA*

Pre Legislation
02/07/11 - 01/07/12
226,513

After Legislation
02/07/12 - 01/07/13
281,357

After Legislation
02/07/13 - 01/07/14
295,043

* Number of ICSRs received in EudraVigilance before de-duplication
Spontaneous reporting by patients in EEA*

* Number of ICSRs received in EudraVigilance before de-duplication
Eudravigilance Data Quality management 07/2013 – 07/2014

Achievements of EV Data Quality management

• Recoding of medicinal product terms reported in safety reports: 84,288 terms recoded

• Duplicate detection & management of individual safety reports: 85,677 duplicate cases removed from the system

• EudraVigilance Data Quality Assessments: 136 assessments performed and senders (MAHs/Sponsors/NCAs) provided feedback
Signals: new potential safety issues or changes to known safety issues

• 163 signals (255 signal discussions) managed by PRAC in the first two years
• Unprecedented transparency for stakeholders
• Delivers rapid assessments to that product information can be updated to support safety and effective use of products
Median: 10 signals per month
Additional monitoring

- Mandatory for following some products e.g. Medicines containing a new active substance / biological medicinal products and medicines with obligation for post authorisation safety studies

- Optional for other products at the request of the EC or a national agency, following consultation with the PRAC

- Additional monitoring list published every months by EMA
  - Currently 1459 products (as of 31 July 2014 compared to 105 in April 2013)
Number of products included in the Additional Monitoring List over time

- Total: 1459
- CAPs: 179
- NAPs: 1280

Month/Year:
- Apr-13
- May-13
- Jun-13
- Jul-13
- Aug-13
- Sep-13
- Oct-13
- Nov-13
- Dec-13
- Jan-14
- Feb-14
- Mar-14
- Apr-14
- May-14
- Jun-14
- Jul-14

Number of Products per marketing authorisation type:
- NAPs
- CAPs
- Total

Graph showing the increase in the number of products included in the Additional Monitoring List from April 2013 to July 2014.
## Distribution of products included in the additional monitoring list

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1308</td>
<td>Product with a PASS imposed as condition to the marketing authorisation</td>
</tr>
<tr>
<td>82</td>
<td>Product containing a new active substance</td>
</tr>
<tr>
<td>18</td>
<td>Product containing a new active substance with a PASS imposed as condition to the marketing authorisation</td>
</tr>
<tr>
<td>16</td>
<td>New biological medicinal product</td>
</tr>
<tr>
<td>16</td>
<td>Medicinal product authorised under exceptional circumstances</td>
</tr>
<tr>
<td>10</td>
<td>Product containing a new active substance with a conditional authorisation</td>
</tr>
<tr>
<td>4</td>
<td>Medicinal products with a conditional authorisation</td>
</tr>
<tr>
<td>4</td>
<td>Medicinal product containing a new active substance and authorised under exceptional circumstances</td>
</tr>
<tr>
<td>1</td>
<td>New biological medicinal product authorised under exceptional circumstances</td>
</tr>
</tbody>
</table>
Referrals: safety or benefit risk reviews of medicines

- Number of referrals (July 2012 – July 2014\(^1\)):

<table>
<thead>
<tr>
<th>Referral type</th>
<th>Started</th>
<th>Finalised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Art. 20</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Art. 107i</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Art. 31</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>31(^2)</td>
<td>22(^3)</td>
</tr>
</tbody>
</table>

1 Also includes procedures started and finalised by PRAC in July 2014
2 In 8 procedures (26%) an ad-hoc expert meeting has been organised
3 Finalised means final outcome obtained at either CHMP or CMDh
Pharmacovigilance inspection procedures

European Union pharmacovigilance inspectors have developed Union procedures and guidance on pharmacovigilance inspections of marketing-authorisation holders of human medicines.

The Union procedures support harmonisation for the mutual recognition of pharmacovigilance inspections and to facilitate administrative collaboration and the exchange of inspection-related information. They apply to inspections conducted following adoption by the Committee for Medicinal Products for Human Use (CHMP) or under the national inspection programmes of concerned Member States.

National competent authorities of all Member States are expected to take account of the Union procedures and use them as the basis for standard operating procedures on the quality systems established within the inspectorates themselves.

The European Medicines Agency is responsible for maintaining and publishing the Union procedures.

Send all queries regarding this content to gcp@ema.europa.eu.

### Union procedures

<table>
<thead>
<tr>
<th>Document(s)</th>
<th>Language</th>
<th>Status</th>
<th>First published</th>
<th>Last updated</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Union procedure on the coordination of EU pharmacovigilance inspections</td>
<td>(English only)</td>
<td>adopted</td>
<td>20/06/2014</td>
<td></td>
<td>01/06/2014</td>
</tr>
<tr>
<td>Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections</td>
<td>(English only)</td>
<td>adopted</td>
<td>20/06/2014</td>
<td></td>
<td>01/06/2014</td>
</tr>
<tr>
<td>Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products</td>
<td>(English only)</td>
<td>adopted</td>
<td>20/06/2014</td>
<td></td>
<td>01/06/2014</td>
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<tr>
<td>Union procedure on sharing of pharmacovigilance inspection information</td>
<td>(English only)</td>
<td>adopted</td>
<td>20/06/2014</td>
<td></td>
<td>01/06/2014</td>
</tr>
<tr>
<td>Union recommendations on the training and experience of inspectors performing pharmacovigilance inspections</td>
<td>(English only)</td>
<td>adopted</td>
<td>20/06/2014</td>
<td></td>
<td>01/06/2014</td>
</tr>
</tbody>
</table>
Publication of RMP summaries

- In March 2014, the Agency began publishing summaries of RMPs for centrally authorised medicines.

