Overview of the new process for Signal Detection and Management

PCWP and HCPWP joint meeting
25 February 2014

Presented by: Georgy Genov
EMA/Inspections & Human Medicines Pharmacovigilance Division
Agenda for presentation

- EU Pharmacovigilance Legislation
- Overview of Signal Management Process
- Pharmacovigilance Risk Assessment Committee
- Trends in requests for access to information/documents
- Transparency
- Summary
Main pillars of the new EU PV Legislation

<table>
<thead>
<tr>
<th>Proactive and proportionate risk management</th>
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<tr>
<td>Higher quality of safety data</td>
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<td>Strengthened transparency, communication and patient involvement</td>
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<td>Stronger link between safety assessments and regulatory action</td>
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<td>Clear tasks and responsibilities for all parties (marketing authorisation holders, competent authorities, EMA)</td>
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<td>Improved EU decision-making procedures (harmonised decisions and efficient use of resources)</td>
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<td>Establishment of the Pharmacovigilance Risk Assessment Committee</td>
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New EU PV Legislation: four topic areas

1. Collection of key information on medicines:
   - Risk Management Plans (RMPs)
   - Periodic Safety Update Reports (PSURs)
   - Post-authorisation safety and efficacy studies (PASS/PAES)
   - Electronic submission of core medicine information by pharmaceutical industry
   - Reporting by patients

2. Better analysis and understanding of data and information:
   - EudraVigilance and signal detection
   - Additional Monitoring
   - IT systems to support processing and analysis of data

3. Regulatory Action to safeguard public health:
   - Scientific committees and decision-making
   - Strengthening referral procedures

4. Communication with stakeholders:
   - Online publishing of information
   - Coordination of safety messages
   - Public hearings
Those directly involved in Pharmacovigilance

Healthcare professionals working with medicines

Pharmaceutical companies and companies importing and/or distributing the medicines

Patients who use the medicines

Regulatory Authorities and Member States responsible for monitoring the medicines

European Medicines Agency coordinating the EU's safety-monitoring and Pharmacovigilance for medicines
Definition of a Signal

“Information that arises from one or multiple sources (including observations and experiments), which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action”

Report of Council for International Organisations of Medical Sciences WG VIII
Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010)
Sources of information

- Spontaneous ADR reporting systems
- Clinical trials data
- Scientific literature
- Pharmacoepidemiological studies
- Non clinical trial data e.g non-interventional studies
ICSR reporting pre- and post new PV legislation

02/07/2011 – 01/07/2012
Total number 833,938

02/07/2012 – 01/07/2013
Total number 1,054,169

- Only HCP
  - Pre Leg: 554,299
  - After Leg: 607,150

- Only Patient
  - Pre Leg: 142,087
  - After Leg: 250,891

- Patient + Others (HCP / Legal)
  - Pre Leg: 125,234
  - After Leg: 180,686

- Others (Legal / Not reported)
  - Pre Leg: 12,318
  - After Leg: 15,442
Proportion of ICSR reporting pre- and post new PV legislation

- **Before Legislation (Pre Leg)**
  - Only HCP: 66.5%
  - Only Patient: 17.0%
  - Patient + Others (HCP / Legal): 15.0%
  - Others (Legal / Not reported): 1.5%

- **After Legislation (After Leg)**
  - Only HCP: 57.6%
  - Only Patient: 23.8%
  - Patient + Others (HCP / Legal): 17.1%
  - Others (Legal / Not reported): 1.5%

Total Number Pre Leg: 833,938
Total Number Post Leg: 1,054,169
How do we review EudraVigilance data?

- Statistical analysis

- Clinical review of individual case safety reports

- Validation meeting

  - Clinical relevance: exposure, temporal association, plausible mechanism, de/re-challenge, severity of reaction and outcome; novelty of reaction
  - Previous awareness (SmPCs/PL; PSURs)
  - Other relevant sources (literature, experimental findings)

- Signal Confirmation
European Pharmacovigilance Issues Tracking Tool (EPITT)

- All validated signals are entered into EPITT by the authority who detected and validated it.
- Validated signals undergo further analysis and are either:
  - CONFIRMED: Added to agenda for the Pharmacovigilance Risk Assessment Committee (PRAC)
  - NOT CONFIRMED: Justification to be provided as to why signal is not confirmed.
Signal Management Process

Signal Detection → Signal Validation → Signal Confirmation → Signal Analysis and Prioritisation → Signal Assessment → Signal Recommendation for action → Exchange of information and implementation

- EMA MAHs MSs
- EMA MSs
- PRAC
- All stakeholders
Trends in Adverse Event reports and signals in 2013 (Jan – Dec)

- 1,200,000 ICSRs received per year in EV – European database of suspected adverse drug reaction reports
- 980,000 medical terms reviewed yearly by P-PH-SMA
- 2,449 signals evaluated and discussed yearly at P-PH-SMA team level
- 100 signals discussed at PRAC; 43 detected by EMA

Adverse Reactions reported by:
- Patients
- HCPs
- Pharmaceutical companies

- Update SmPC/PIL
- Referral
- PASS
- MA varied, suspended...
Source of all signals evaluated by EMA in 2013 (n=2449)
Therapeutic area of all 2013 PRAC signals (n=100)

- CNS: 23%
- ECV: 28%
- ONC: 9%
- RGI: 20%
- AIV: 20%
EMA shall make public on the European medicines web-portal a list of active substances/medicinal products and the authority (lead Member State, co-lead Member State or the Agency) responsible for their monitoring in EudraVigilance.
Pharmacovigilance Risk Assessment Committee (PRAC)

Responsible for assessing and monitoring safety issues for human medicines
HCP and patient representatives

HAS ADOPTED THIS DECISION:

Sole Article

1. The following are hereby appointed members and alternates of the Pharmacovigilance Risk Assessment Committee to represent healthcare professionals for a term of three years from 1 March 2013:
   
   — Member: Filip Babylon,
   
   — Alternate: Kirsten Myhr.

