EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Patient and Consumer organisations Training session:

Signal Detection and Management

29 November 2012

Presented by: Georgy Genov
EMA/Pharmacovigilance and Risk Management

Agenda

- **What** is signal detection
- **How** are signals detected and managed
- **Who** is responsible

The new EU PV Legislation: four topic areas.

- **Collection of key information on medicines**
  Risk management plans
  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

- **Regulatory action to safeguard public health**
  Scientific committees and decision-making
  Strengthening referral procedures

- **Better analysis and understanding of data and information**
  EudraVigilance and signal detection
  Additional monitoring
  IT systems to support processing and analysis of data

- **Communication with stakeholders**
  Online publishing of information
  Coordination of safety messages
  Public hearings

A new Pharmacovigilance Risk Assessment Committee (PRAC) will focus on the planning, assessment and monitoring of safety issues. The CHMP will start to adopt opinions based on recommendations from the PRAC.

Sources of information

Non-clinical and clinical trial data

EudraVigilance Human

Spontaneous ADR reposting systems

SCIENTIFIC JOURNAL ARTICLES

Scientific literature

Pharmacoepidemiological studies

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"

Practical Aspects of Signal Detection in Pharmacovigilance

Report of CIOMS Working Group VIII, Geneva 2010

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2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

- Responsibility for Marketing Authorisation Holder (D104.3.e)
  monitor pharmacovigilance data to determine whether there are **new risks** or whether **risks have changed** or whether there are changes to the benefit risk balance

- Responsibility for EMA and Member States (D107h)
  monitor the data in the EudraVigilance database to determine whether there are **new risks** or whether **risks have changed** and whether those risks impact on the risk benefit balance'

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

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European Medicines Agency publishes active substance list with lead Member State responsible for safety monitoring

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News

05/10/2012

European Medicines Agency publishes active substance list with lead Member State responsible for safety monitoring

The European Medicines Agency has published the first list of active substances contained in authorised medicines for which a lead Member State has been appointed to monitor data in EudraVigilance, in order to validate and confirm signals on behalf of the EU regulatory network.

The overall goal of the work-sharing model, whereby one Member State is responsible for monitoring a single active substance contained in a medicine authorised through national, mutual recognition or decentralised procedures, is to further strengthen the signal detection system in the European Union and optimise use of resource across the network for the benefit of public health.

Related information

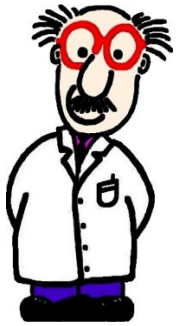
- List of active substances subject to worksharing for signal management (05/10/2012)
- Guideline on good pharmacovigilance practices: Module IX – Signal management (25/06/2012)

How do we review EudraVigilance data?

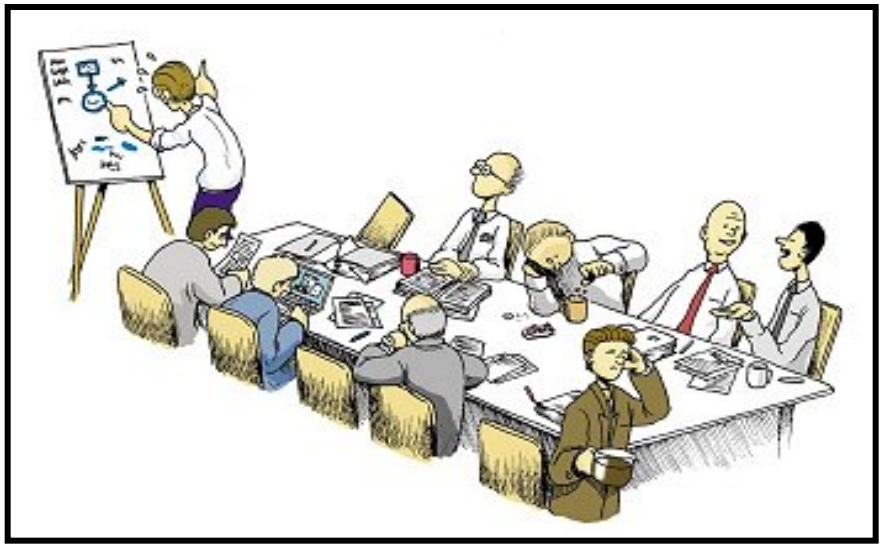
Statistical analysis

Clinical review of individual case safety reports:

