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SCIENCE MEDICINES HEALTH

Two years of Operation of the Pharmacovigilance Risk Assessment Committee

June M Raine
Chair, PRAC

8th Stakeholders' Forum
15 September 2014

Scope of presentation

- What has PRAC delivered via new public health tools in first two years of operation?
- What have been some of the challenges and opportunities?
- What is PRAC's current focus, moving from compliance with Pharmacovigilance legislation to optimal use?

Reminder - Mandate of Pharmacovigilance Risk Assessment Committee

All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit

What has PRAC delivered in first 2 years using new public health protection tools?

nature REVIEWS DRUG DISCOVERY

nature.com ▸ journal home ▸ current issue ▸ correspondence ▸ full text

NATURE REVIEWS DRUG DISCOVERY | CORRESPONDENCE

Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee

Peter Arlett, Geraldine Portier, Roberto de Lisa, Kevin Blake, Noel Wathion, Jean-Michel Dogne, Almath Spooner, June Raine & Guido Rasi

22 meetings

Over 600 risk management plans

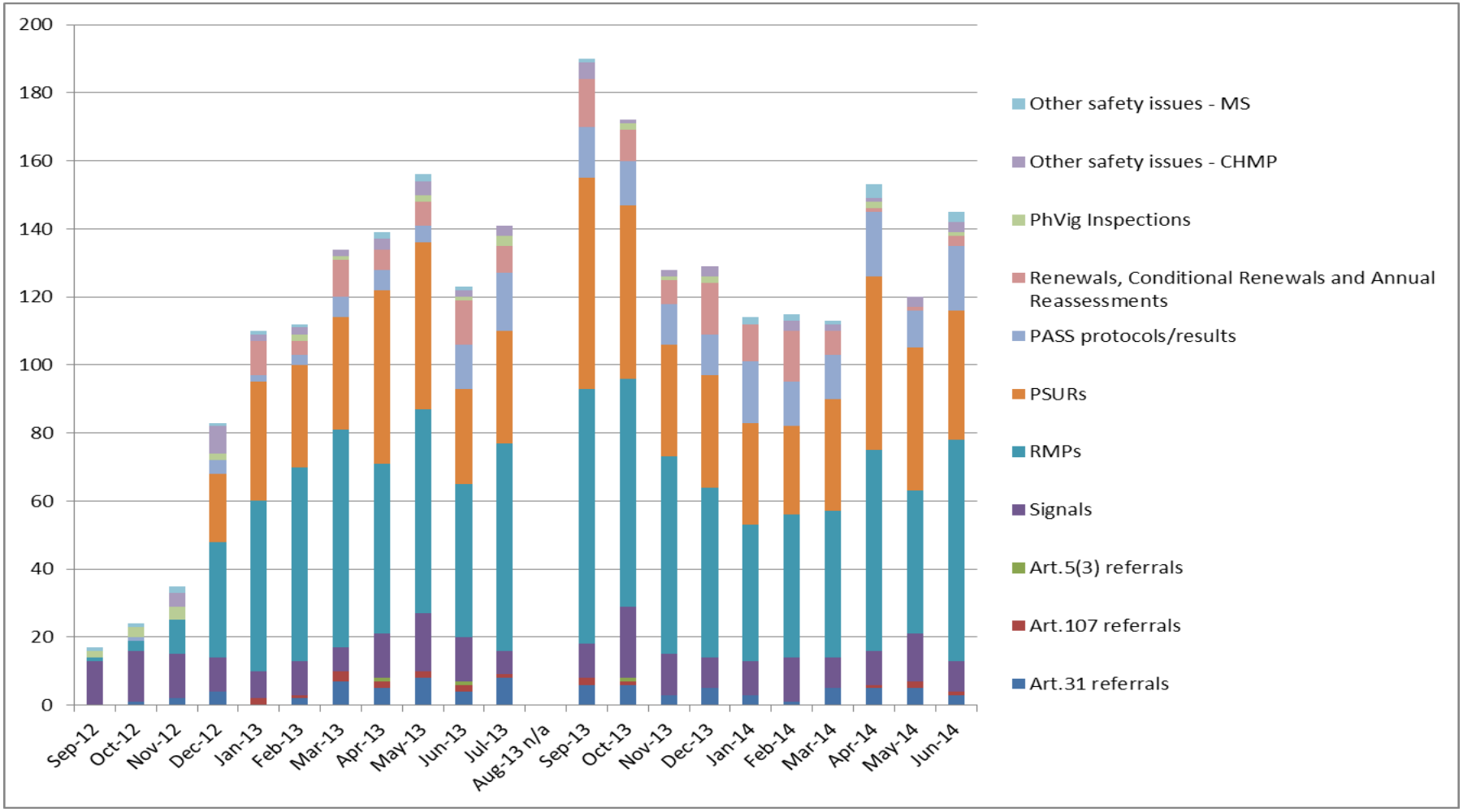
150 protocol reviews

31 safety referrals

Over 650 PSURs

163 signals

PRAC monthly activities



First 2 years - 4 main objectives

