EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Implementing the pharmacovigilance legislation: focus on EU level activities

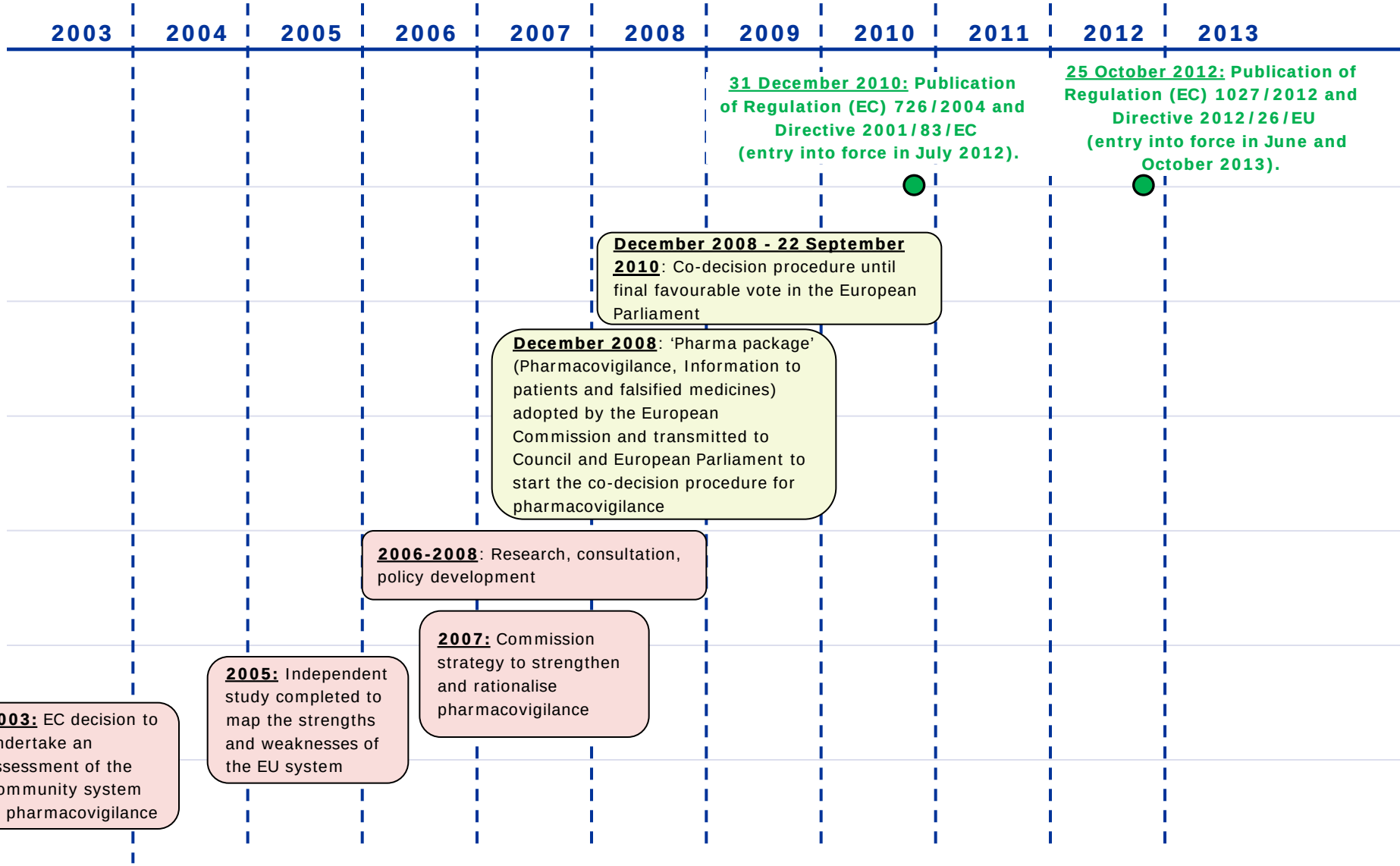
7th Stakeholders forum on the implementation of the new Pharmacovigilance legislation

Peter Arlett,
Pharmacovigilance Department, EMA
27 September 2013

# In this presentation

1. Objectives, where we have come from: where we are going
2. What has been delivered in 2012 – 2013 and what are now routine activities
3. What remains to be done
4. Moving forward together

# Where we have come from



# Where we are going: legislation objectives

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

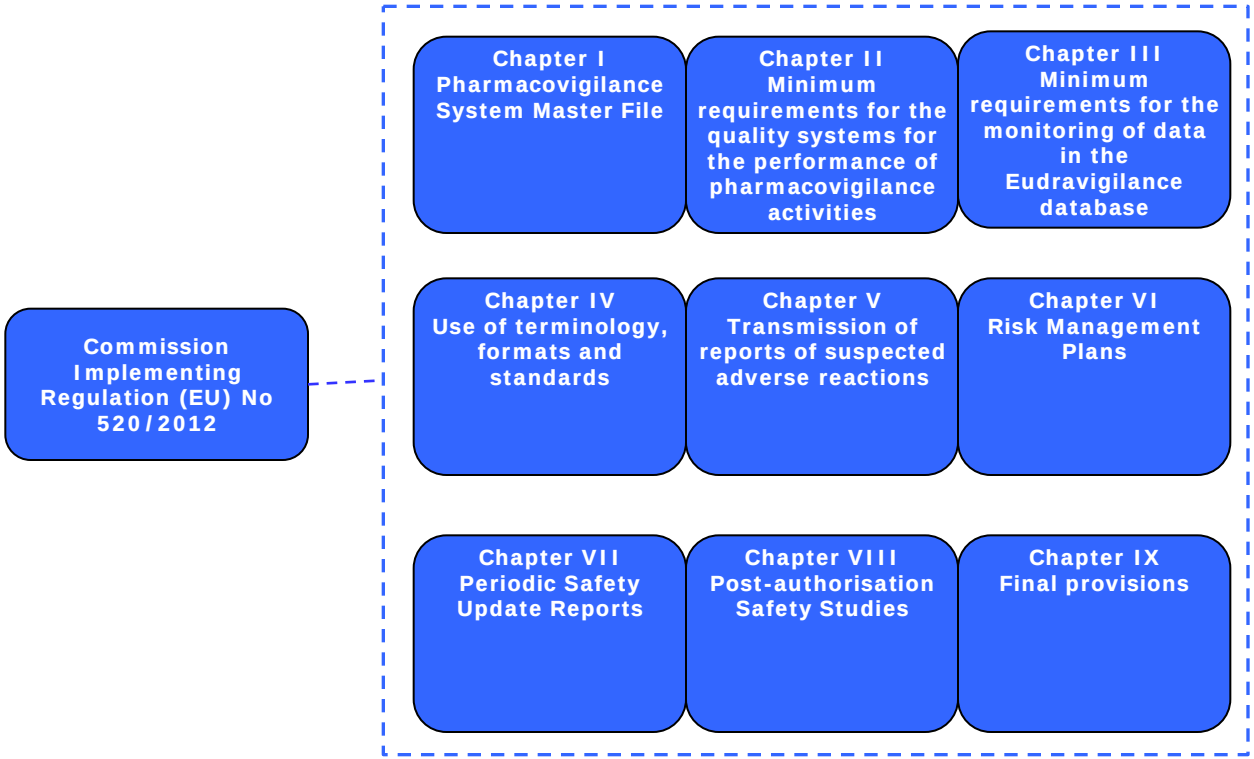
- Clear roles and responsibilities
- Science based
- Risk based/proportionate
- Increased proactivity/planning
- Reduced duplication/redundancy
- Integrate benefit and risk
- Ensure robust and rapid EU decision-making
- Strengthen the EU Network
- Engage patients and healthcare professionals
- Increase transparency and accountability
- Provide better information on medicines

# Challenges

- Major resource constraints
- Size of change
- Product lifecycle impacted
- Number of stakeholders impacted

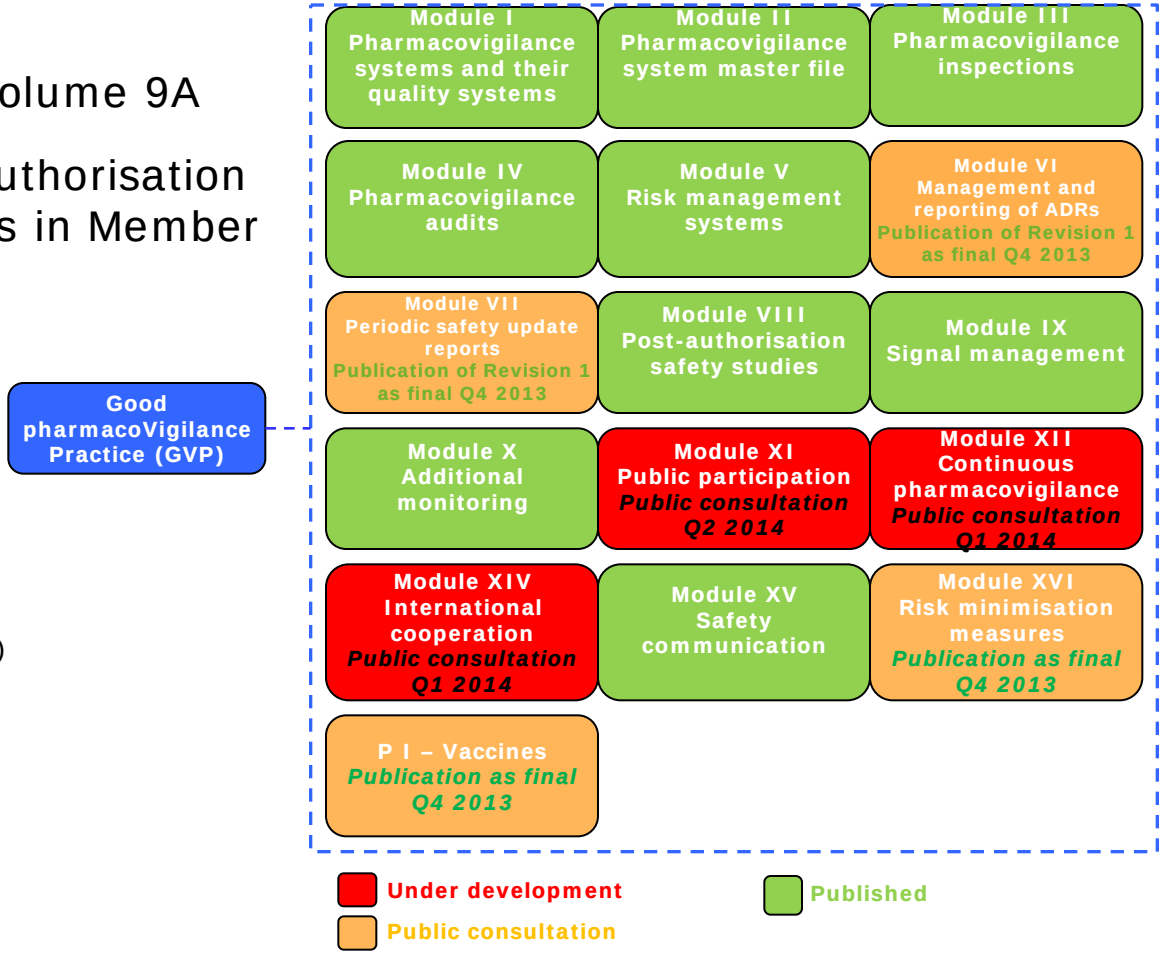
# Commission implementing regulation (EU) No 520/2012

