EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

- Proactive and proportionate risk management
- Higher quality of safety data
- Strengthened transparency, communication and patient involvement
- Stronger link between safety assessments and regulatory action
- Clear tasks and responsibilities for all parties (marketing authorisation holders, competent authorities, EMA)
- Improved EU decision-making procedures (harmonised decisions and efficient use of resources)
- Establishment of the Pharmacovigilance Risk Assessment Committee

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

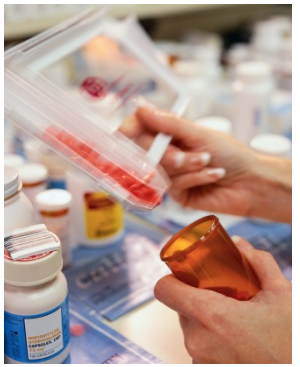
4. Communication with stakeholders:

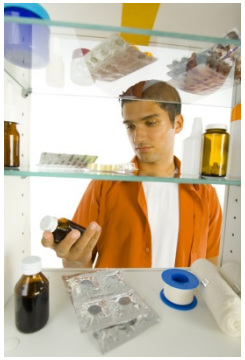
- Online publishing of information
- Coordination of safety messages
- Public hearings

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

Clinical trials data

EudraVigilance Human

Spontaneous ADR reporting systems

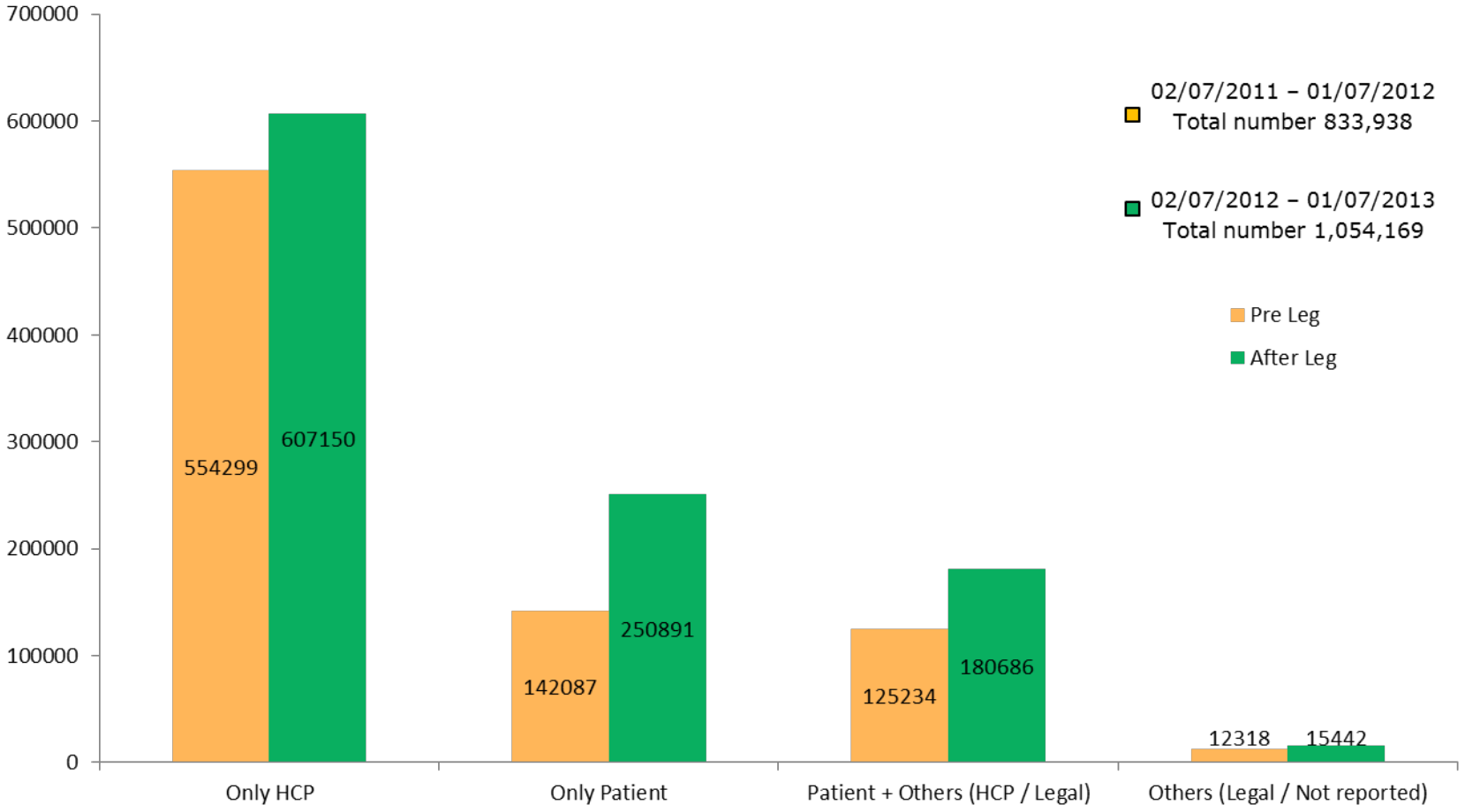
Pharmacovigilance

Scientific literature

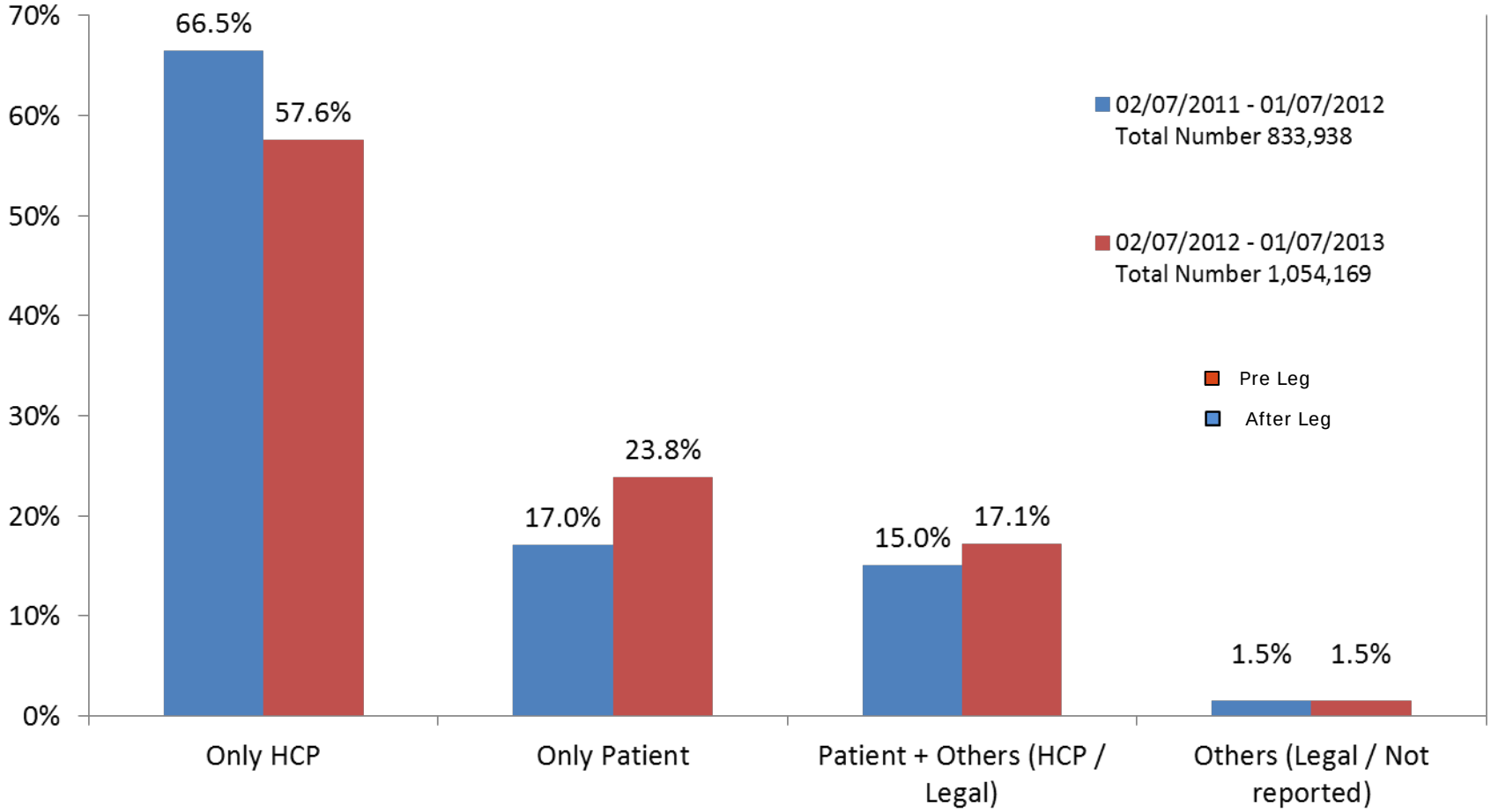
Non clinical trial data e.g non-interventional studies

Pharmacoepidemiological studies

ICSR reporting pre- and post new PV legislation



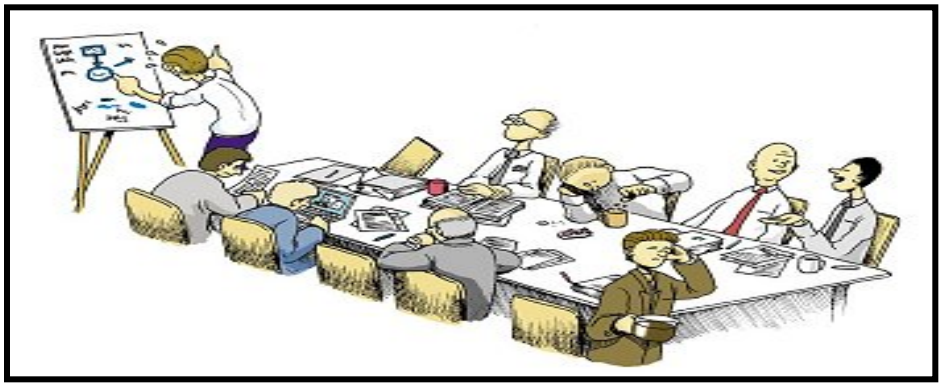
Proportion of ICSR reporting pre- and post new PV legislation

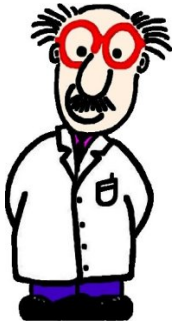


Signal Detection, Validation & Confirmation

How do we review EudraVigilance data?