- Proactively investigating drug safety using risk management plans, post-authorisation studies and continuous signal detection
- Responding to safety and benefit risk issues with robust scientific decisions to rigorous timescales
- Driving forward the new era in transparency, real time access to information on PRAC activities
- Increasing involvement of stakeholders in decision-making – health professionals, patients and public

Proactive investigation of drug safety

- From reactive vigilance to proactive inverstigation of drug safety
- To fill in gaps in knowledge, Risk Management Plans and PASS protocols PRAC's major priority
- PRAC experts in pharmacoepidemiology provide specialist contributions on design and methodology
- Innovative approaches to generate safety in clinical use

Example: RMP on new ICS/LABA for Chronic Obstructive Pulmonary Disease

Salford Lung Study

Please note:

The Salford Lung Study is only available to patients who are residents of the City of Salford in the UK.

REGISTER TODAY!

Speak to your GP or practice nurse

Call 0161 246 9884

Text 'Study' to 81066

(Texts will be charged at your standard message rate)

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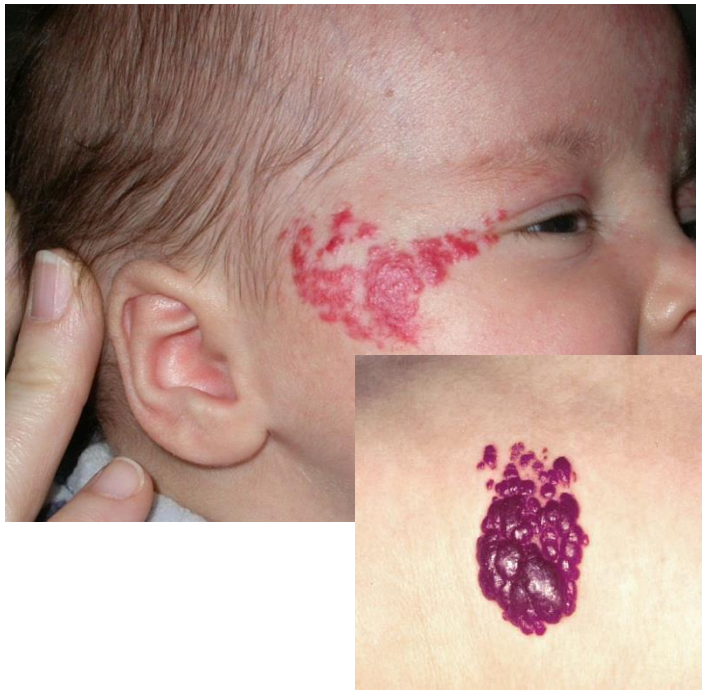
The Salford Lung Study.

Researching treatment of chronic obstructive pulmonary disease in Salford.