- Legally binding
- 9 Chapters



# Good pharmacoVigilance Practice (GVP)

- Self-standing guidance on pharmacovigilance replacing Volume 9A
- Addressed to EU Marketing Authorisation Holders, Competent Authorities in Member States and Agency
- Developed within EU network
- 8 weeks public consultation
- 2 types of 'Chapters':
  - Modules for major processes
  - Product or populations specific (P)
- GVP structure:
  - A: Introduction
  - B: Structures and processes
  - C: Operation of the EU network



# Prioritised implementation agreed by EMA Management Board in December 2011 and 2012

- **Criteria for prioritisation:**
  - Firstly, public health activities
  - Secondly, transparency and communication activities
  - Thirdly, simplification activities (primarily for pharmaceutical industry)
- **Activities grouped into four main topic areas:**
  - Collection of key information on medicines
  - Better analysis and understanding of data and information
  - Regulatory action to safeguard public health
  - Communication with stakeholders
- **Traffic light:**

# What has been delivered and what is now routine

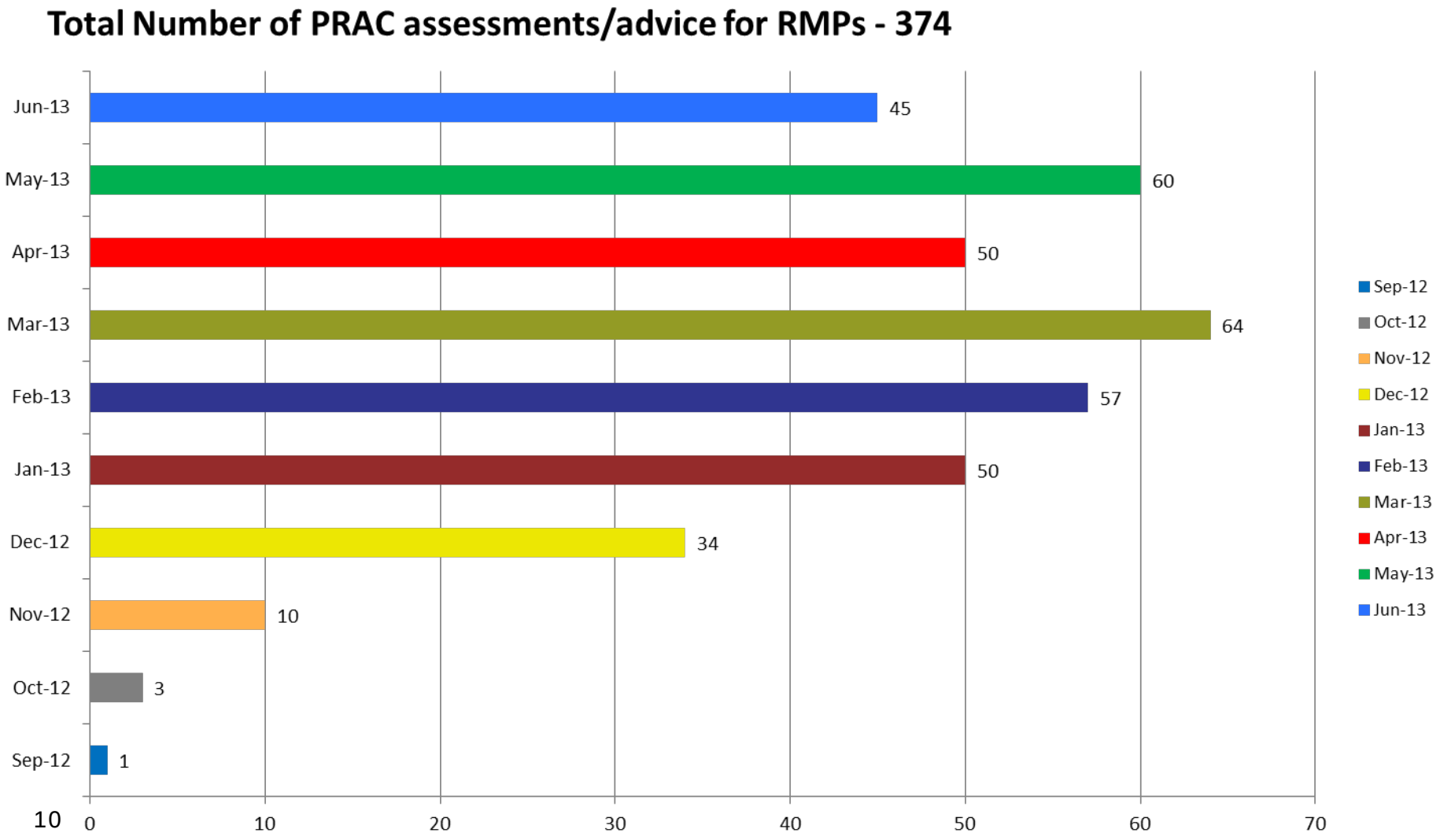
While date period for most of the slides relates to July 2012 to July 2013, a small number of slides use a different data period

# Prioritised implementation of the pharmacovigilance legislation

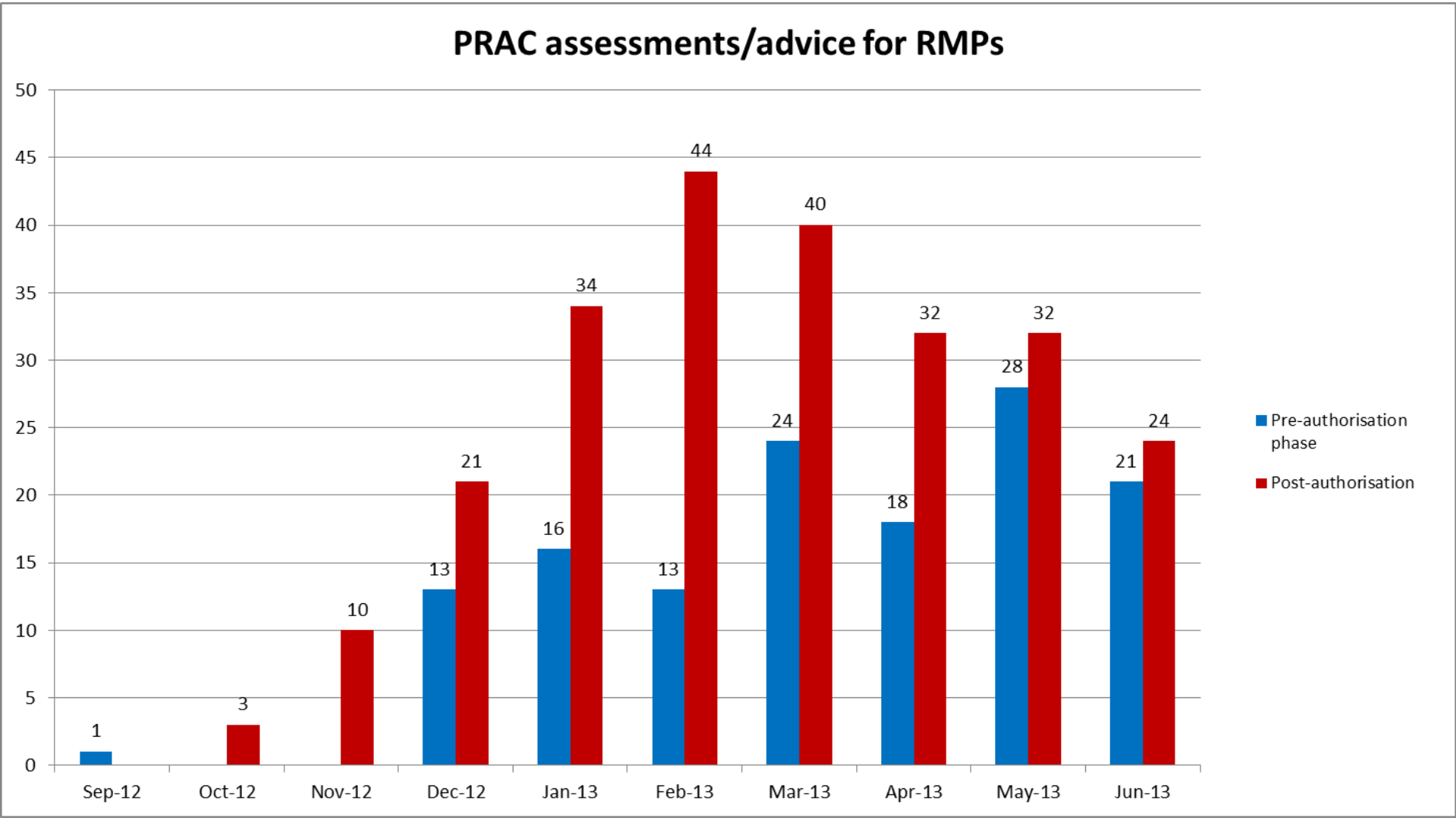
## Collection of key information on medicines

| Risk Management Plans: | 2012 | 2013 | |
|---|---|---|---|
| Establishment and operation of new procedure for requesting and assessing RMP | | | - Started July 2012<br>- Templates for industry (Oct)<br>- Format compulsory (Jan 2013) |

# RMP data


Total Number of PRAC assessments/advice for RMPs - 374
Jun-13
May-13
Apr-13
Mar-13
Feb-13
Jan-13
Dec-12
Nov-12
Oct-12
Sep-12
45
60
50
64
57
50
34
10
3
1
0
10
20
30
40
50
60
70
Sep-12
Oct-12
Nov-12
Dec-12
Jan-13
Feb-13
Mar-13
Apr-13
May-13
Jun-13

# RMP Data


PRAC assessments/advice for RMPs
50
45
40
35
30
25
20
15
10
5
0
1
3
10
13
21
16
34
13
44
24
40
18
32
28
32
21
24
Sep-12
Oct-12
Nov-12
Dec-12
Jan-13
Feb-13
Mar-13
Apr-13
May-13
Jun-13
Pre-authorisation phase
Post-authorisation

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25 July 2013
EMA/465932/2013 Rev.1[1]
Patient Health Protection

# Guidance on format of the risk management plan (RMP) in the EU – in integrated format

| | |
|---|---|
| Active substance(s) (INN or common name): | |
| Pharmaco-therapeutic group (ATC Code): | |
| Name of Marketing Authorisation Holder or Applicant: | |
| Number of medicinal products to which this RMP refers: | Choose one of the following:<br>• 1<br>• 2<br>• 3<br>• 4<br>• 5<br>• 6 |
| Product(s) concerned (brand name(s)): | |

| | | | |
|---|---|---|---|
| Data lock point for this RMP | <Enter a date> | Version number | <Enter a version no> |
| Date of final sign off | <Enter a date> | | |

[1] Please note that under section VI.1.4 Summary table of Risk Minimisation Measures "Copy table from Part V: 5.2" should have read "Copy table from Part V: V.3"

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25 July 2013
EMA/465933/2013 Rev.1[1]
Patient Health Protection