Statistical analysis





Clinical review of individual case safety reports

Validation meeting → **Signal Confirmation**

- 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)

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:

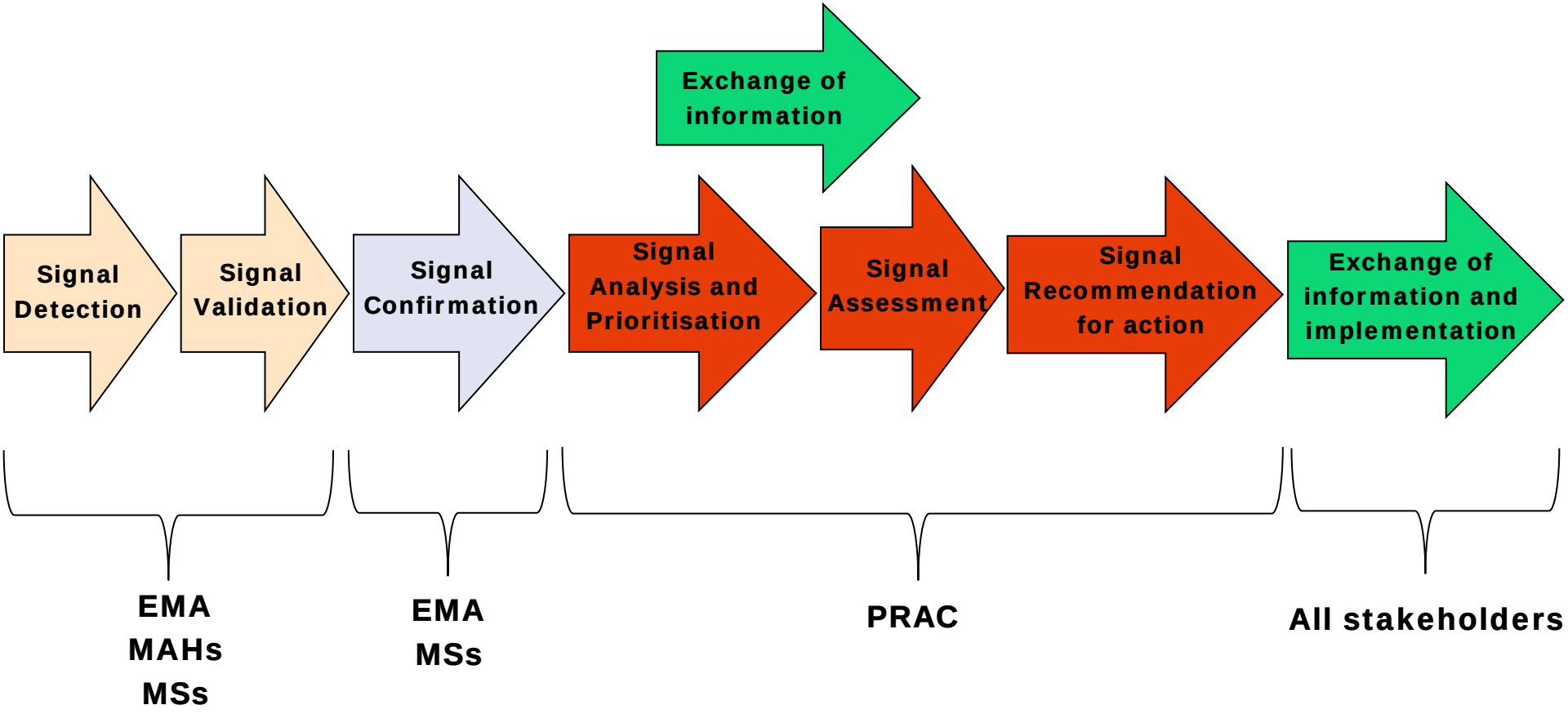
CONFIRMED

Added to agenda for the Pharmacovigilance Risk Assessment Committee (PRAC)