- Analysis of experience acquired during pilot phase (and way forward) to be made public in 2015

- 31 RMP summaries published as of 31st August 2014

For further information on RMP summaries and their role, see: Questions and answers on the RMP summary


Summary of the risk management plan (RMP) for Gazyvaro (obinutuzumab)

This is a summary of the risk management plan (RMP) for Gazyvaro, which details the measures to be taken in order to ensure that Gazyvaro is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Gazyvaro, which can be found on Gazyvaro’s EPAR page.

Overview of disease epidemiology

Gazyvaro is a medicine used for the treatment of chronic lymphocytic leukaemia (CLL). CLL is a rare cancer of B-lymphocytes, a type of white blood cell. Gazyvaro is used in combination with chlorambucil (another cancer medicine), in previously untreated patients who have other medical conditions that make them ineligible for a fludarabine-based cancer treatment.

In the European Union, Gazyvaro has been designated an orphan medicine due to the rarity of the condition. In Europe, in 2013, the estimated prevalence of CLL was approximately 3 per 10,000 people. CLL is almost twice as common in men as in women, and its incidence increases with age.

Summary of treatment benefits
Looking forward

• Continued delivery for public health
• Process improvement to increase effectiveness and efficiency
  – Based on experience
  – Based on better scientific methods
  – Based on delivering IT systems and business change
• Enhanced stakeholder engagement
• Demonstrating impact
Process improvement to increase effectiveness and efficiency
Better IT systems to support stakeholders – see session 3

<table>
<thead>
<tr>
<th>Topics</th>
<th>Activities</th>
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<tbody>
<tr>
<td>Literature monitoring</td>
<td>EMA service to industry for population of EudraVigilance with case reports of old substances.</td>
</tr>
<tr>
<td>EudraVigilance</td>
<td>Delivery of enhanced functionalities and IT system audit results in centralised reporting for industry</td>
</tr>
<tr>
<td>Article 57(2) data submission and handling</td>
<td>Updates (variations) to the data can be submitted by industry and data fully used to support regulation, safety and stakeholder needs.</td>
</tr>
<tr>
<td>Periodic Safety Update Reports</td>
<td>Delivery of PSUR repository and single PSUR assessment process for NAPs allowing centralised reporting for industry and faster warnings for NAPs</td>
</tr>
<tr>
<td>Risk Management System</td>
<td>Implement risk-based system for measuring the effectiveness of risk minimisation</td>
</tr>
<tr>
<td>Transparency and communication</td>
<td>Delivery of EU Medicines web-portal and public hearings.</td>
</tr>
</tbody>
</table>
Process improvement and simplification, based on experience and better science

Translating regulatory science into practice
Best Evidence to support assessments

- EMA studies: in house, commissioned
- ENCePP contribution
- FP7 studies to date
Building capacity

- SCOPE Joint Action (Strengthening Collaborations for Operating Pharmacoepidemiology and Pharmacovigilance)
- ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)
Data, information and knowledge for excellent pharmacovigilance: complementary strategies

**Best Evidence to support regulatory decision**
- Examples:
  - Signal strengthening

**Impact of Pharmacovigilance (and new legislation)**
- Examples:
  - Patient knowledge on ADR reporting

**Effectiveness of risk minimisation**
- Examples:
  - Company monitoring of implementation of measures
Engaging stakeholders:
Public hearings

European Medicines Agency launches public consultation on rules of procedures for public hearings

Citizens are invited to review the proposed draft rules and send their comments to the Agency by 15 October 2014.
Measuring **performance*** and **impact**** – types of measures

1. **Performance***: Structure and process measures of implementation of activities in new PhV legislation (i.e., ‘outputs’, e.g., implementation milestones and process measures)

2. **Impacts****: 
   - Behavioural change
   - Outcomes (impacts on health system and industry)

**Important because:**
- Make process more effective and efficient
- Demonstrate added value
- Justify activity and spending
- Support for future reviews
Conclusions Pharmacovigilance legislation: Building on two years of operation

Delivered:

- Proactive planning of studies and risk minimisation
- Increased patient reporting of ADRs
- Signals managed through PRAC
- Benefit risk assessment delivered through referrals and periodic safety updates
- Increased transparency
- EU coordination of safety messages
Conclusions Pharmacovigilance legislation: Building on two years of operation

Focus on:

- Continued delivery for public health
- Process improvement to increase effectiveness and efficient,
  - Based on experience
  - Based on better scientific methods
  - Based on delivering IT systems and business change
- Enhanced stakeholder engagement
- Demonstrating impact
Thank you for your attention