# Guidance on format of the risk management plan (RMP) in the EU for Generics

| | |
|---|---|
| Active substance(s) (INN or common name): | |
| Pharmaco-therapeutic group (ATC Code): | |
| Name of Marketing Authorisation Holder or Applicant: | |
| Number of medicinal products to which this RMP refers: | Choose one of the following:<br>• 1<br>• 2<br>• 3<br>• 4<br>• 5<br>• 6 |
| Product(s) concerned (brand name(s)): | |

| | | | |
|---|---|---|---|
| Data lock point for this RMP | <Enter a date> | Version number | <Enter a version no> |
| Date of final sign off | <Enter a date> | | |

[1] Please note that under section VI.1.4 Summary table of Risk Minimisation Measures "Copy table from Part V: 5.2" should have read "Copy table from Part V: V.3"

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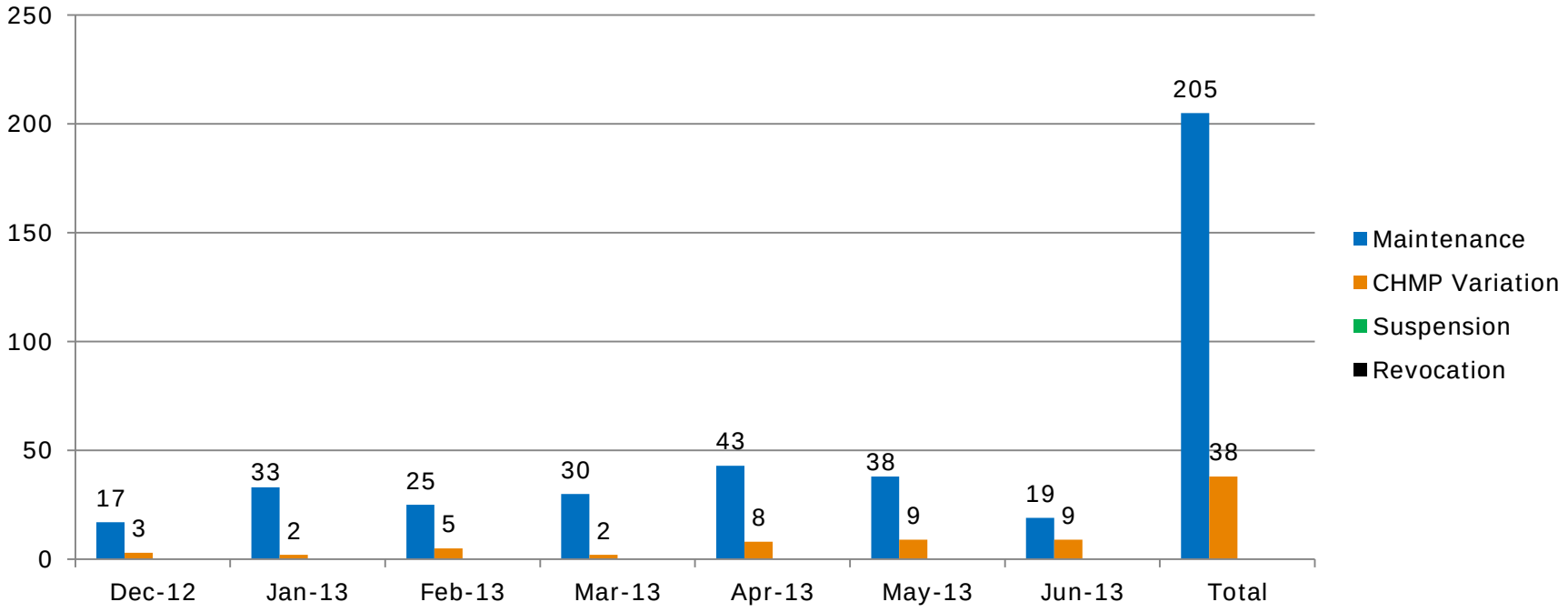
# Prioritised implementation of the pharmacovigilance legislation

## Collection of key information on medicines

| Periodic Safety Update Reports (PSUR): | 2012 | 2013 | |
|---|---|---|---|
| Operation of new procedures related to PSURs for CAPs* | ■ | ■ | - Started July 2012 |
| Development, maintenance and publication of harmonised birthdates to support PSUR submission | ■ | ■ | - First list published in Oct 2012 (monthly update) |
| Handling of PSURs for active substances contained in both CAPs and NAPs* in accordance with URD* list | | ■ | - Started in June 2013 |

# PSURs: Outcomes at PRAC




- 243 PSUR PRAC recommendations (single CAPs) from Dec 2012 till June 2013
- 38 (16%) PRAC recommendations to vary MA
- No suspensions, no revocations

# PSURs: Observations

- Procedure now better understood by all concerned parties – clear improvements noted.
- Increasing number 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
- Still room for further improvement in terms of better understanding the new procedure:
  - For regulators:
    - requests for additional information to be more clearly phrased
    - requests for labelling to be explicit and clearly justified
  - For pharmaceutical industry: key success factor is the provision by companies of clear positions and proposals for regulatory action/follow-up

⇨ Further training to be provided

# Prioritised implementation of the pharmacovigilance legislation

## Collection of key information on medicines

| Post-Authorisation Safety and Efficacy Studies: | 2012 | 2013 | |
|---|---|---|---|
| Implementation of the PASS procedure for protocols approval and results management for CAPs | | | - Started July 2012 |
| Public consultation on delegated act on PAES by the Commission | | | - From 28/11/2012 to 18/02/13 |
| PASS: Operate the procedure for initial protocol and protocol amendment endorsement and results management for NAPs | | | |
| PASS: Establish a procedure to encourage MAHs to collaborate on PASS affecting multiple medicinal products | | | |
| PAES: Deliver scientific guidance on methodological aspects (expert workshop) | | | - PAES workshop on 24/10/13-25/10/13 |

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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Home > EU PAS Register

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- Training in PhEpi and PV
- Code of Conduct
- Standards & Guidances
- ENCePP Study Seal
- Public Consultation
- Glossary of terms
- Resources Database
- Partners Forum
- E-Register of Studies
- EU PAS Register

## EU PAS Register

EU PAS Register Guide

One of the ENCePP guiding principles is transparency to the public of ongoing research relating to medicines used in clinical practice, in particular information on post-authorisation studies. Registration of protocols and study reports in the ENCePP E-Register of Studies is a means to achieve these objectives.

The 2010 pharmacovigilance legislation also requires the EMA to publish in a publicly available register the protocols and abstracts of results of **post-authorisation safety studies (PASS) imposed as an obligation** by a competent authority in accordance with Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC. It also specifies that the final report of such studies must provide the date of registration in this register.

Information about PASS which are initiated, managed or financed **voluntarily** by a MAH and which are required in the **Risk Management Plan (RMP)** to further investigate safety concerns or to evaluate the **effectiveness of risk minimisation activities, or any other PASS** should also be entered into this register in order to support the same level of transparency, scientific and quality standards.

Further information about the requirements for the registration of PASS is available in the guideline on Good Pharmacovigilance Practices (GVP) module VIII, chapter VIII.B.4.

The publicly available register referred to as the 'EU PAS Register' in the GVP is to be maintained by the EMA and will be built as an upgrade of the ENCePP E-Register of Studies.

**Before the EU PAS Register is fully operational, the E-Register of Studies, therefore, serves as the 'EU PAS Register' for all pharmacoepidemiological and pharmacovigilance studies** regardless of whether they are initiated, managed or financed by a MAH, or whether they are conducted by a research centre that is a partner of the ENCePP network or any other research centre, including from outside the European Union.

**For now, MAHs should therefore register their non-interventional PASS in the E-Register of Studies.**

135 studies registered: most since July 2012

# Prioritised implementation of the pharmacovigilance legislation

## Collection of key information on medicines

| Electronic submission of core medicine information by MAHs ('Article 57'): | 2012 | 2013 | |
|---|---|---|---|
| Start validation of received information | | | |
| Initiate limited quality assurance of data being submitted on medicinal products authorised in EU | | | |
| Achieve an agreement with pharmaceutical industry on the submission of varied marketing authorisations in view of operating the process for submission of maintenance data at a later stage | | | - Last workshop with Industry representatives held on 22/05/13 |

# Article 57(2) data content

**Substance Information:**
- S1: Substance names
- S2: Substance Translations
- S3: Substance synonyms
- S4: Substance class
- S5: Reference source
- S6: International Codes

Business Service **Substance** — S

**Reference Terminology:**
- R1: Pharmaceutical form
- R2: Route of Administration
- R3: ATC codes
- R4: Units of Measurement
- R5: Units of presentation
- R6: Reference source

Business Service **Referentials** — R


**Organisation information:**
- O1: MAH (Legal Entity)
- O2: QPPV
- O3: PhV Enquiries
- O4: PhV System Master File

Business Service **Organisation** — O

**Structured Medicinal Product Information:**
- P1: MAH (Legal Entity)
- P2: QPPV
- P3: PhV Enquiries
- P4: PSMF
- P5: Authorisation country code
- P6: Authorisation procedure
- P7: Authorisation status
- P8: Authorisation number
- P9: Authorisation date
- P10: MRP/DCP/EU number
- P11: Date of withdrawal/revocation/suspension
- P12: Package description
- P13: Orphan drug designation
- P14: Comments (e.g. paediatric use)
- P15: Medicinal product name
- P16: Medicinal product invented name
- P17: Product generic name
- P18: Product company name
- P19: Product strength name
- P20: Product form name
- P21: Pharmaceutical Form
- P22: Route of administration(s)
- P23: Active ingredient(s), Adjuvant(s)
- P24: Excipients
- P25: Medical device(s)
- P26: Strength of active ingredient(s)/adjuvant(s)
- P27: Therapeutic Indication(s)
- P28: ATC code

Business Service **Product** — P

**Unstructured Medicinal Product Information:**
- P29: Summary of Medicinal Product Characteristics

# Article 57(2) data: business case

- Better analysis and understanding of data/information
  - EudraVigilance data analysis, safety signal detection
- Regulatory action to safeguard public health
  - Support to referral procedures (e.g. interaction with MAHs)
  - Provision of other PRAC outputs to MAHs
  - Facilitation of PhV inspections
  - Longer term (ISO) – quality defects of medicines and counterfeits can be linked to the correct products

# Article 57(2) data: business case

- Communication with stakeholders
  - European medicines web portal (search for all human medicines authorised in the EU)
  - Publication of lists (work-sharing purposes, products under additional monitoring, PSUR list, list of withdrawn products)
  - Access to EudraVigilance data (proactive and reactive)
  - EU/international data exchange

# Article 57(2) Implementation status

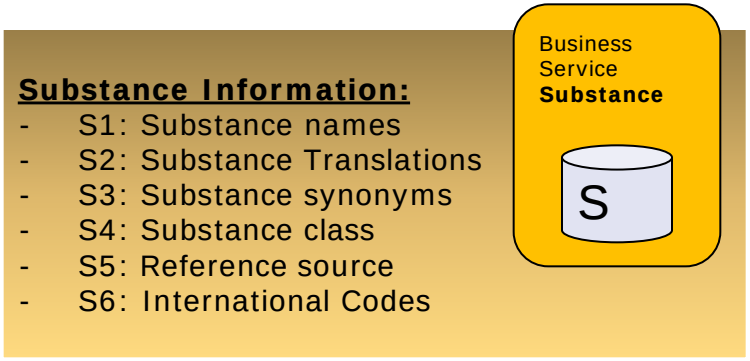
- As of 23rd September, MAHs have submitted a total of **443,000** medicinal product entries to the Agency.
- New entries in the XEVMPD are received on a daily basis