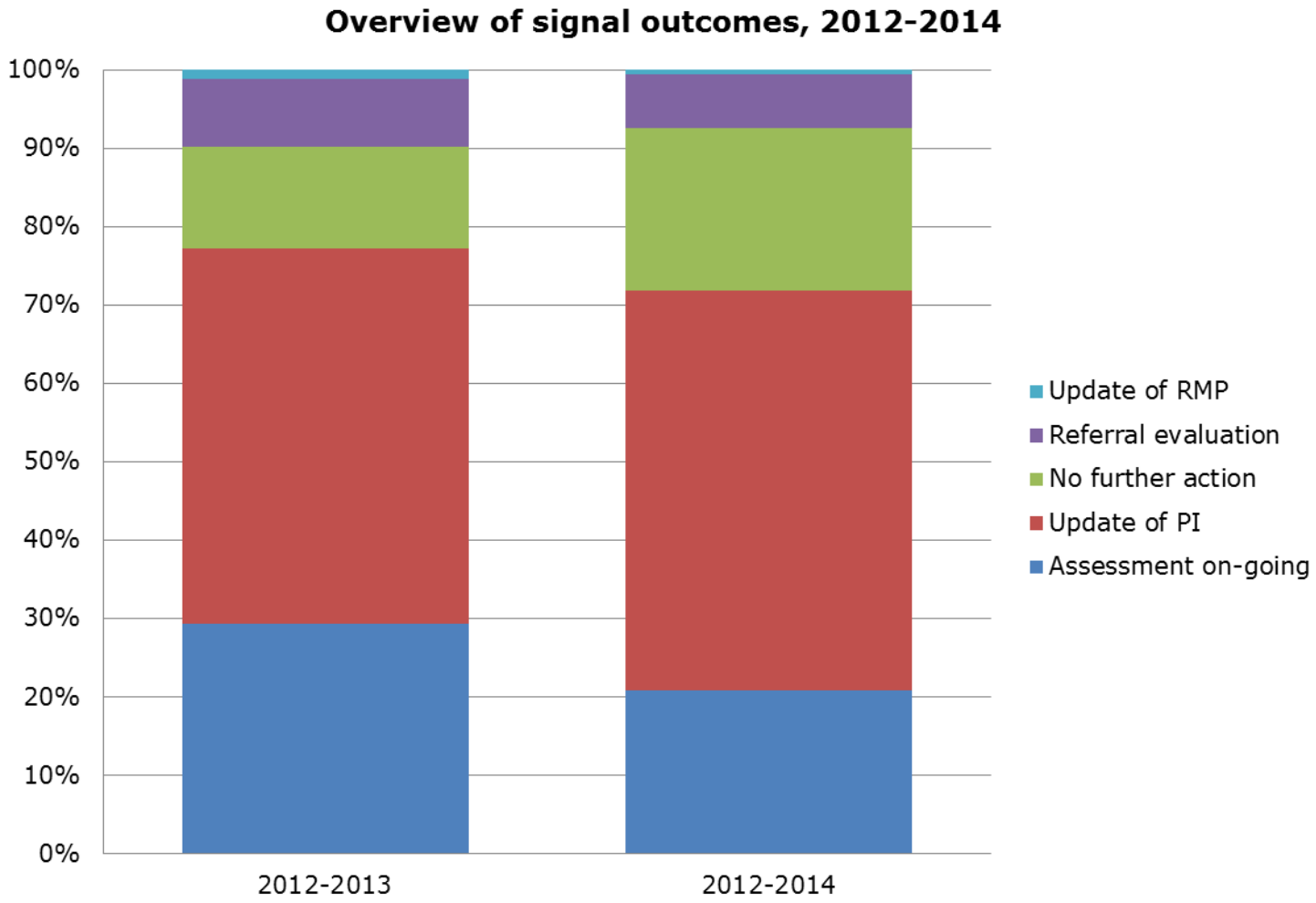
Find out if the COPD study is right for you →

Example: Propranolol for haemangioma

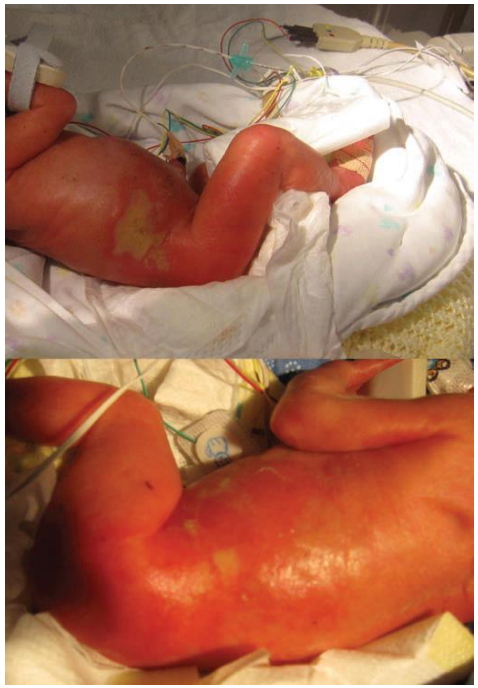


- Example – Haemangiol (propranolol 3.75 mg/ml) for treatment of proliferating infantile haemangioma
- PRAC advised on RMP and considered recruitment into PASS study