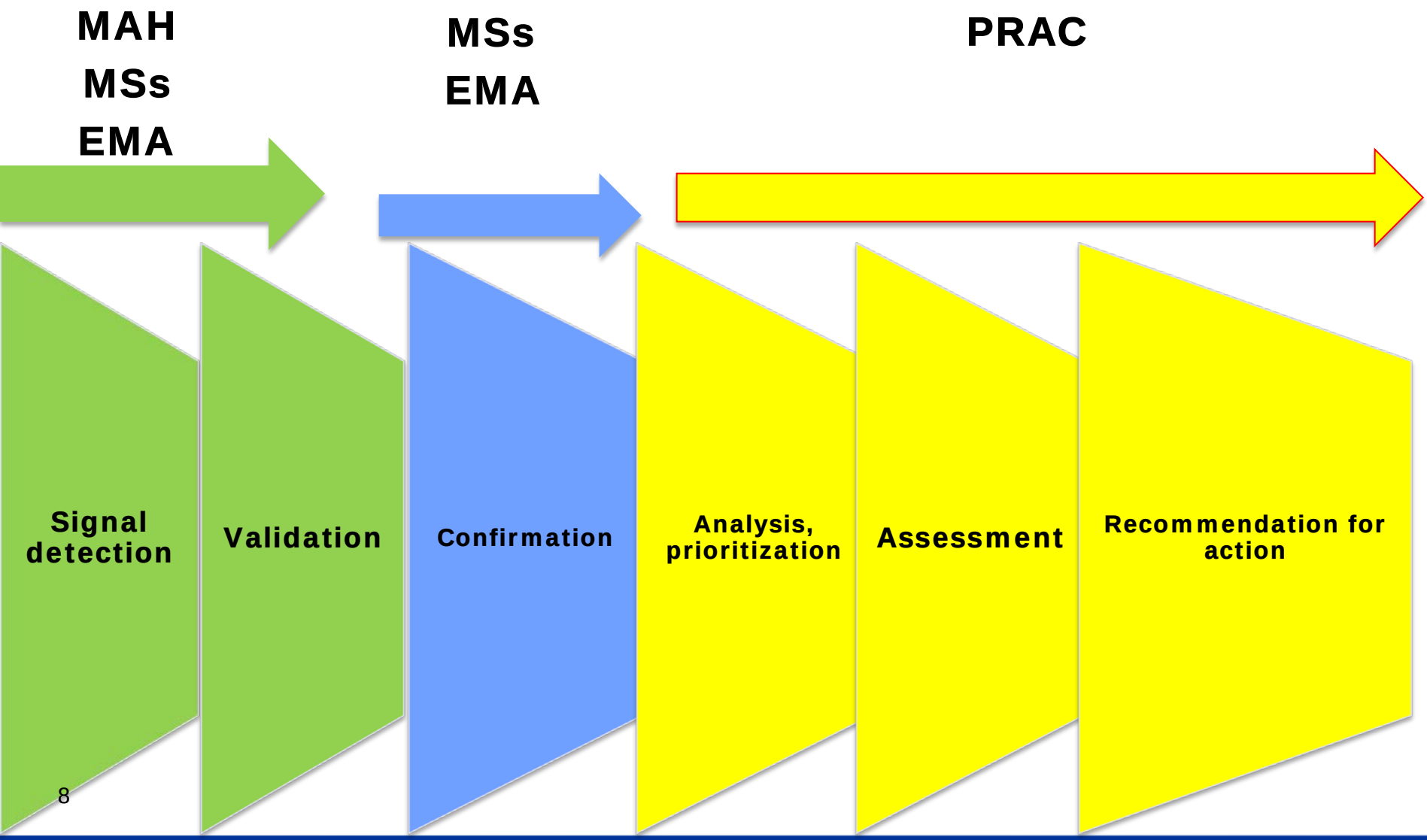
- Temporal association
- Biological plausibility
- Dechallenge/Rechallenge