# Strategy for achieving reliable Article 57(2) data

- Two step approach is envisaged:
  - Longer term: achieve QA (quality assurance) built into the overall process, alongside targeted ex-post controls
  - Short to medium term: built on current* QA activities complemented with QC (quality control)

* Note
- Systematic semi-automatic monitoring via SAS routines of the new/updated received data
- Publication of detailed submission guidances
- Free training to stakeholders
- Dedicated helpdesk system
- Comparisons with references sources (e.g. SmPC)
- Monitoring/evaluation of (limited) received feedback from stakeholders

# Article 57(2) Substance data Quality Control




This is one of the initial Quality Control activities started by the Agency to improve the quality of the Art57 submissions

Two aspects need to be considered:

- De-duplication of substance names
- Completion of substance information content

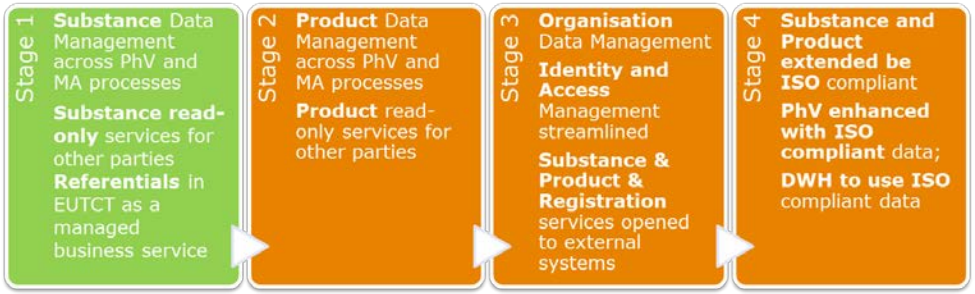
Currently the EMA is focusing on the first aspect above: De-duplication of substance names

# Next Steps

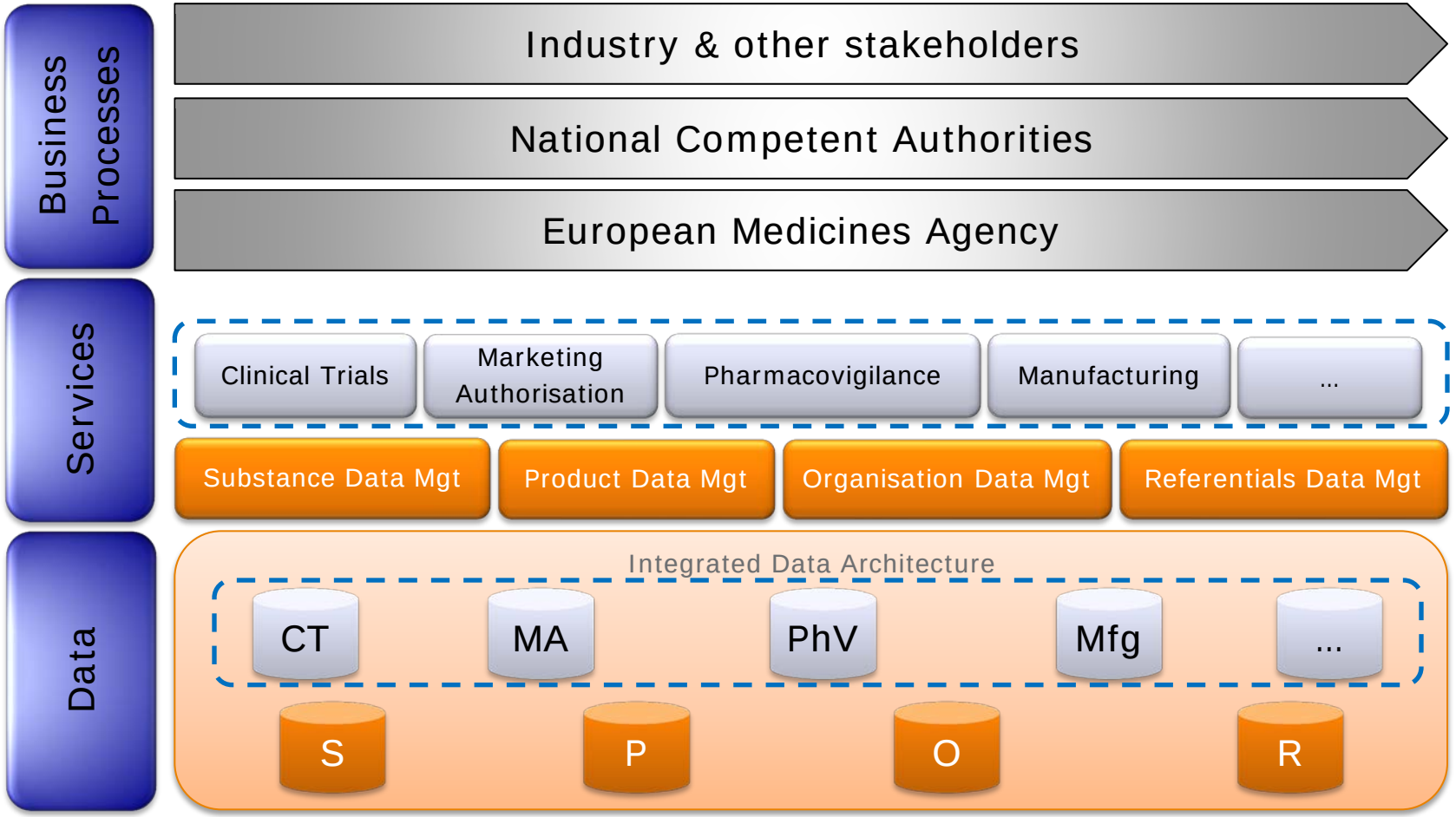
The next steps in the Art57 implementation, including strategy and timelines for the kick-off of the maintenance phase, will be presented and discussed with the EU Pharmaceutical Industry Associations in the Art57 Implementation Working Group on 23 October 2013.

Summary of the discussion will be published soon after the meeting.

Supporting the wider EU data architecture strategy…..



# Extension of the Data Architecture Roadmap to cover other entities

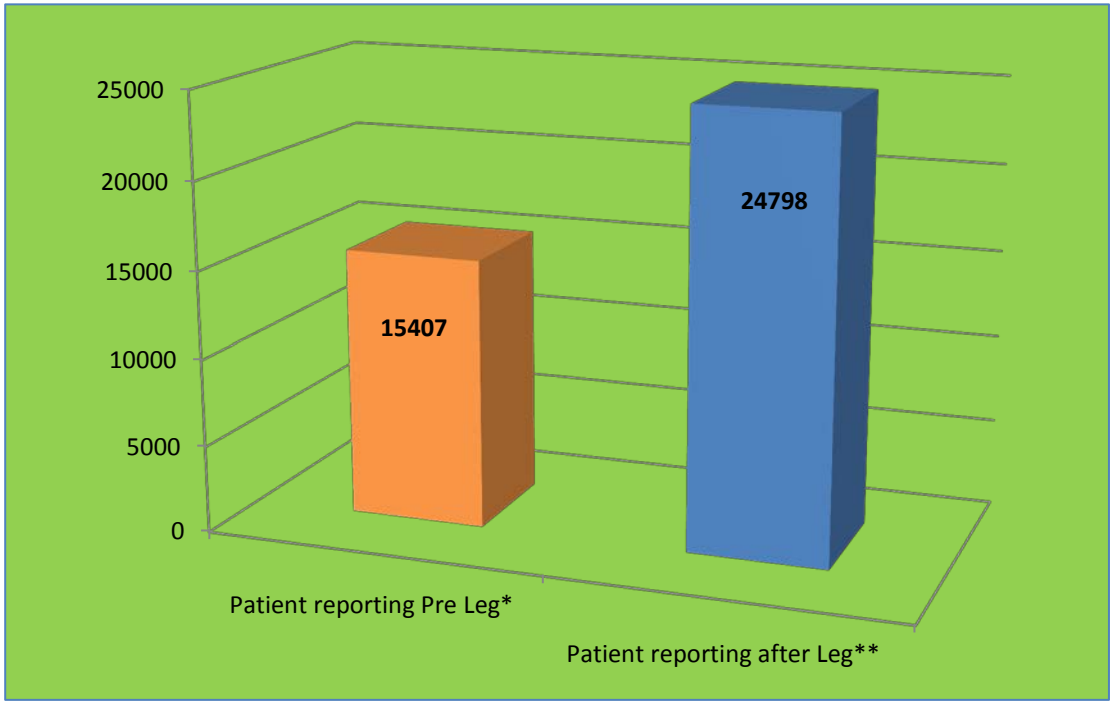


# Prioritised implementation of the pharmacovigilance legislation

## Collection of key information on medicines

| Reporting by patients: | 2012 | 2013 | |
|---|---|---|---|
| Cooperation with Member States to provide information to patients on direct reporting | | | - Core data fields agreed by Member States (June 2012) |
| Prepare guidance on patient reporting in cooperation with the Member States | | | |

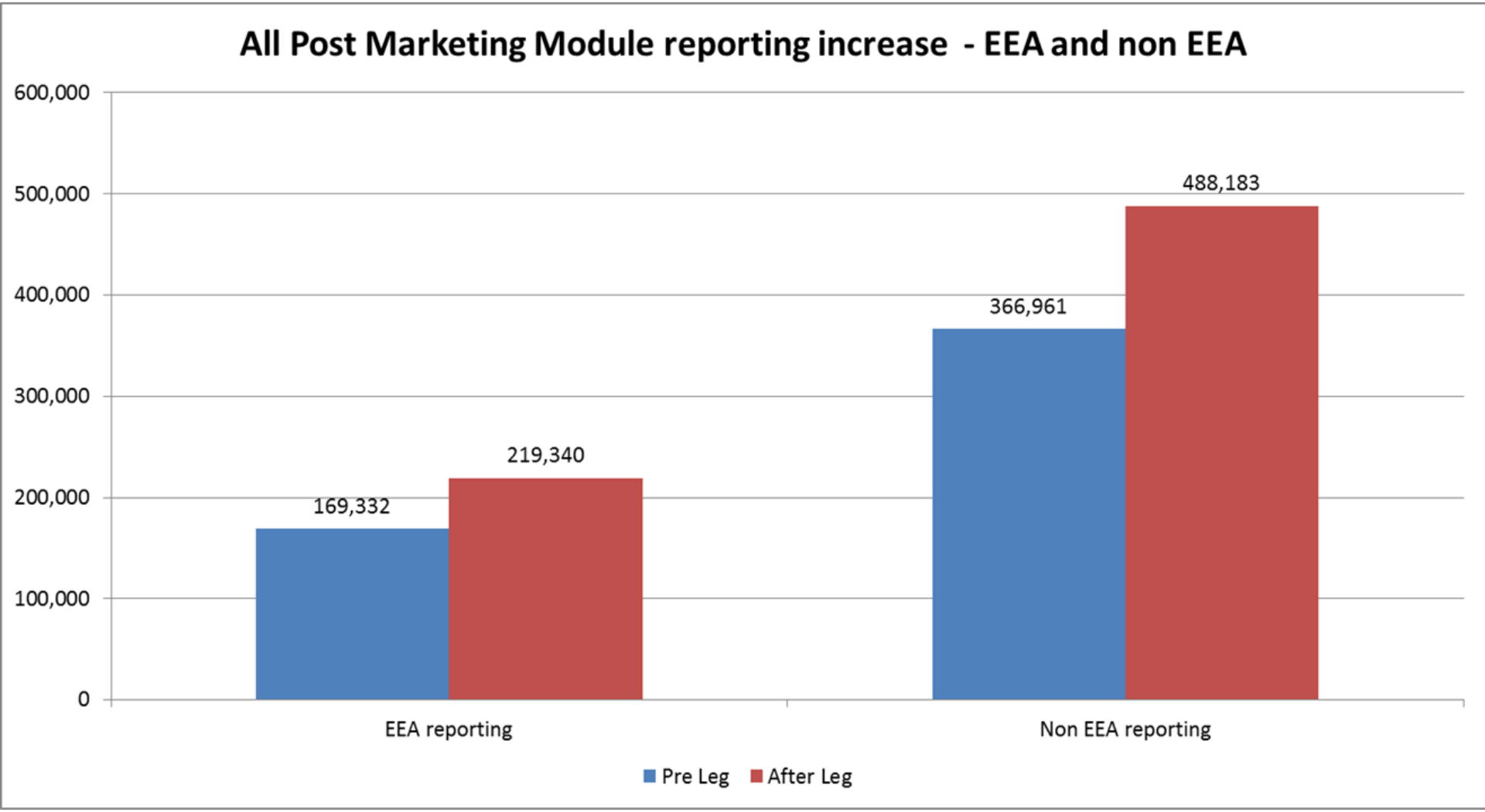
# Spontaneous reporting by patients in EEA