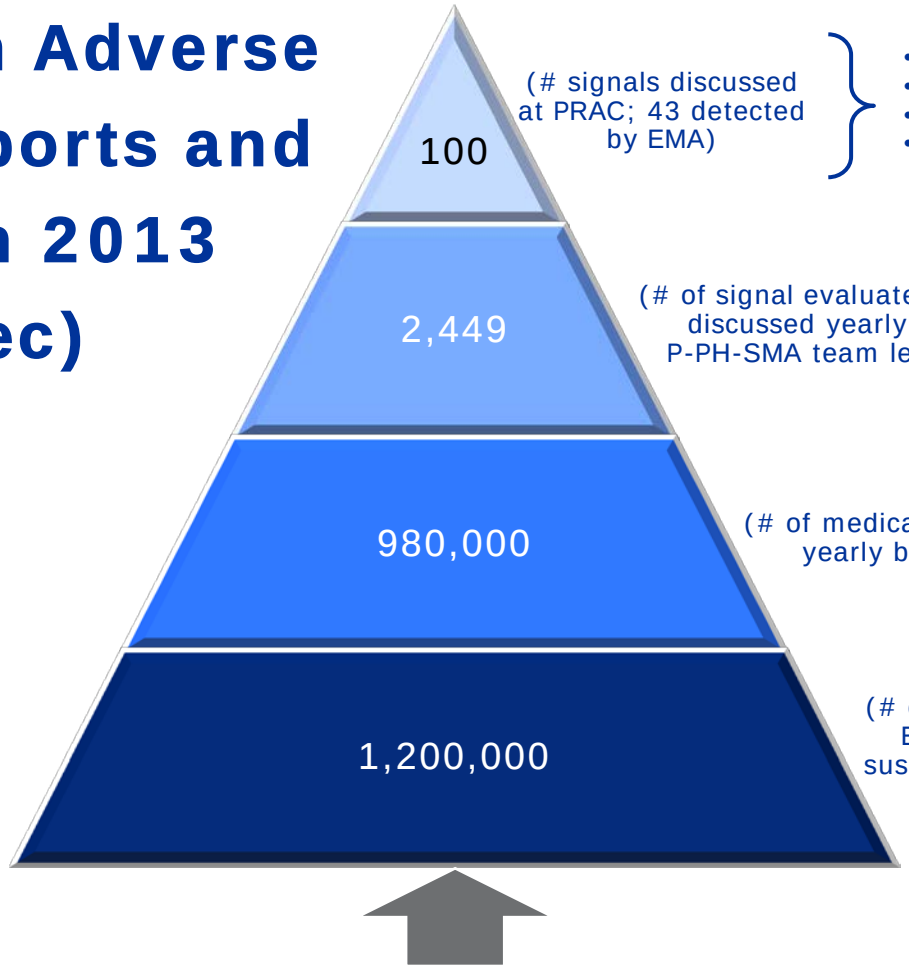
NOT CONFIRMED

Justification to be provided as to why signal is not confirmed

Signal Management Process



Trends in Adverse Event reports and signals in 2013 (Jan – Dec)



(# signals discussed at PRAC; 43 detected by EMA)

- Update SmPC/PIL
- Referral
- PASS
- MA varied, suspended…

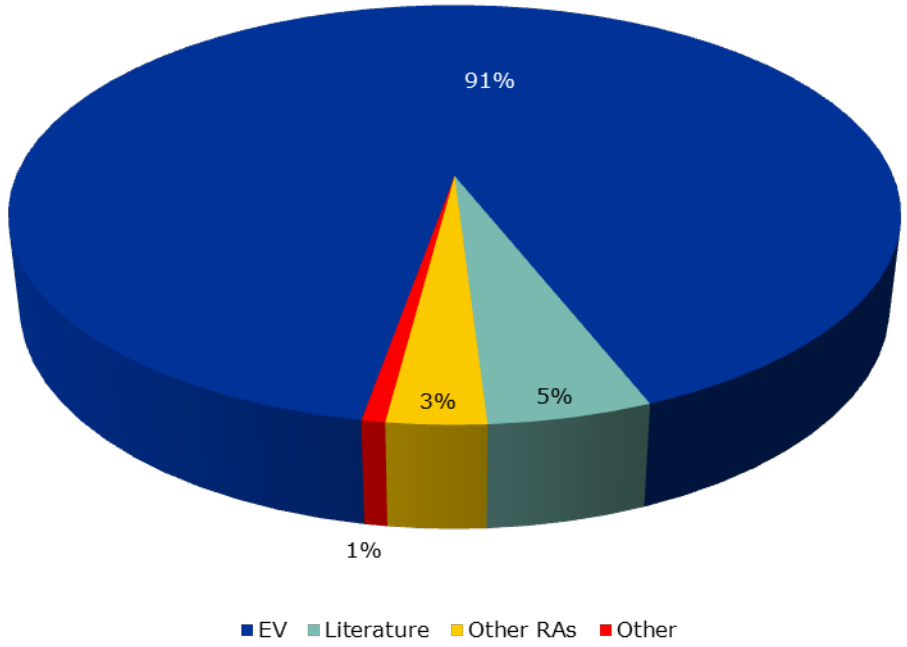
(# of signal evaluated and discussed yearly at P-PH-SMA team level)

(# of medical terms reviewed yearly by P-PH-SMA)

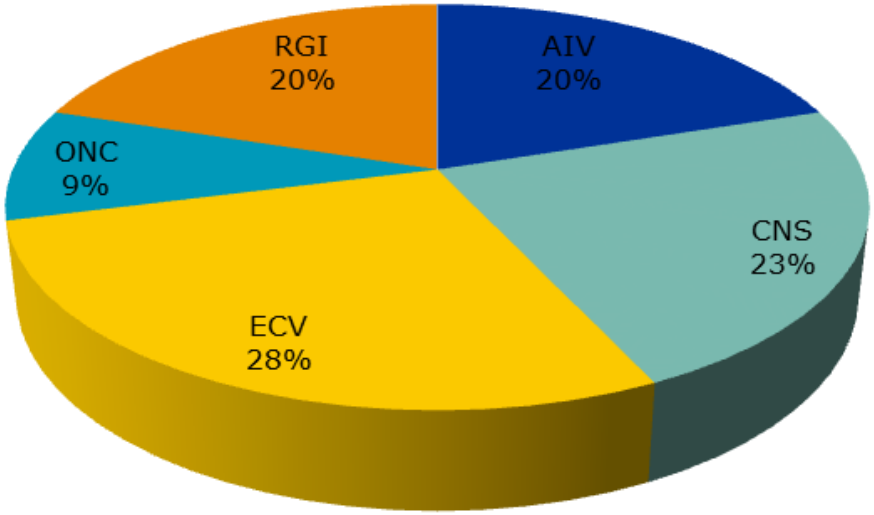
(# of ICSRs received per year in EV – European database of suspected adverse drug reaction reports)

Adverse Reactions reported by:
Patients, HCPs, Pharmaceutical companies

Source of all signals evaluated by EMA in 2013 (n=2449)



Therapeutic area of all 2013 PRAC signals (n=100)



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)

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,

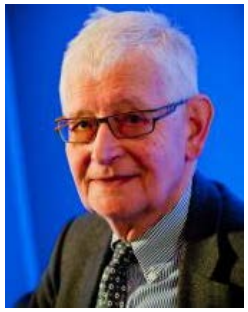
— Alternate: Kirsten Myhr.