Proactive safety monitoring - signals



Example – chlorhexidine solution and chemical burns in neonate



Images in neonatal medicine

Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant

Arch Dis Child Fetal Neonatal Ed: F64 January 2012

Example–fentanyl patch & medication error

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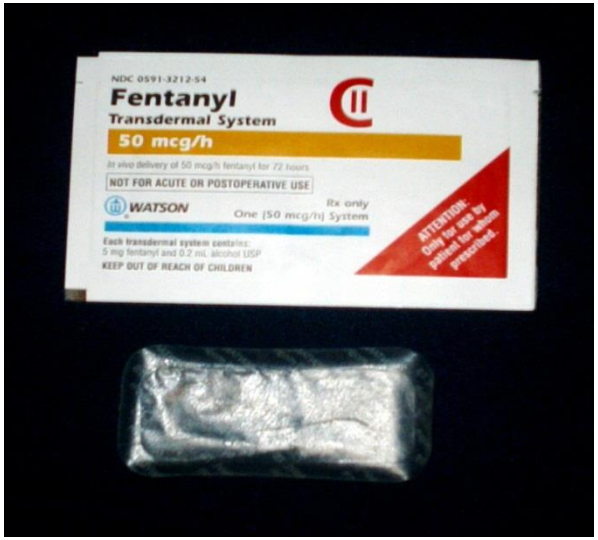
Consumer Updates

Fentanyl Patch Can Be Deadly to Children



Proactive monitoring - signal detection

Major PRAC focus on signal detection – SMART (Signal Management Review Team):

- Tools and processes
- Methodological guidance
- Signal detection methods

Implementing Regulation 520/2012 "the Pharmacovigilance Risk Assessment Committee shall regularly review the methodology(ies) used and publish recommendations, as appropriate" [Art 20(3)]

Prompt benefit risk recommendations

- Binding outcomes from referrals
- Rigorous adherence to legal timeframes
- PSURs as benefit risk decision-making tool

Referrals: safety or benefit risk reviews

Number of referrals (July 2012 – July 2014[1]):

Referral type	Started	Finalised
Art. 20	7	5
Art. 107i	6	6
Art. 31	18	11
Total	**31**	**22**[2]

[1] Also includes procedures started & finalised in July 2014

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

Completed referrals

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Article 20

- Tredaptive
- Trevaclyn
- Pelzont
- Kogenate/ Helixate
- Protelos/ Osseor

Article 31

- Almitrine
- Codeine
- Diclofenac
- HES
- SABAs
- CHCs
- Nicotinic acid
- Diacerein
- Zolpidem
- Domperidone
- RAS agents
- Bromocriptine

Article 107i

- Tetrazepam
- Cyproterone EE
- Flupirtine
- Numeta
- HES
- Methadone

Ongoing referral procedures

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Procedure name	Article	Started	Issue
Valproate related substances	31PhV	Oct-13	neurodevelopmental effects following exposure in utero
Ponatinib	20PhV	Dec-13	vascular occlusive events
Testosterone	31PhV	Apr-14	cardiovascular events
Codeine for cough in paediatric population	31PhV	Apr-14	respiratory depression
Ambroxol/Bromhexine	31PhV	Apr-14	hypersensitivity reactions in children
Hydroxyzine	31PhV	May-14	pro-arrhythmogenic potential
Ivabradine	20PhV	May-14	CV death + non-fatal MI in symptomatic angina patients
Ibuprofen and dexibuprofen	31PhV	Jun-14	thrombotic risk potential as of COX-2 inhibitors and of low-dose aspirin