* Pre legislation data period - 02/07/2011 - 01/07/2012

** Post legislation data period -02/07/2012 - 01/07/2013

# Reporting numbers: Pre and Post legislation



# Prioritised implementation of the pharmacovigilance legislation

## Collection of key information on medicines

| List of medicines withdrawn for safety reasons: | 2012 | 2013 | |
|---|---|---|---|
| Develop a business process for establishing, maintaining and publishing such list | |  | Based on 2012 changes to pharmacovigilance legislation |

# Prioritised implementation of the pharmacovigilance legislation

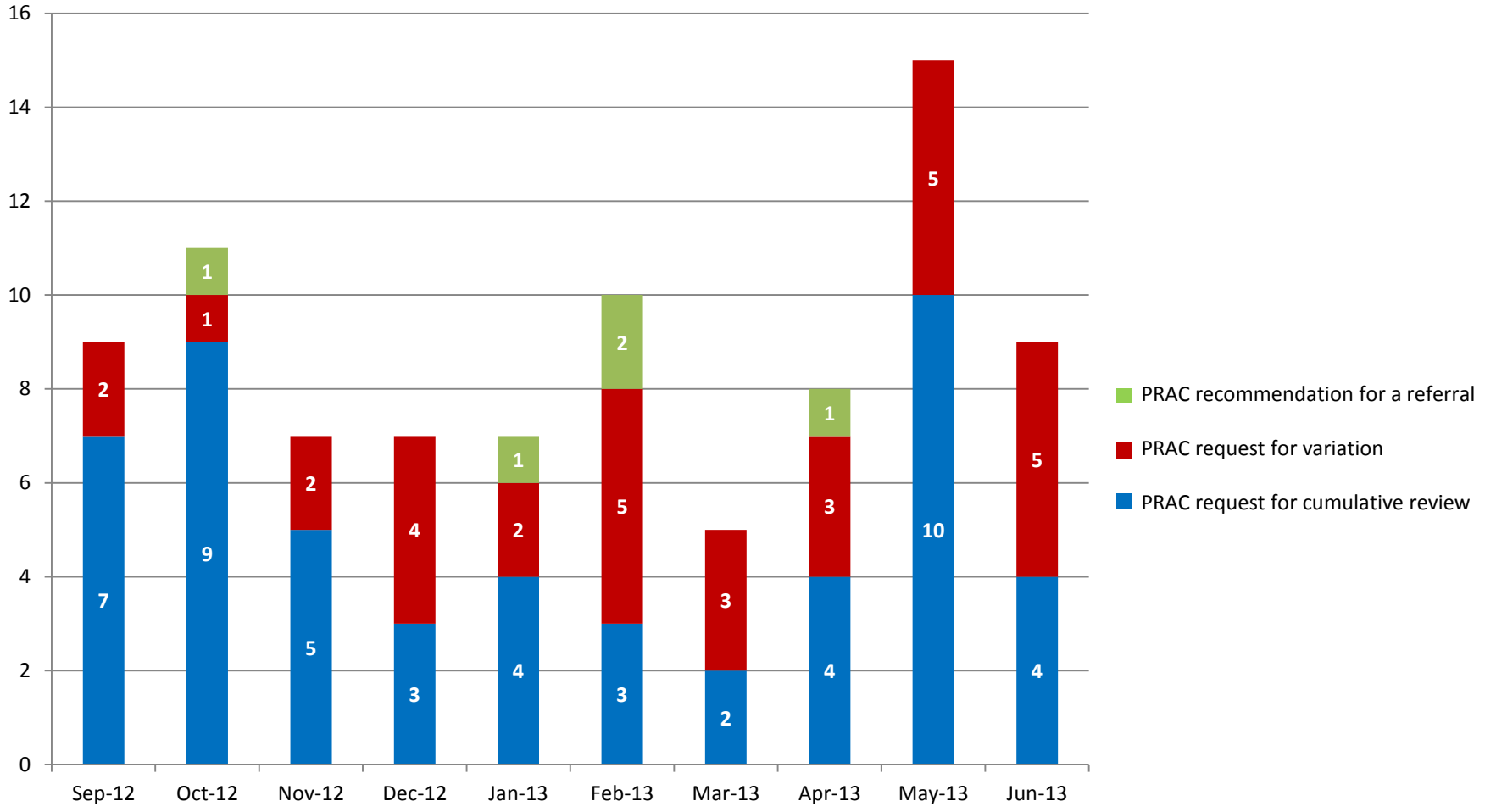
## Better analysis / understanding of data and information

| EudraVigilance and signal detection | 2012 | 2013 | |
|---|---|---|---|
| Operation of revised signal detection process for CAPs | ■ | ■ | - Started July 2012 |
| Support Member States to operate the new EU signal detection processes for NAPs | ■ | ■ | - Started July 2012<br>- Signal work-sharing list published (Oct 2012) |
| Start of signal management through the Pharmacovigilance and Risk Assessment Committee (PRAC) | ■ | ■ | - Started Sept 2012 |
| Continuation of maintenance work for the current EV system including data quality | ■ | ■ | - As planned |
| Implementation of web-publishing of adverse reaction data (further to the EV Access Policy) | ■ | ■ | - Delivered in May 2012 |
| Perform analyses of EV data for NAPs (in collaboration with MSs Competent Authorities through work-sharing) | | ■ | |

# Achievements of EV Data Quality management 07/2012 – 07/2013

- Recoding of medicinal product terms reported in safety reports: 87,388 terms recoded
- Duplicate detection & management of individual safety reports: 101,800 duplicate cases removed from the system
- EudraVigilance Data Quality Assessments: 242 assessments performed and senders (MAHs/Sponsors/NCAs) provided feedback

# Signals: Data and PRAC Outcomes



# Signal descriptions – first publication in coming days

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23 September 2013
EMA/550442/2013
Patient Health Protection

## PRAC recommendations on signals

Adopted at the PRAC meeting of 2-5 September 2013

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 2-5 September 2013.

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 Member States and 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 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 (16-19 September 2013) 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)

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10 September 2013
EMA/530804/2013
Pharmacovigilance Department

## 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 establishement. It will be updated after each monthly plenary meeting. PRAC recommendations on signals adopted each month are published here [include link to standalone recommendations] 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
[Insert link when available]

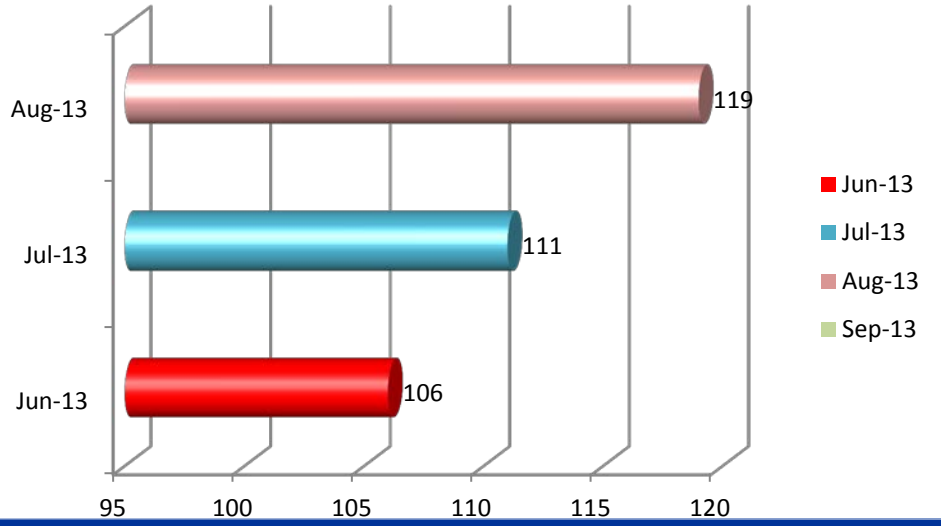
| INN | Signal | PRAC meeting | Update of product information recommended by |
|---|---|---|---|
| Adalimumab | Dermatomyositis | 03-05 September 2012 PRAC meeting minutes | No |
| | | 26-29 November 2012 PRAC meeting minutes | Yes |
| | | 13-16 May 2013 PRAC meeting minutes | Yes |
| Adalimumab | Glioblastoma and brain neoplasms | 08-11 April 2013 PRAC meeting minutes | No |
| Adalimumab | Immune Reconstitution Inflammatory Syndrome (IRIS) | 10-13 June 2013 PRAC meeting minutes | No |
| Adalimumab | Skin ulcers | 08-11 April 2013 PRAC meeting minutes | No |
| Agents acting on the renin-angiotensin system | Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials (signal from literature) | 08-11 April 2013 PRAC meeting minutes | No[1] |

# Prioritised implementation of the pharmacovigilance legislation

## Better analysis of data and information

| Additional monitoring: | 2012 | 2013 | |
|---|---|---|---|
| Develop and publish the list of medicines with additional monitoring status | | | - Initial list published on 25 April 2013 |
| Monitor that product information for relevant CAPs is updated to reflect this status | | | - First black triangles starting to appear |

The current number of the additionally monitored drugs – **119** (published 9 August 2013)



# Additional monitoring

- Mandatory for following products:
  - ✓ Medicines containing a new active substance authorised after 1 January 2011
  - ✓ Any biological medicinal product authorised after 1 January 2011
  - ✓ Conditional or exceptional conditions of marketing
  - ✓ Obligation for post authorisation safety studies
  - ✓ Stricter reporting of adverse reactions
- EMA publishes the list