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.

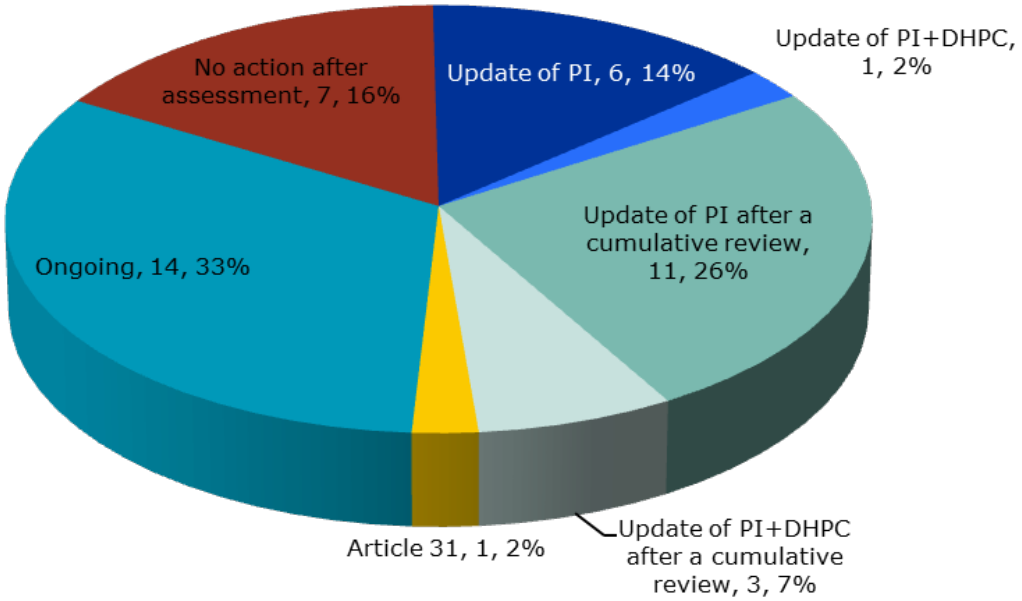
Done at Brussels, 28 February 2013.



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)

Labelling change with Sections 4.4 and 4.8 of SmPC updated

Recommendation(s):

The MAH should perform a cumulative review of cases of cholecystitis and related terms associated with sunitinib with particular focus on acalculous 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 **malfunction** 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** *