Outcomes of safety & benefit risk referrals

- Range of actions proportionate to risk, taking into account therapeutic context (variation, suspension, revocation)
- Prompt decisions- from 1 to 16 months (average 7 months)
- One fifth were Urgent Union procedures (3 months)
- Involvement of Scientific Advisory Group in 8 procedures (26%)

PRAC's challenges and opportunities

- Best scientific evidence
- Established medicines and EU diversity
- Involving stakeholders in decisions
- Extended definition of adverse drug reaction
- Interface with academia
- SAGs advice on therapeutic role
- Meeting with patient groups
- Medication error, misuse

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Example: Diclofenac & CVS risk

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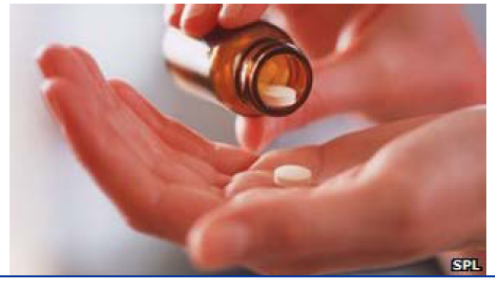
Common painkillers 'pose heart risk'

By James Gallagher
Health and science reporter, BBC News

Two common painkillers, ibuprofen and diclofenac, can slightly increase the risk of heart problems if taken in high doses for a long time, data suggests.



People with severe arthritis often take the drugs, which also calm inflammation, to go about daily life.

The researchers said some patients would deem the risk acceptable, but they should b

A study, **published in the Lancet**, shov greater risks for smokers and the overweigh

The risks have been reported before, but a University of Oxford analysed the issue in u to help patients make an informed choice.

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2014
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3594

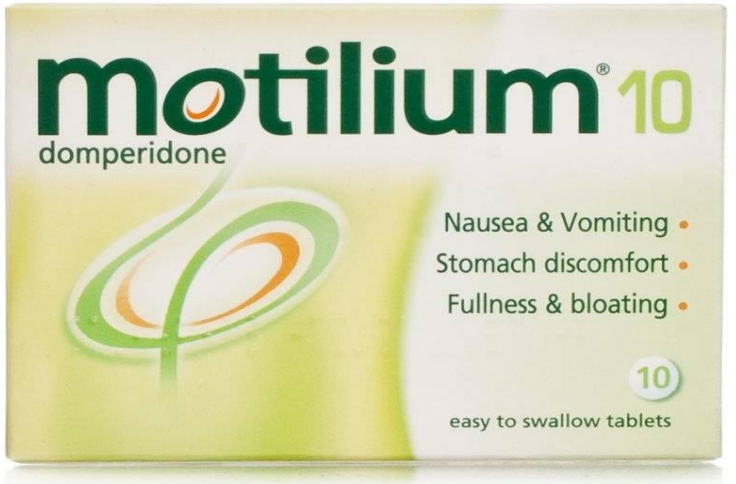
COMMENTARY

The European Medicines Agency's use of prioritised independent research for best evidence in regulatory action on diclofenac†

Peter Arlett[1]*, Sinan B. Sarac[2], Andrew Thomson[3], Claire Davies[3], Tania Teixeira[1], Kevin V. Blake[1] and Doris Stenver[2]

Example -Domperidone and CVS risk

- Cardiac safety reviewed by PRAC after data accrued
- Large pharmepi study confirmed increased risk of sudden cardiac death in over 60s
- Restriction of indication to nausea and vomiting, dose restriction and duration limit
- Data on efficacy in children to be generated



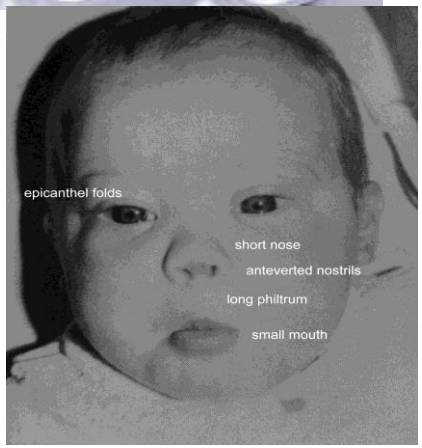
Example - Sodium valproate in pregnancy

Indications in EU include epilepsy, bipolar disorder & migraine

Use in women of child bearing potential varies across Europe

Nature and magnitude of developmental risk needs to be better understood

Patient representatives contributing to decision



Example – methadone containing povidone and renal failure

- PVP oral solution to minimise injection risk
- Reports of renal failure from Norway
- Local pathologists found povidone deposits in specimens
- Suspension of high MW products