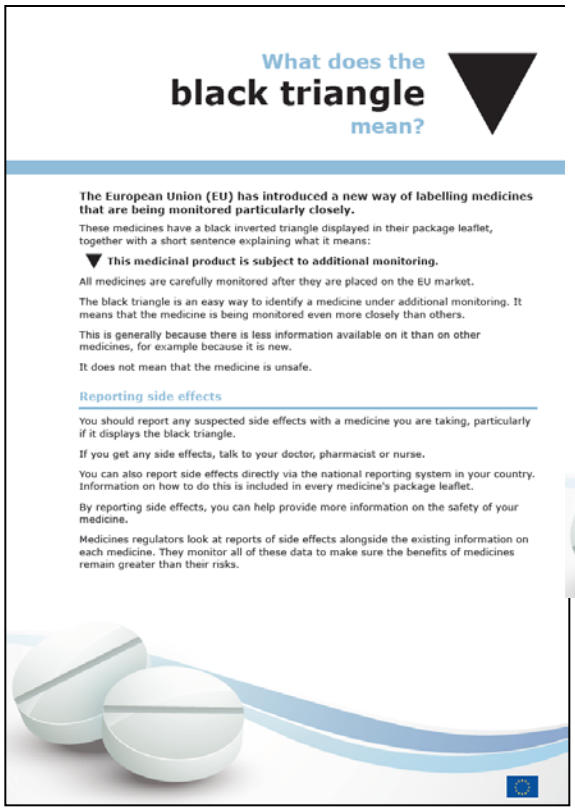
# ‘Black symbol’ for products under additional monitoring (1/2)

- Black symbol:
  - Selected by the European Commission following a recommendation of the PRAC (after involving stakeholders) on 7 March 2013
  - Inverted equilateral black triangle 
- New text in Product Information
  - *SPC text: <{Black symbol}> This medicinal product is subject to additional monitoring. This is to allow any safety information to be identified rapidly. Healthcare professionals are encouraged to report any suspected adverse reactions. See section 4.8.>*
  - *PL text: <{Black symbol} This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.*
- List of products under additional monitoring
  - initial list published on 25th April 2013 and updated every month

# New communication material on additional monitoring (1/2)

## Factsheet + Video

- Consultation: EC, HMA WGCP and Project Team 3 involved in preparation
- PRAC informed at September meeting
- All EU languages
- Easily printable
- Based on already published information



What does the
**black triangle**
mean?

**The European Union (EU) has introduced a new way of labelling medicines that are being monitored particularly closely.**

These medicines have a black inverted triangle displayed in their package leaflet, together with a short sentence explaining what it means:

▼ **This medicinal product is subject to additional monitoring.**

All medicines are carefully monitored after they are placed on the EU market.

The black triangle is an easy way to identify a medicine under additional monitoring. It means that the medicine is being monitored even more closely than others.

This is generally because there is less information available on it than on other medicines, for example because it is new.

It does not mean that the medicine is unsafe.

**Reporting side effects**

You should report any suspected side effects with a medicine you are taking, particularly if it displays the black triangle.

If you get any side effects, talk to your doctor, pharmacist or nurse.

You can also report side effects directly via the national reporting system in your country. Information on how to do this is included in every medicine's package leaflet.

By reporting side effects, you can help provide more information on the safety of your medicine.

Medicines regulators look at reports of side effects alongside the existing information on each medicine. They monitor all of these data to make sure the benefits of medicines remain greater than their risks.

¿Qué significa el
**triángulo negro?**

**La Unión Europea (UE) ha introducido una nueva forma de identificar aquellos medicamentos que están siendo sometidos a un seguimiento particularmente riguroso.**

Dichos medicamentos muestran en su prospecto un triángulo negro invertido, así como la siguiente frase:

▼ **"Este medicamento está sujeto a seguimiento adicional."**

Una vez comercializados en la UE, todos los medicamentos se someten a un seguimiento riguroso. Sin embargo, los medicamentos con el triángulo negro son controlados aún más que los demás.

Esto sucede generalmente porque hay menos información sobre ellos en comparación con otros, por ejemplo porque son nuevos en el mercado.

No significa que el medicamento sea menos seguro.

**Cómo notificar efectos adversos**

Como paciente, usted debe informar de cualquier efecto adverso del que sospeche tras tomar un medicamento, sobre todo si dicho medicamento presenta el triángulo negro,

Puede notificar los efectos adversos a su médico, farmacéutico o enfermera.

También puede notificarlos directamente a las autoridades sanitarias de medicamentos en su país, utilizando el sistema de notificación vigente en dicho país. Puede encontrar información al respecto en el prospecto del medicamento o en la página web de las autoridades sanitarias de medicamentos en su país.

Notificando estos efectos, usted puede ayudar a las autoridades sanitarias a evaluar si los beneficios de un medicamento se mantienen mayores que sus riesgos.

# Prioritised implementation of the pharmacovigilance legislation

## Better analysis / understanding of data and information

| Medication errors: | 2012 | 2013 | |
|---|---|---|---|
| Establish guidance/best practice considerations on medication error prevention and reporting | |  | - Stakeholder workshop held on 28/02/13-01/03/13 |


http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143163.pdf - Windows Internet Explorer
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143163.pdf
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Safety
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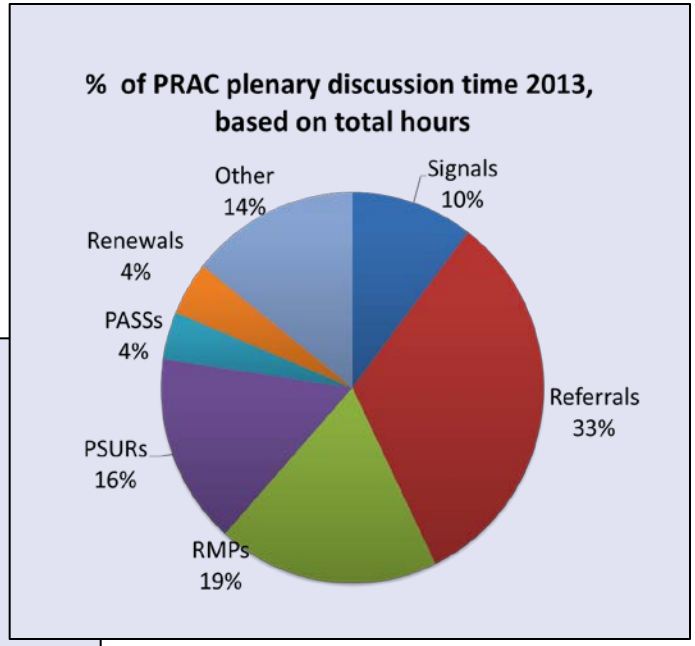
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
6 May 2013
EMA/144458/2013
Patient Health Protection
Medication-errors workshop
Workshop report
28 February – 1 March 2013
European Medicines Agency, London, United Kingdom

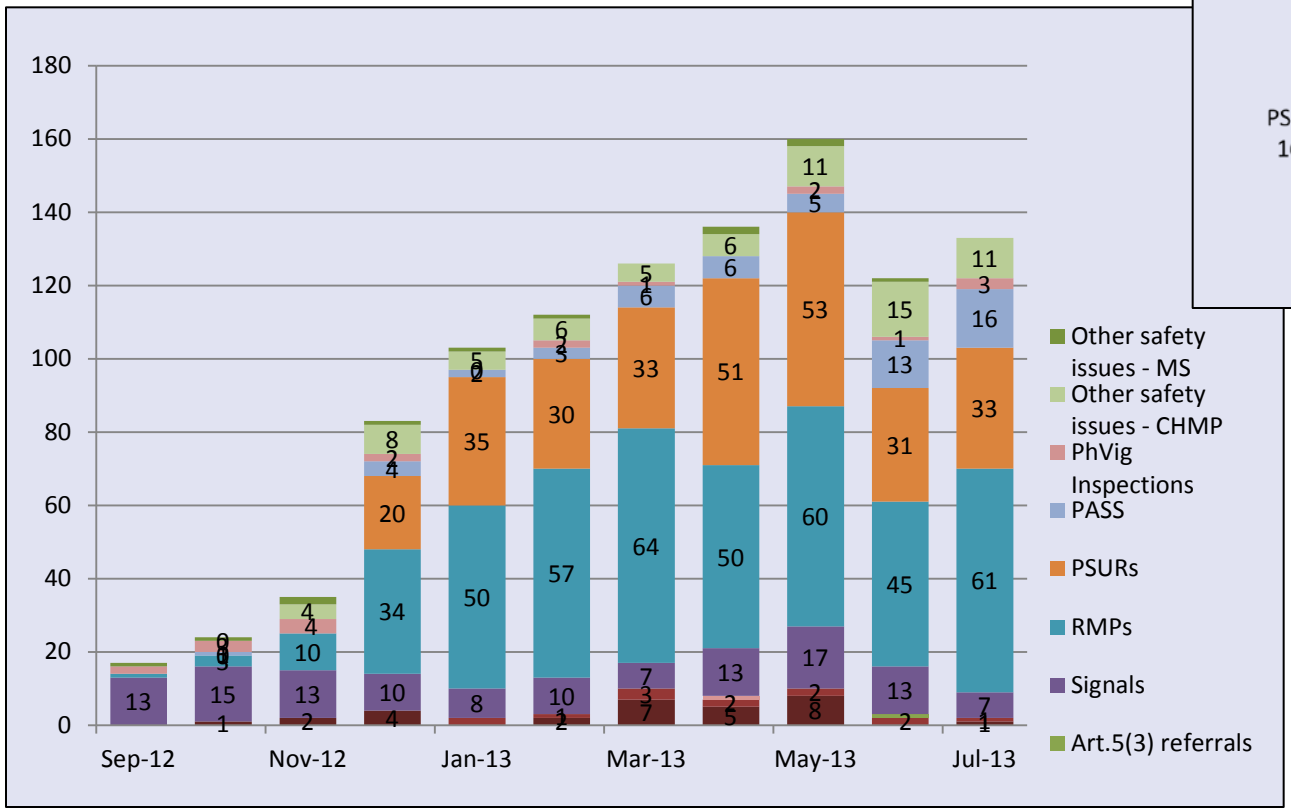
# Prioritised implementation of the pharmacovigilance legislation