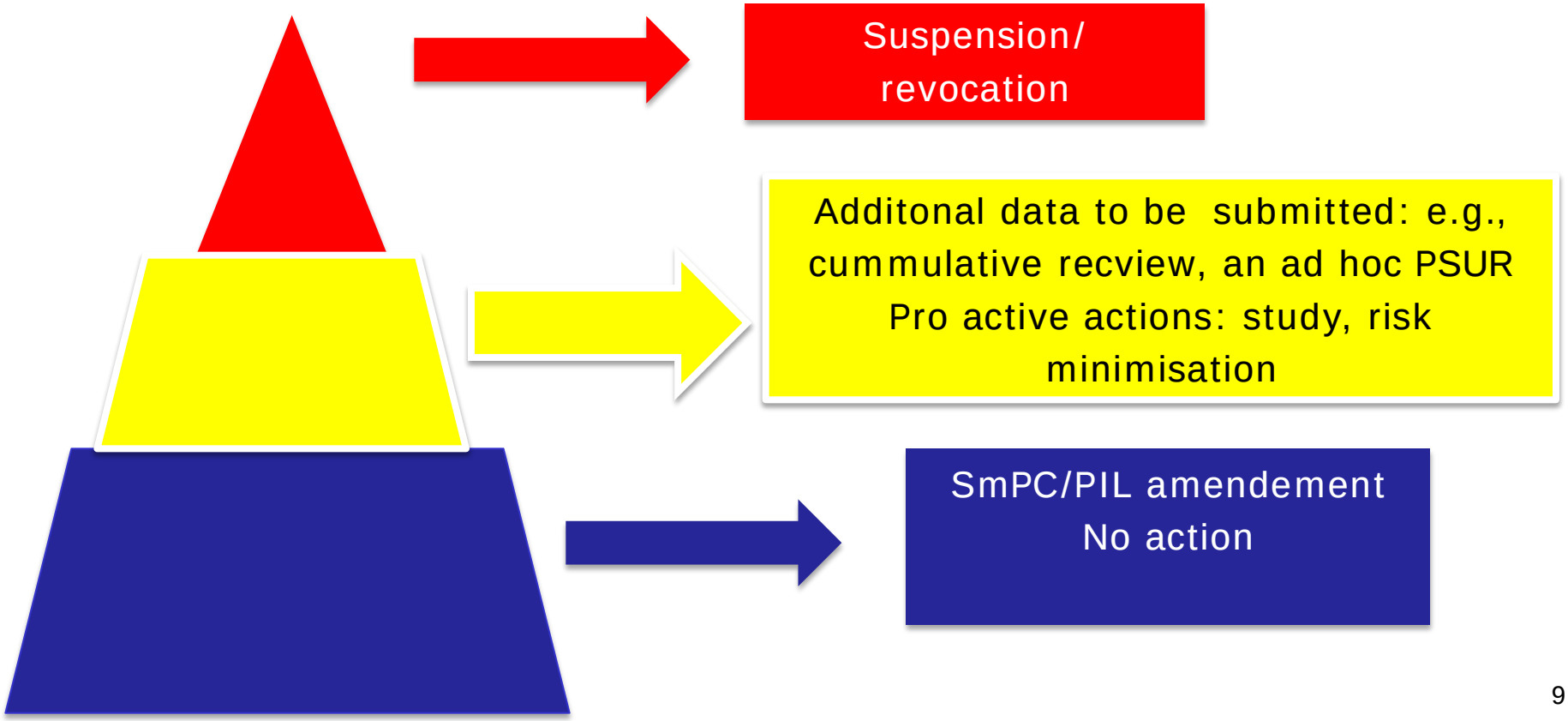
Validation meeting



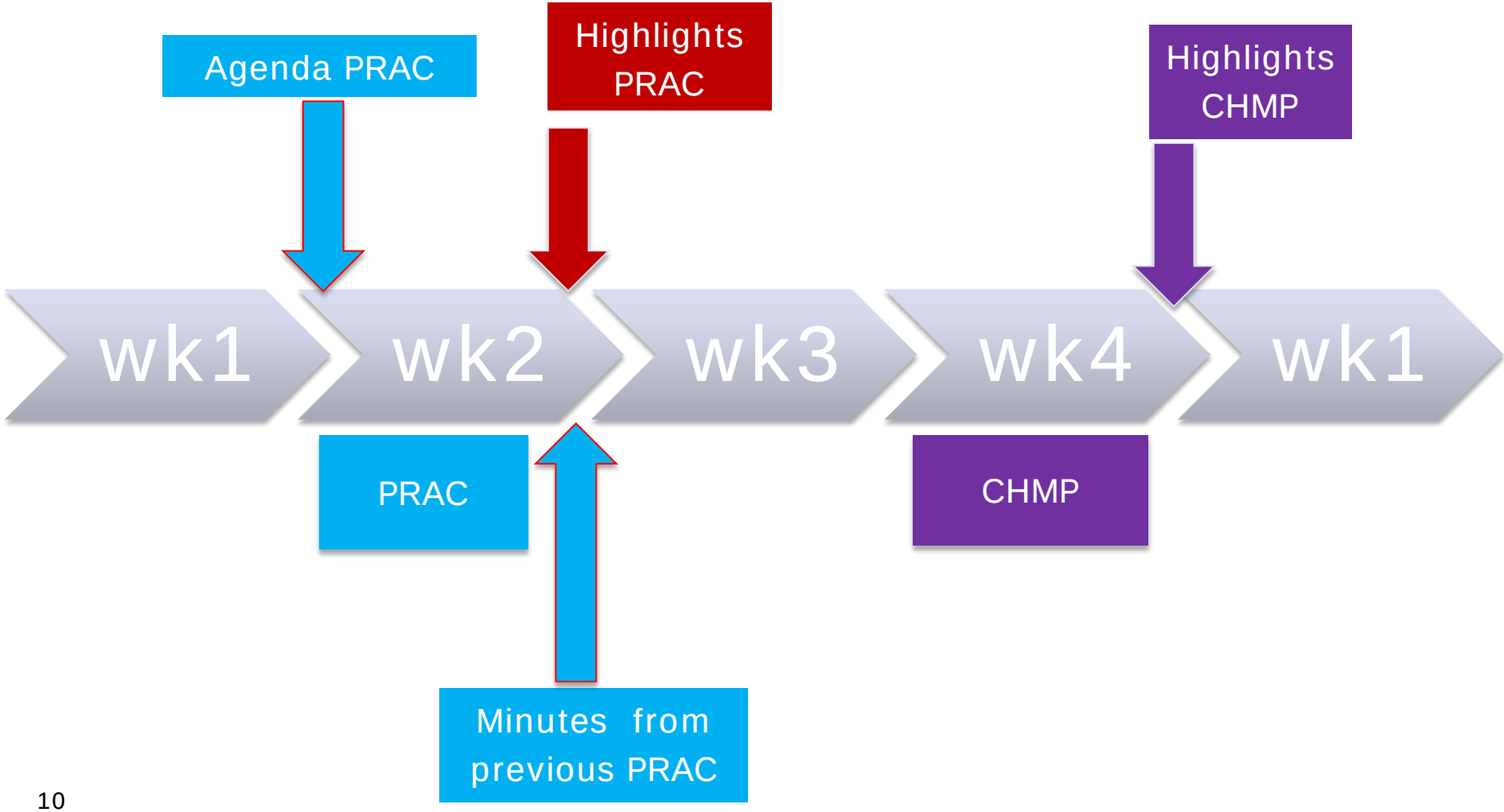
Signal Management Process



PRAC : recommendation/advice for action following the signal assessment including time table