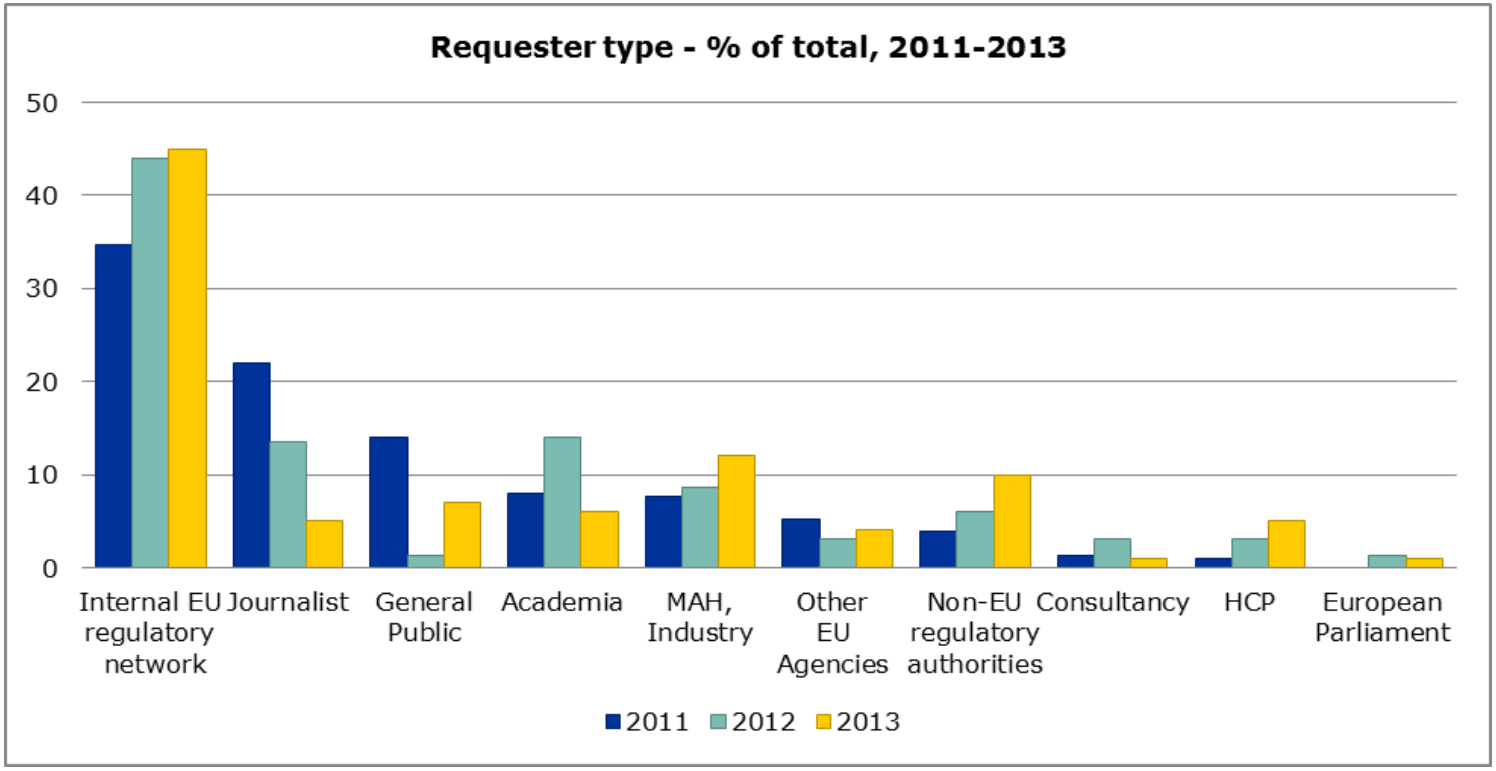
Temozolomide - **Hepatic failure** *

Ticagrelor **- Interaction** with grapefruit juice *

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

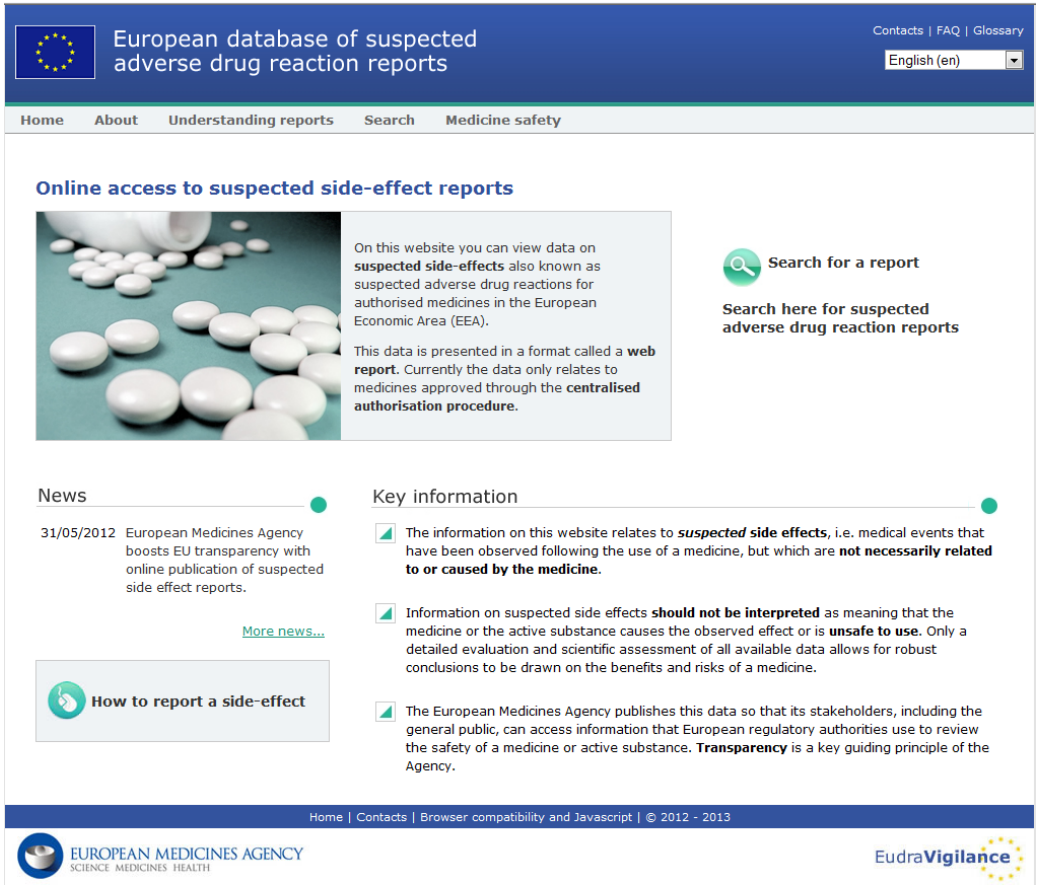
* Represents those resulting in labelling changes