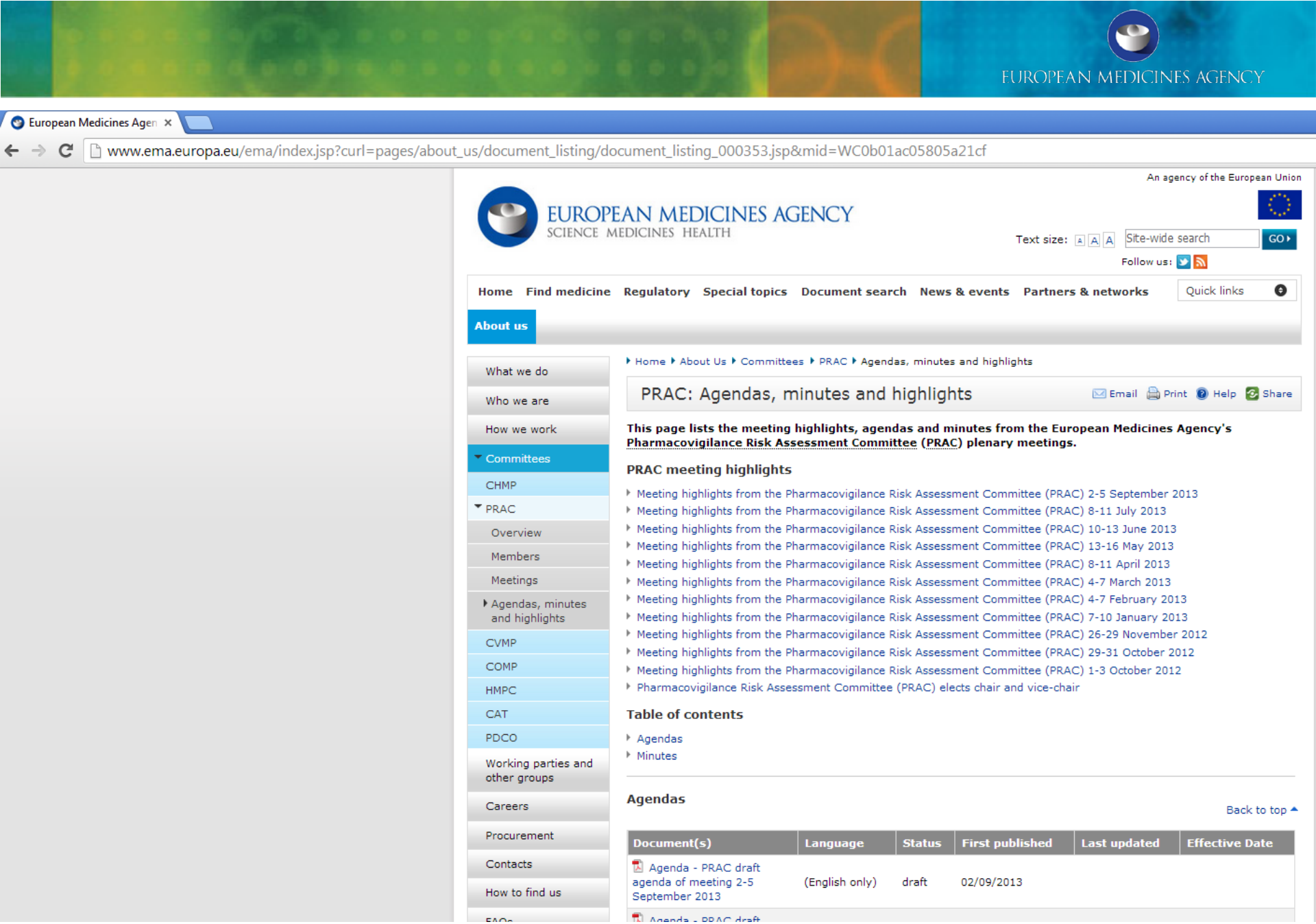
## Regulatory action to safeguard public health

| Scientific committees and decision-making: | 2012 | 2013 | |
|---|---|---|---|
| Establishment and running of new committee (PRAC) and new responsibilities for CMD(h) |  |  | - Established July 2012 |
| PRAC outputs: establish a strategy for supporting PRAC assessments and recommendations with best evidence, including aspects of effectiveness of risk minimisation/impact of regulatory action | |  | - Monthly meetings held with PRAC<br>- Strategy document to be finalised |

# PRAC volumes (July 2012 – July 2013)

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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.
PRAC meeting highlights
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 2-5 September 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 July 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 10-13 June 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 13-16 May 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 April 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 4-7 March 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 4-7 February 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 January 2013
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 26-29 November 2012
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 29-31 October 2012
Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 1-3 October 2012
Pharmacovigilance Risk Assessment Committee (PRAC) elects chair and vice-chair
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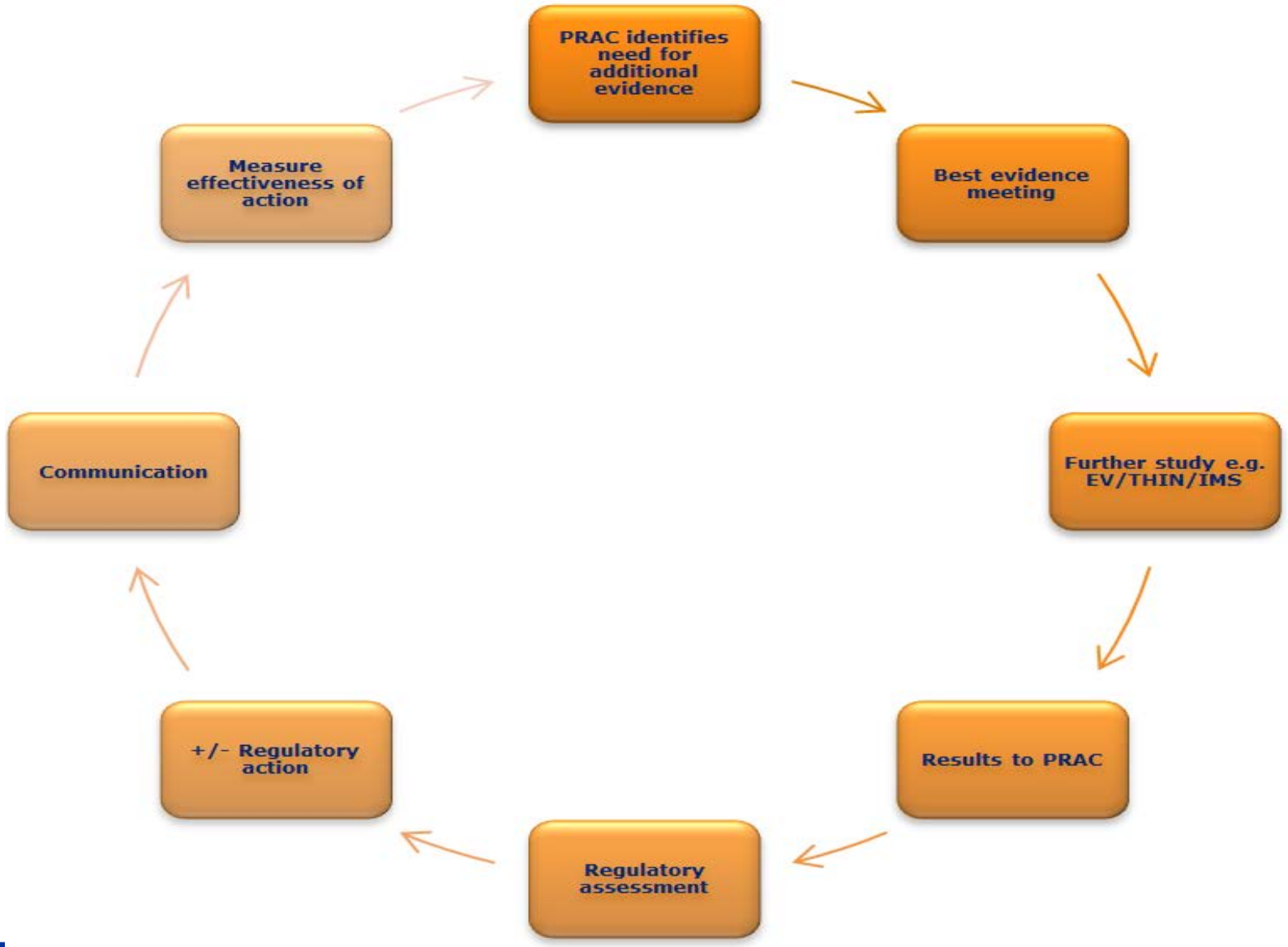
Document(s)
Language
Status
First published
Last updated
Effective Date
Agenda - PRAC draft agenda of meeting 2-5 September 2013
(English only)
draft
02/09/2013

# Evidence – decision cycle



# Prioritised implementation of the pharmacovigilance legislation

## Regulatory action to safeguard public health

| Strengthening referral procedures: | 2012 | 2013 | |
|---|---|---|---|
| Operation of new referral procedure (Urgent Union Procedure) | ■ | | - First referral launched in Oct 2012 |
| Redesign the 2012 implemented procedure and business process to include 2012 changes | | ■ | |

# Referrals: Data

- Number of referrals (July 2012 – July 2013[1]):

| Referral type | Started | Finalised |
|---|---|---|
| Art. 20 | 5 | 3 |
| Art. 107i | 5 | 3 |
| Art. 31 | 11 | 3 |
| **Total** | **21**[2] | **9**[3] |

[1] Also includes procedures started and finalised by PRAC in July 2013

[2] In 6 procedures (29%) an ad-hoc expert meeting has been organised

[3] Finalised means final outcome obtained at either CHMP or CMDh

# Referrals: Outcomes

- Overview of finalised referrals:

| Procedure name | Article | Finalised | Committee | Grounds | Outcome | EC Decision | Duration (calender days) |
|---|---|---|---|---|---|---|---|
| Tredaptive | 20 | Jan-13 | CHMP | B-R | Suspension | Yes | 1 month |
| Trevaclyn | 20 | Jan-13 | CHMP | B-R | Suspension | Yes | 1 month |
| Pelzont | 20 | Jan-13 | CHMP | B-R | Suspension | Yes | 1 month |
| Tetrazepam | 107i | Apr-13 | CMDh | S | Suspension | Yes | 3 months |
| Cyproterone, ethinylestradiol - DIANE 35 & other medicines containing cyproterone acetate 2mg and ethinylestradiol 35 micrograms | 107i | May-13 | CMDh | S | Variation | Yes | 3 months |
| Almitrine | 31PhV | May-13 | CMDh | B-R | Revocation | No | 7 months |
| Codeine-containing medicinal products | 31PhV | Jun-13 | CMDh | B-R | Variation | No | 8 months |
| Diclofenac-containing medicinal products | 31PhV | Jun-13 | CMDh | B-R | Variation | Yes | 8 months |
| Flupirtine | 107i | Jun-13 | CMDh | S | Variation | Yes | 6 months |

- Time taken: 1 to 8 months

# Referrals: Observations

- Positive experience:
  - High acceptance rate by CHMP/CMDh of PRAC outcome
  - Compliance with legal deadlines
  - Shortening of scientific review process for Art 31 procedures
  - Excellent teamwork EMA Secretariat – PRAC Rapporteurs (in terms of procedural, content and data support aspects)
- Issues requiring consideration:
  - Optimal use of referrals tools for public health
  - Workload for Network high and remains unpredictable
  - Communication and planning:

⇒ Need to continue to comply with existing communication platform (RAS-IRN involvement) to support the MSs

⇒ Better workload planning to be encouraged, identified safety concerns and public health consequences permitting

# On-going procedures to date

| Procedure name | INN | Article | Issue |
|---|---|---|---|
| Combined hormonal contraceptives | desogestrel, gestodene, norgestimate, etonogestrel, drospirenone, dienogest, chlormadinone, norgestimate, nomegestrol acetate/estradiol, norelgestromin/ethinylestradiol | 31 | risk of venous thromboembolism |
| Domperidone | domperidone | 31 | adverse heart effects, including QT prolongation and arrhythmias |
| Substances related to nicotinic acid (acipimox) | acipimox | 31 | Follow-up procedure to nicotinic acid and laropiprant, where study results showed a higher frequency of non-fatal but serious side effects and a failure to reduce the risk of major vascular events. |
| Kogenate Bayer/Helixate NexGen | octocog alfa | 20 | children given 2nd-generation full-length recombinant F-VIII products more likely to develop antibodies than those given 3rd-generation recombinant products whereas this increase was not seen with other recombinant or plasma-derived F-VIII products |
| Renin-angiotensin system (RAS)-acting agents | captopril, imidapril, zofenopril, candesartan, delapril, telmisartan, aliskiren, moexipril, enalapril, valsartan, fosinopril, irbesartan, perindopril, quinapril, ramipril, eprosartan, olmesartan, trandolapril, losartan, azilsartan, lisinopril, spirapril, benazepril, cilazapril | 31 | Concerns that the combination use of several RAS-acting agents could increase the risk of hyperkalaemia, low blood pressure and kidney failure. The benefits of combination use of RAS-acting agents in reducing overall mortality is questionned. |
| Protelos/Osseor | strontium ranelate | 20 | increased risk of serious heart problems, blood clots and rare serious skin reactions |
| Zolpidem-containing medicinal products | zolpidem | 31 | drowsiness and slower reactions the day after taking the medicine and potential increased risk of accidents during activities that require alertness |
| Hydroxyethyl starch (HES) - containing medicinal products | hydroxyethyl starch | 31 | increase risk of mortality and renal replacement treatment/failure: re-examination 31 |
| Hydroxyethyl starch (HES) - containing medicinal products | hydroxyethyl starch | 107i | increase risk of mortality and renal replacement treatment/failure: suspension UK |
| Bromocriptine-containing medicines | bromocriptine | 31 | rare but potentially serious or fatal cardiovascular, neurological and psychiatric side effects |
| Short-acting beta agonists (SABAs) | terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol, isoxsuprine | 31 | cardiovascular risk of the medicines when used as tocolytics compared with their benefit, particularly if used for a prolonged period (more than 48 hours). |
| Diacerin | diacerein | 31 | safety concerns (very frequent digestive disorders, some serious cases of liver disorders and skin reactions) and also evidence from clinical trials and the scientific literature suggesting that the effectiveness of diacerein in osteoarthritis was weak |