European Monitoring Centre for Drugs and Drug Addiction

Periodic Safety Update Reports

- Major tool for updating benefit risk
  - Strontium ranelate
  - Ferumoxytol colloidal iron
  - Agomelatine
- Evolving experience with single PSUR assessment

Advancing the new era of transparency

Establishing the Pharmacovigilance Risk Assessment Committee – **Major advances in transparency for EU pharmacovigilance activities**

Authors
Almath Spooner, Irish Medicines Board (IMB) and Pharmacovigilance Risk Assessment Committee (PRAC); Roberto De Lisa, European Medicines Agency, London, UK; Monika Benstetter, European Medicines Agency, London, UK; Juan García Burgos, European Medicines Agency, London, UK; June Raine, Medicines and Healthcare products Regulatory Agency (MHRA) and Pharmacovigilance Risk Assessment Committee, London, UK.

Keywords
Pharmacovigilance Risk Assessment Committee (PRAC); Transparency; Agendas; Minutes; Signals; Referrals; Periodic safety update report (PSUR) assessments.

and transparency is recognition of the importance of establishing and maintaining trust in the regulatory system. Transparency has been considered a prerequisite for further stakeholder engagement.

Agendas and minutes

The publication of agendas and minutes provides visibility of PRAC activity to all stakeholders, whose efforts collectively contribute to the risk management process. While the agendas and minutes are primarily intended to support the operation of the committee's processes, the importance of providing content accessible to a wider audience has been recognised. The drafting style has taken into account the need for procedural background information, the scientific rationale behind the advice and clarity on committee recommendations. While once considered novel, the publication of PRAC agendas and minutes is now routine, with the publication of agendas during PRAC week and minutes following one month later. Meeting highlights provide the

PRAC's high transparency
- Regular timely publications on activities

Agenda	Day 1 of PRAC by mid-day
Highlights	Friday of PRAC week
Safety referrals	Friday of PRAC week
Minutes	Following month after adoption

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 September 2014

News

12/09/2014

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 September 2014

PRAC concludes review of Valdoxan/Thymanax (agomelatine)

The Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its regular benefit-risk assessment (known as a periodic safety update report or PSUR) of Valdoxan/Thymanax (agomelatine), two identical medicines used to treat major depression in adults.

As part of this assessment, the PRAC looked at cumulative data on severe side effects on the liver with Valdoxan/Thymanax and recommended further measures to

Related information

- Valdoxan: EPAR
- Thymanax: EPAR
- PRAC recommendations on safety signals
- Periodic safety update reports
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Pharmacovigilance Risk Assessment Committee (PRAC): 8-11 September 2014
- European Medicines Agency launches public consultation on

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22 November 2013
EMA/709120/2013

Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation

Product information to be updated to help women make informed decisions about their choice of contraception

Example – combined hormonal contraceptives and thromboembolism

Deadly risk of pill used by 1m women: Every GP in Britain told to warn about threat from popular contraceptive

- Bestselling brands of birth control tablets linked to fatal blood clots
- They are believed to double the risk compared to older varieties
- 'Third-generation' contraceptives caused 14 deaths a year in France
- UK doctors have been ordered to alert women to the alarming dangers

NHS choices Your health, your choices

Health A-Z | Live Well | Care and support | Health

Media hype blood clot risk of birth control pills

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Monday February 3 2014

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"Deadly risk of pill used by 1m women: Every GP in Britain told to warn about threat from popular contraceptive," reports the Mail Online.

Combined hormonal contraceptives (or "the pill") are in the news after letters were sent to doctors to tell them about the latest evidence on the risk of thromboembolism (blood clots) associated with combined

Contraceptive pills are both safe and effective

© PA Archive/Press Association Images

What is PRAC's current focus?