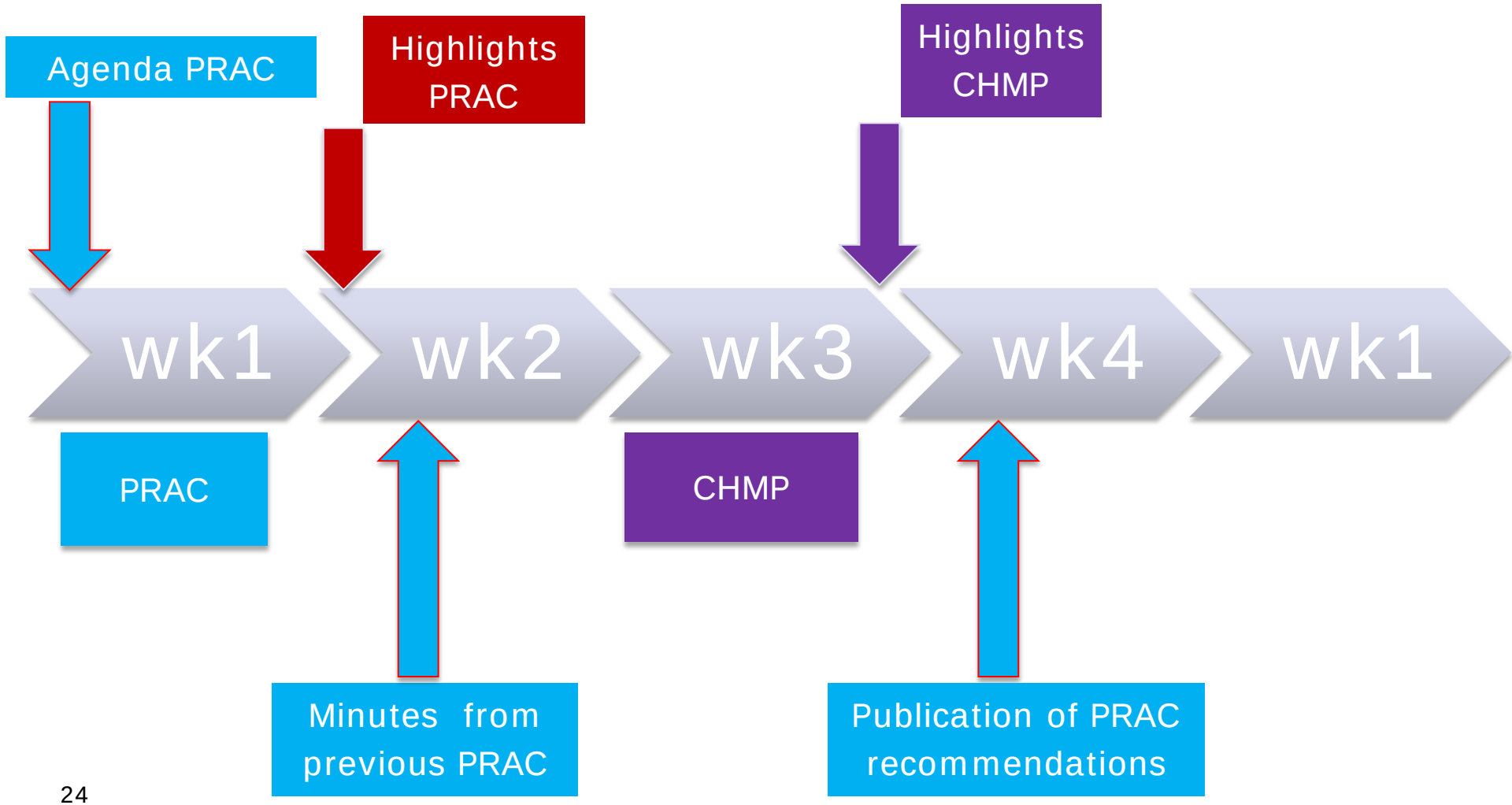
Requests for EudraVigilance data analyses: Type of requester (2011 - 2013)



Transparency

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




Agenda PRAC
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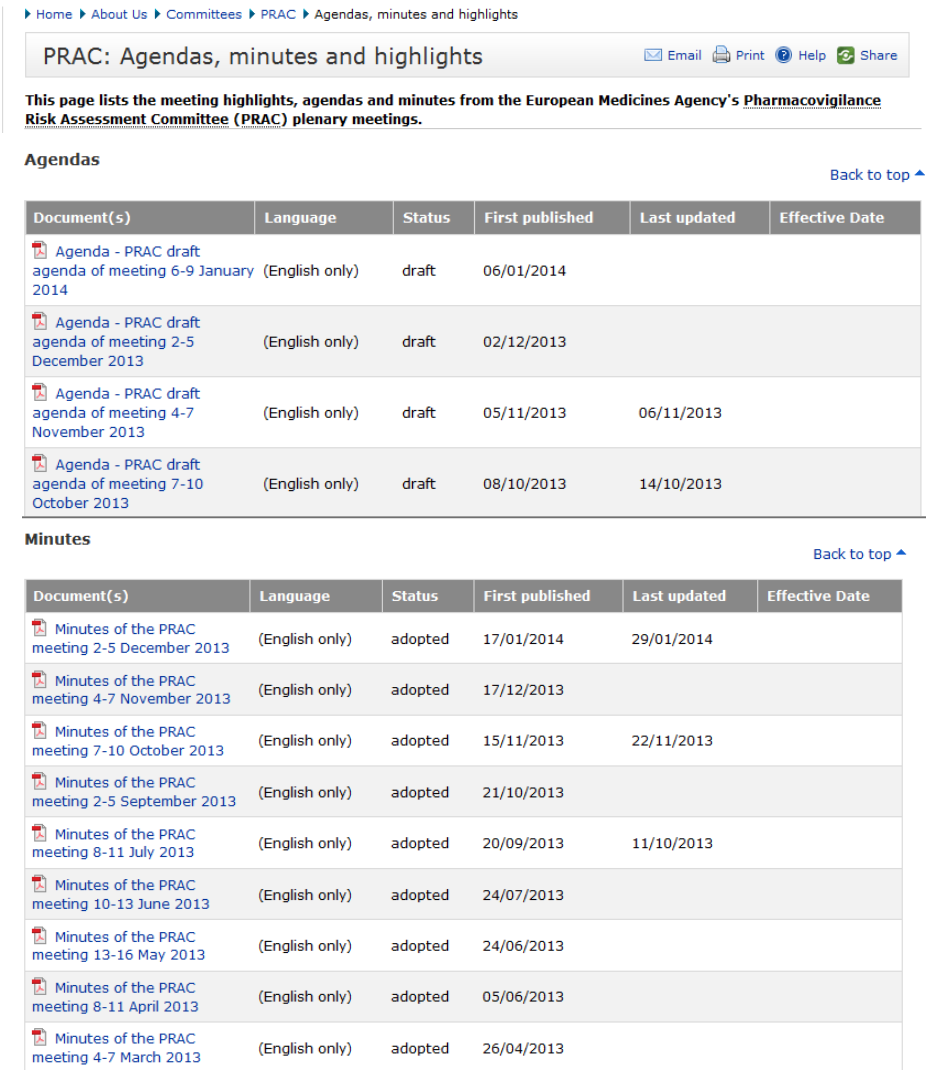
Publication of PRAC recommendations