# Prioritised implementation of the pharmacovigilance legislation

## Regulatory action to safeguard public health

| Pharmacovigilance Inspections: | 2012 | 2013 | |
|---|---|---|---|
| Develop and implement a revised process for the coordination of pharmacovigilance inspections | |  | - SOPs under finalisation |

# Prioritised implementation of the pharmacovigilance legislation by the EMA

## Communication with stakeholders

| Online publishing of information: | 2012 | 2013 | |
|---|---|---|---|
| Publication (on EMA website) of agendas, minutes, assessments, approvals, recommendations, opinions and decisions of PRAC, CMD(h) and CHMP. |  |  | - Started July 2012 for PRAC agendas and minutes<br>Publish agendas and minutes of CHMP meetings (target end of 2013) |

# Transparency of activities for Pharmacovigilance Risk Assessment Committee

- **Agenda** is published on Day 1 of PRAC by mid-day
- **Meeting highlights** are published on Friday of PRAC week
- **Safety referrals** are published on Friday of PRAC week
- **Minutes** are published on the following month after adoption

# Prioritised implementation of the pharmacovigilance legislation by the EMA

## Communication with stakeholders

| Coordination of safety messages: | 2012 | 2013 | |
|---|---|---|---|
| Operation of the coordination of Member States' safety announcements for non-CAPs. |  |  | - Started July 2012 |

## Risk of hematologic second primary malignancies in patients treated with thalidomide

Dear Healthcare Professional:

Celgene Europe Limited would like to inform you of the following:

### Summary

- A statistically significant increase in the risk of hematologic second primary malignancies (acute myeloid leukaemia and myelodysplastic syndromes) has been observed in an ongoing study in patients with previously untreated multiple myeloma receiving melphalan, prednisone, and thalidomide, compared with patients treated with lenalidomide plus dexamethasone.
- The risk of hematologic second primary malignancies with thalidomide increased over time, to approximately 2% after 2 years and 4% after 3 years.
- Before starting thalidomide treatment in combination with melphalan and prednisone, take into account both the benefit achieved with thalidomide and the risk of acute myeloid leukaemia and myelodysplastic syndromes.
- Carefully evaluate patients before and during treatment using standard cancer screening and provide appropriate treatment.

This information is being sent in agreement with the [insert name of national competent authority here] and the European Medicines Agency.

#### Further information on the safety concern and the recommendations

Thalidomide (Celgene) is licensed in the European Union for use in combination with melphalan and prednisone as first-line treatment of patients with untreated multiple myeloma who are aged ≥65 years or ineligible for high-dose chemotherapy.

## Vistide (Cidofovir) 75 mg/ml concentrate for solution for infusion (EU/1/97/037/001)

**Direct Healthcare Professional Communication regarding a product recall leading to a shortage in commercial supply in the EU**

Dear Healthcare Professional,

Gilead Sciences International Limited would like to inform you of the following:

### Summary

- Gilead has initiated a voluntary recall of Vistide lot B120217D at the wholesaler and hospital pharmacy levels due to presence of visible particulate matter. In the European Union, this particular batch was distributed in Germany, Austria, Italy and Spain. The recall was a precautionary measure and it is not based on any reported adverse medical events.
- Gilead is conducting a review of the supply of Vistide following the product recall. At the present time, there are no available lots of Vistide in the supply chain to replace the affected lot.
- Gilead recommends that healthcare professionals consider alternative treatment options until this is resolved.
- Gilead takes the opportunity to remind healthcare professionals that Vistide is only approved for the treatment of CMV retinitis in adults with acquired immunodeficiency syndrome (AIDS) without renal dysfunction.

This information is being sent in agreement with the national competent authority and the European Medicines Agency.

#### Further information on the safety concern and the recommendations

During routine packaging operations, floating particles were observed in one Vistide lot (B120217D). An investigation has been initiated to identify the particles and determine the extent of the problem across the batch affected.

# Prioritised implementation of the pharmacovigilance legislation by the EMA

## Communication with stakeholders

| Public hearings: | 2012 | 2013 | |
|---|---|---|---|
| Develop concept of public hearings (incl. criteria and methodologies) |  |  | - Public consultation foreseen end of 2013 |
| Introduction of public hearings in the context of Urgent Union Procedure |  |  | - Unlikely in 2013. |

# Prioritised implementation of the pharmacovigilance legislation by the EMA

## Communication with stakeholders

| Risk Management Plans summaries: | 2012 | 2013 | |
|---|---|---|---|
| Agree modalities to publish summary information for RMPs | |  | |

# Publication of RMP summaries

Pilot phase to be initiated in October 2013.

- Summary (Part VI.2 of RMP) to be published at the time of the EPAR publication.
- Summary to be updated in case of important changes to RMP.
- Summary is aligned with other information (EPAR summary, product information).
- For **all** newly - authorised CAPs;
- For other (not newly authorised) CAPs, RMP summary to be published when RMP is updated.

# Prioritised implementation of the pharmacovigilance legislation by the EMA

## Communication with stakeholders

| European Medicines web-portal: | 2012 | 2013 | |
|---|---|---|---|
| Initiate research and design work | |  | |

**Legal notice: EMA website serves as the EU Medicines Web-portal**

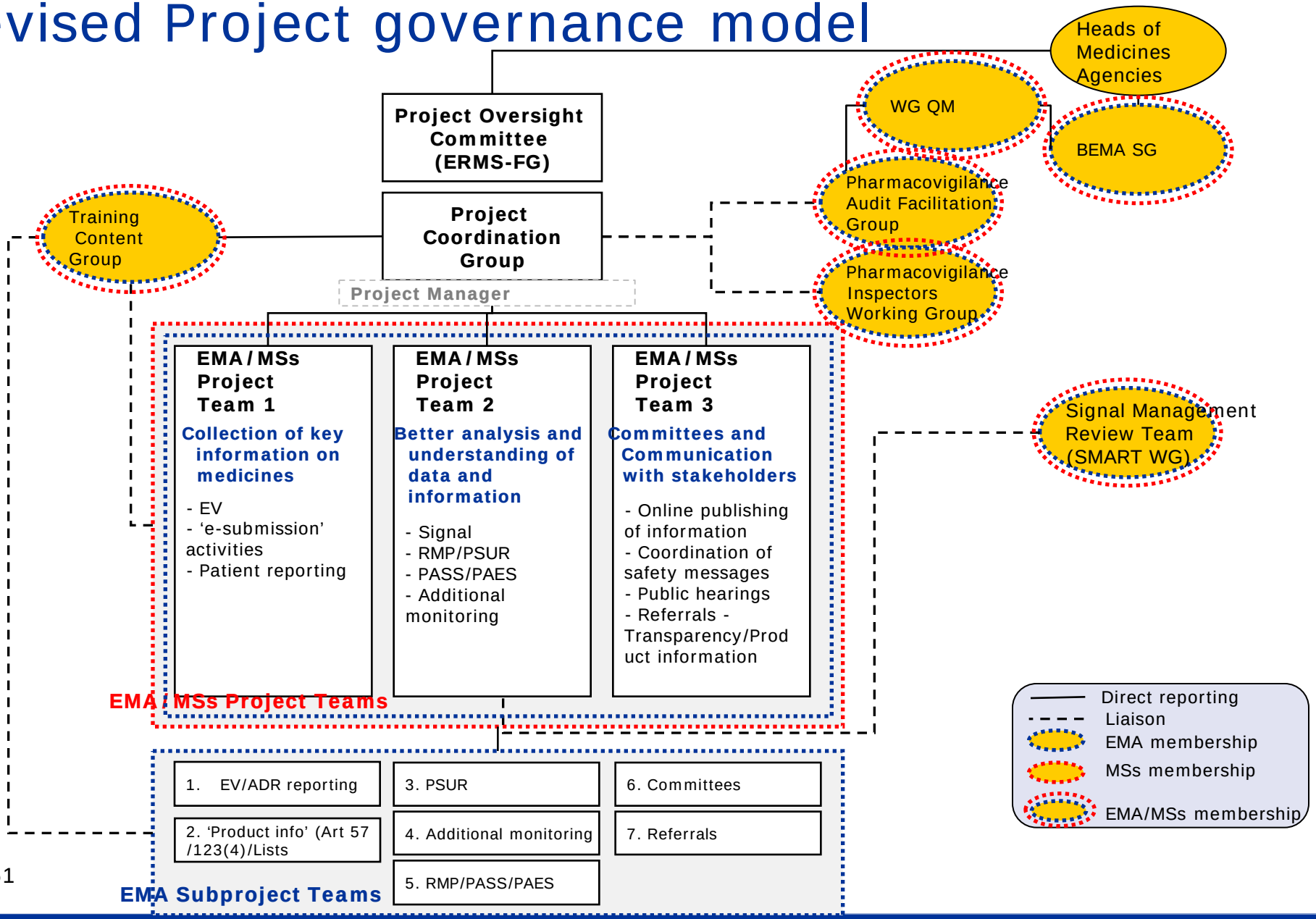
# Beyond 2013…what still needs to be done

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

# Beyond 2013…what still needs to be done

**We will get there…..working together**

# Revised Project governance model



# What have we achieved

A huge change has been delivered for better public health improvement:

- Better public participation
  - increase of patient reports by 10,000
  - Patients and HCPs voting on PRAC
- Better planning – risk management plans now routine
- Better evidence – routine identification of data needs for referrals
- Faster decision-making
  - Referrals finalised in 1 to 8 months
  - PSURs directly lead to label changes
- Greater transparency – agendas, minutes, signals
- Better information – black triangle, ADR reporting, warnings

# But there is still more to do

Deliver on the simplifications:

- Further improve on the processes already implemented
- Centralised ADR reporting
- Centralised PSUR reporting
- Literature monitoring by EMA for industry

Full delivery on better information:

- EU medicines webportal

**Together we can**

# Conclusions

Major change has been delivered:

- Collaboration
- Consultation
- Concentration

Public health has been improved:

- Better evidence
- Faster decisions and labelling
- Greater transparency
- Greater participation and empowerment