- Managing **high workload** - focus on participation, efficiency, establishing single PSUR procedure, generic RMPs

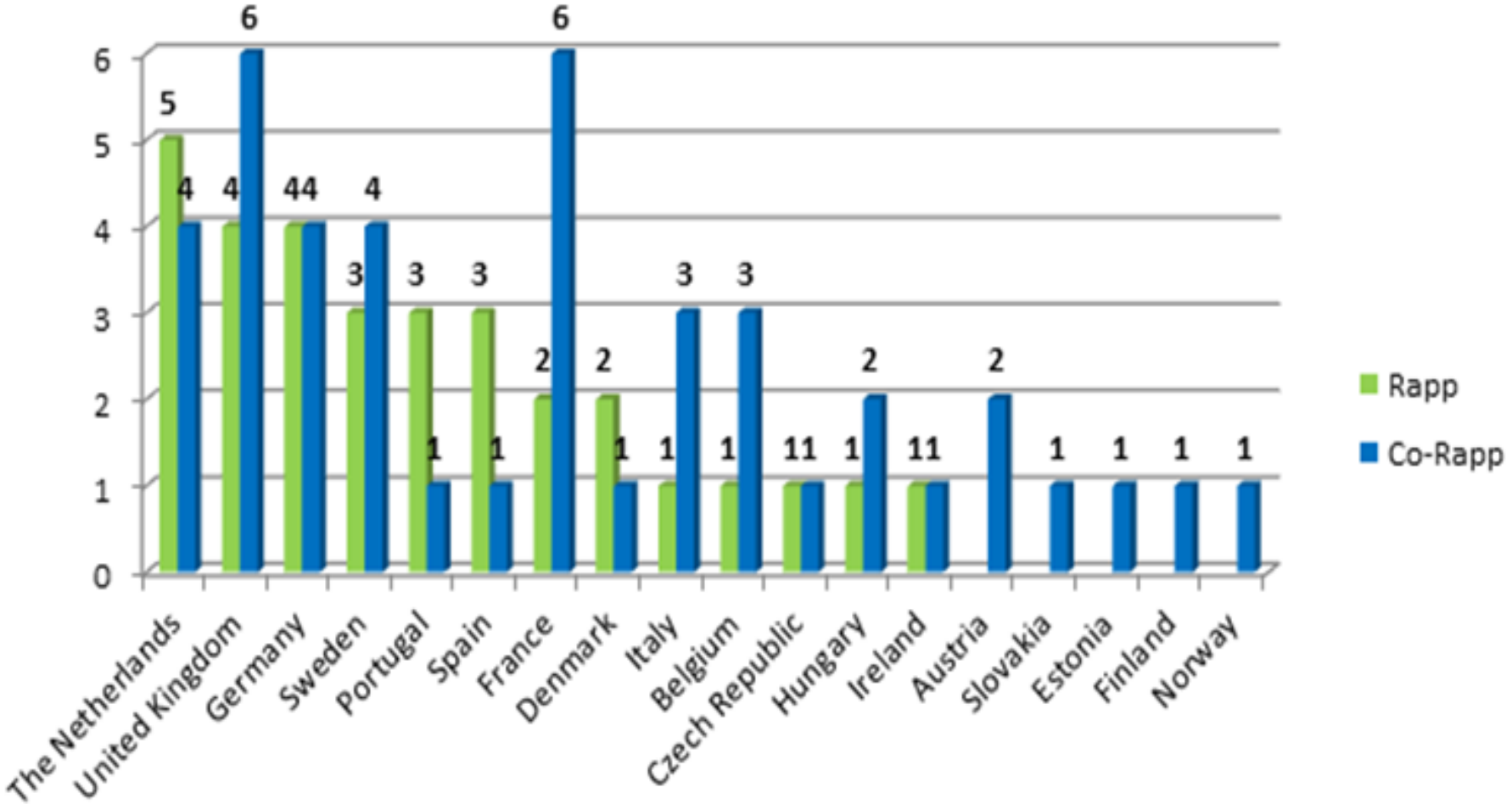
- Building **effective committee interfaces** with CHMP, CMDh, PDCO, CAT, COMP and SAWP