2. The following are hereby appointed members and alternates of the Committee to represent patient organisations for a term of three years from 1 March 2013:
   
   — Member: Albert van der Zeijden,
   
   — Alternate: Marco Greco.

Done at Brussels, 28 February 2013.
PRAC recommendations for action

- No need for further evaluation or action at this point in time

- Request for additional data to be submitted:
  - Monitor any relevant emerging information on the signal as it becomes available
  - Address the signal in the following PSUR or submit an ad-hoc PSUR
  - Submit additional data (such as cumulative review)
  - Collect further information or perform additional analyses in EudraVigilance or other data sources
  - Conduct a post-authorisation safety study

- Need for regulatory action:
  - The product information and/or RMP should be updated through a variation
  - The Member States or the Commission, should initiate a referral procedure
  - Urgent safety restrictions should be imposed

- A Pharmacovigilance inspection should take place
Outcomes of signals validated by EMA in 2013 (n=43)
Example of signal analysis, prioritisation and assessment of recent signal discussed at PRAC

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.9. Sunitinib - SUTENT (CAP)

• Signal of cholecystitis

**Status:** for initial discussion

**Regulatory details:**

PRAC Rapporteur: Carmela Macchiarulo (IT)

**Recommendation(s):**

The MAH should perform a cumulative review of cases of cholecystitis and related terms associated with sunitinib with particular focus on acaulcalous and emphysematous cholecystitis. This review should be submitted within 2 months of adoption of these conclusions.

In case the MAH considers the need to update the product information further to this cumulative review, please be reminded of your responsibility to submit a variation in accordance with Article 16 of Regulation (EC) No 726/2004.
Some examples of signals discussed at PRAC

Adalimumab - Missed dose due to **malfuction** of the pre-filled pen device

Leuprorelin - **Medication errors** (wrong technique in drug usage process)

Clopidogrel - **Eosinophilic pneumonia** *

Docetaxel - Serious/fatal **drug interactions** *

Bevacizumab - **Anaphylactic shock**

Roxithromycin - **Hearing disorders** *

Temozolomide - **Hepatic failure** *

Ticagrelor - **Interaction** with grapefruit juice *

Cinacalcet - **QT prolongation/ventricular arrhythmias** *

* Represents those resulting in labelling changes
Requests for EudraVigilance data analyses: Type of requester (2011 - 2013)
Transparency

- Publication of data on ADRs
- Currently only for CAPs
- Aim to extend to NAP
Agenda PRAC

wk1

Highlights PRAC

wk2

Minutes from previous PRAC

wk3

CHMP

wk4

Highlights CHMP

wk1

Publication of PRAC recommendations
Publication of PRAC agendas and minutes

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### Agendas

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<th>Last updated</th>
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<td>06/01/2014</td>
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### Minutes

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Publication of PRAC recommendations – first publication October 2013

PRAC recommendations on signals

Adopted at the PRAC meeting of 6-9 January 2014

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 6-9 January 2014.

PRAC recommendations on signals

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 6-9 January 2014.

List of signals discussed at PRAC since September 2012

Introduction:

Each month the PRAC analyses, prioritises and evaluates safety signals concerning medicinal products authorised in the EU. This assessment may result in various recommendations, including an update of the product information (summary of product characteristics and package leaflet). The table below is a cumulative list of signals discussed at PRAC since its establishment. It will be updated after each CHMP/PRAC meeting. PRAC recommendations on signals adopted each month are published here [link to website].

List of signals discussed at PRAC since September 2012

<table>
<thead>
<tr>
<th>INN</th>
<th>Signal</th>
<th>PRAC meeting</th>
<th>Update of product information recommended by PRAC</th>
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</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Angioedema</td>
<td>06-09 January 2014 PRAC meeting minutes</td>
<td>No</td>
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<td>Adalimumab</td>
<td>Dermatomyositis</td>
<td>03-09 September 2012 PRAC meeting minutes</td>
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<td>Dermatomyositis</td>
<td>26-29 November 2012 PRAC meeting minutes</td>
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<td>12-14 May 2013 PRAC meeting minutes</td>
<td>Yes¹</td>
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<td>Dermatomyositis</td>
<td>08-11 April 2013 PRAC meeting minutes</td>
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<td>2-10 October 2013 PRAC meeting minutes</td>
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<td>Dermatomyositis</td>
<td>10-13 June 2013 PRAC meeting minutes</td>
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<td>Adalimumab</td>
<td>Malaria</td>
<td>06-09 January 2014 PRAC meeting minutes</td>
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References:

Directive 2001/83/EC

Regulation (EC) No 726/2004

Regulation (EC) No 726/2004

Module HX – Signal management of the guideline on good pharmacovigilance practices (GVP).

Questions and Answers on signal management

Update of product information recommended by PRAC

No
Summary

• New process for signal management in line with the new EU Pharmacovigilance legislation

• Harmonised process for both CAPs and NAPs

• Increased transparency through communication of information/evidence (EU database on ADR reports, publications of PRAC minutes, recommendations etc.)

• Continued improvement in monitoring the safety of medicines, making it more robust and transparent

• Helping to ensure greater patient safety and improved public health through better detection, assessment, understanding and prevention of adverse reactions.

Thank you!