Publication of PRAC agendas and minutes



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PRAC: Agendas, minutes and highlights

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This page lists the meeting highlights, agendas and minutes from the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) plenary meetings.

Agendas

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Document(s)	Language	Status	First published	Last updated	Effective Date
Agenda - PRAC draft agenda of meeting 6-9 January 2014	(English only)	draft	06/01/2014		
Agenda - PRAC draft agenda of meeting 2-5 December 2013	(English only)	draft	02/12/2013		
Agenda - PRAC draft agenda of meeting 4-7 November 2013	(English only)	draft	05/11/2013	06/11/2013	
Agenda - PRAC draft agenda of meeting 7-10 October 2013	(English only)	draft	08/10/2013	14/10/2013	

Minutes

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Document(s)	Language	Status	First published	Last updated	Effective Date
Minutes of the PRAC meeting 2-5 December 2013	(English only)	adopted	17/01/2014	29/01/2014	
Minutes of the PRAC meeting 4-7 November 2013	(English only)	adopted	17/12/2013		
Minutes of the PRAC meeting 7-10 October 2013	(English only)	adopted	15/11/2013	22/11/2013	
Minutes of the PRAC meeting 2-5 September 2013	(English only)	adopted	21/10/2013		
Minutes of the PRAC meeting 8-11 July 2013	(English only)	adopted	20/09/2013	11/10/2013	
Minutes of the PRAC meeting 10-13 June 2013	(English only)	adopted	24/07/2013		
Minutes of the PRAC meeting 13-16 May 2013	(English only)	adopted	24/06/2013		
Minutes of the PRAC meeting 8-11 April 2013	(English only)	adopted	05/06/2013		
Minutes of the PRAC meeting 4-7 March 2013	(English only)	adopted	26/04/2013		

Publication of PRAC recommendations – first publication October 2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 January 2014
EMA/PRAC/25732/2014
Pharmacovigilance Risk Assessment Committee

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 to provide additional data are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (20-23 January 2014) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

The established procedures and timelines for submission of variation applications pertaining to generic medicinal products are to be followed.

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24 January 2014
EMA/PRAC/530804/2013
Pharmacovigilance Risk Assessment Committee

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/CMDh meeting. PRAC recommendations on signals adopted each month are published here [http://www.ema.europa.eu/ema/index.jsp?curl=/pages/regulation/document_listing/document_listing_000375.jsp] after the relevant plenary meeting. When changes to the product information are recommended, the full text of the recommendation is published. Further information on each recommendation is provided in the PRAC minutes. Please note that some of the signals listed below are still under assessment by PRAC. For those, an update of the product information may be recommended at a later stage, when the PRAC has concluded the assessment.

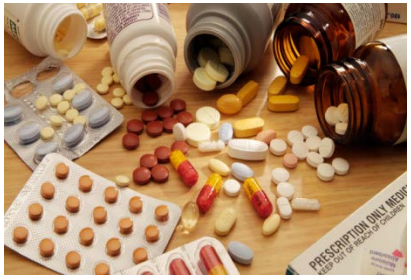
References:

Directive 2001/83/EC
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110721:EN:PDF
Regulation (EC) No 726/2004
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20120702:EN:PDF
Commission Implementing Regulation (EU) No 520/2012
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF
Module IX – Signal management of the guideline on good pharmacovigilance practices (GVP).
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129138.pdf
Questions and Answers on signal management
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/09/WC500150743.pdf

INN	Signal	PRAC meeting	Update of product information recommended by PRAC
Abatacept	Angioedema	06-09 January 2014 PRAC meeting minutes	No
Adalimumab	Dermatomyositis	03-05 September 2012 PRAC meeting minutes	No
		26-29 November 2012 PRAC meeting minutes	Yes[1]
		13-16 May 2013 PRAC meeting minutes	Yes[1]
Adalimumab	Glioblastoma and other brain neoplasms	08-11 April 2013 PRAC meeting minutes	No
		7-10 October 2013 PRAC meeting minutes	No
Adalimumab	Immune Reconstitution Inflammatory Syndrome (IRIS)	10-13 June 2013 PRAC meeting minutes	No
Adalimumab	Missed dose due to malfunction of the pre-filled pen device	4-7 November 2013 PRAC meeting minutes	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!