Transparency



Agendas

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Document(s)	Language	Status	First published	Last updated	Effective Date
Agenda - PRAC draft agenda of meeting 29-31 October 2012	(English only)	draft	29/10/2012		
Agenda - PRAC draft agenda of meeting 1-3 October 2012	(English only)	draft	01/10/2012		
Agenda - PRAC draft agenda of meeting 3-5 September 2012	(English only)	draft	03/09/2012		
Agenda - PRAC draft agenda of the inaugural plenary meeting 19-20 July 2012	(English only)	draft	18/07/2012		

Minutes

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Document(s)	Language	Status	First published	Last updated	Effective Date
Minutes - PRAC meeting 3-5 September 2012	(English only)	adopted	05/10/2012		
Minutes - PRAC inaugural plenary meeting 19-20 July 2012	(English only)		07/09/2012		
Acronyms and abbreviations used in PRAC minutes	(English only)		05/10/2012		

31/10/2012

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 29-31 October 2012

PRAC begins second referral procedure

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) held its fourth meeting from 29 to 31 October 2012.

Since the first meeting of the PRAC in July 2012, the Committee's agenda has expanded substantially. At their most recent meeting, PRAC experts evaluated an increasing volume of information on new safety signals generated from EU reporting systems as well as a growing number of updated risk management plans for certain medicines.

Review of diclofenac-containing medicines started

The second safety review concerns diclofenac-containing medicines in relation to their possible cardiovascular risks. It follows a recent review of scientific studies by the Agency's Committee for Medicinal Products for Human Use (CHMP) on the cardiovascular safety of non-selective non-steroidal anti-inflammatory drugs (NSAIDs). More information on the review of diclofenac started by the PRAC is available in the table below.

Article 31 referrals

The review of diclofenac-containing medicines is the second safety review of a medicine under the new European Union (EU) rules on pharmacovigilance. It has been initiated at the request of the UK medicines agency, under Article 31 of Directive 2001/83/EC. This procedure is used to address public health concerns with medicines that are only authorised nationally, at the level of EU Member States, such as diclofenac.

The PRAC will now assess all available information and make a recommendation to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). Under the new rules, the coordination group leads on decision-making based on recommendations from the PRAC for nationally-authorised medicines. These changes ensure harmonised implementation of safety recommendations across the EU.

Signals at the PRAC (September to December)

September PRAC
***13 signals*:**
- 11 signals from EU spontaneous reporting systems
- 1 signal from other sources
- 1 signal follow-up

01-03 October PRAC:
15 signals:
- 12 signals from EU spontaneous reporting systems
- 3 signal follow-ups

29-31 October PRAC
12 signals:
- 6 signals from EU spontaneous reporting systems
- 6 signal follow-ups

26-30 November PRAC
9 signals
- 5 signals from EU spontaneous reporting systems
- 4 signal follow-ups

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Adalimumab – HUMIRA** (CAP)

- Signal of dermatomyositis

Status: *for initial discussion*

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

Recommendation(s)

- The Marketing Authorisation Holder (MAH) for Humira (adalimumab) and MAH for Remicade (infliximab) should submit within 30 days a cumulative review of dermatomyositis, discuss plausible pathophysiologic mechanisms and consider labelling change. A 60 day-assessment timetable was supported to assess the results of this review, leading to a further PRAC recommendation.

The EMA will review cases of dermatomyositis reported to EudraVigilance in association with pharmacologically related substances and report back to the PRAC.

Product information update??


Thank You