- **Strengthening science for PRAC decisions**– GVP on biologics, lifecycle B:R, effectiveness of risk minimisation, post authorisation efficacy studies, medication error

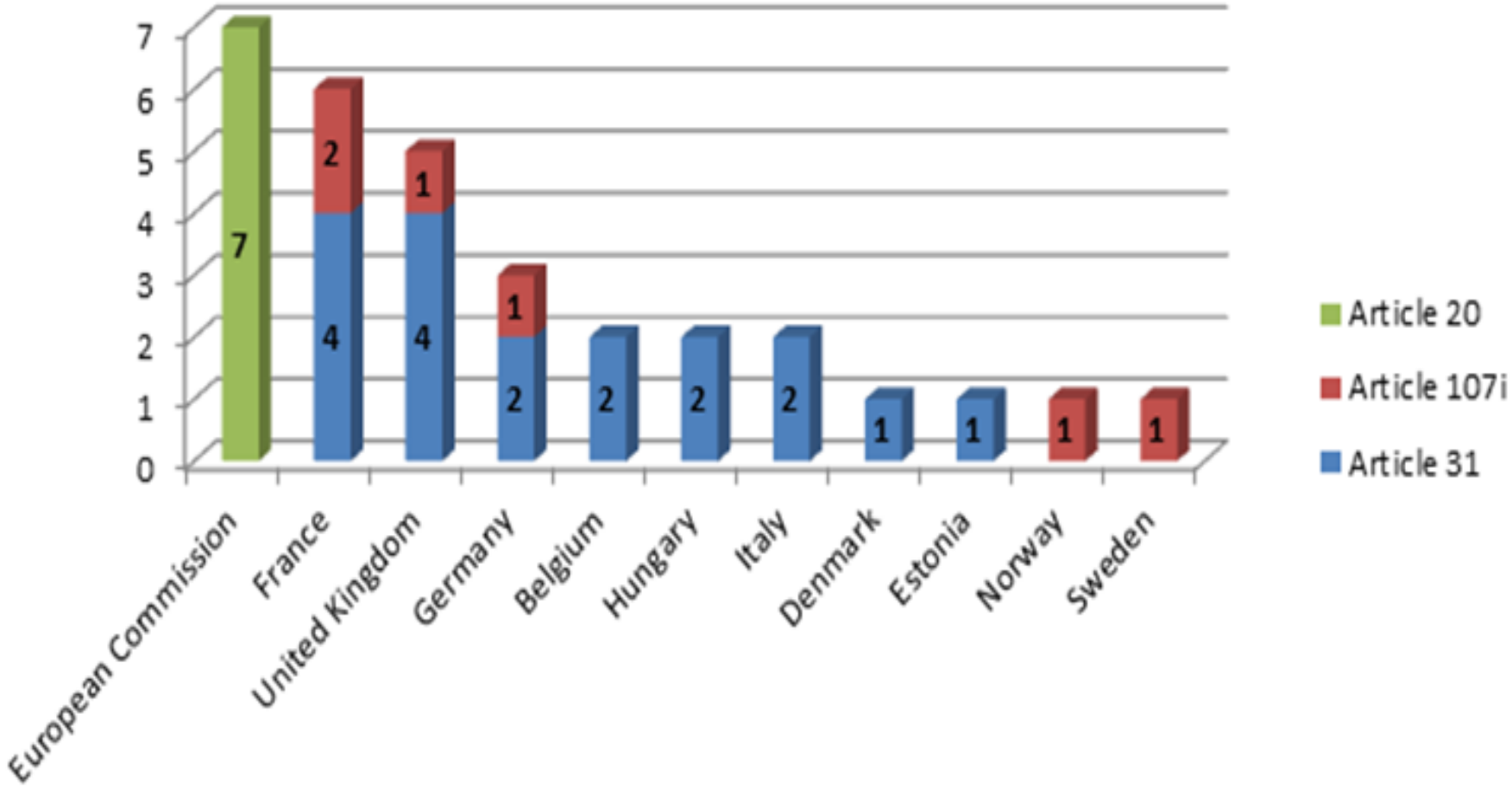
- **Building stakeholder engagement** – expanding monthly communications, public hearings to come

(Co) Rapporteurship per Member State

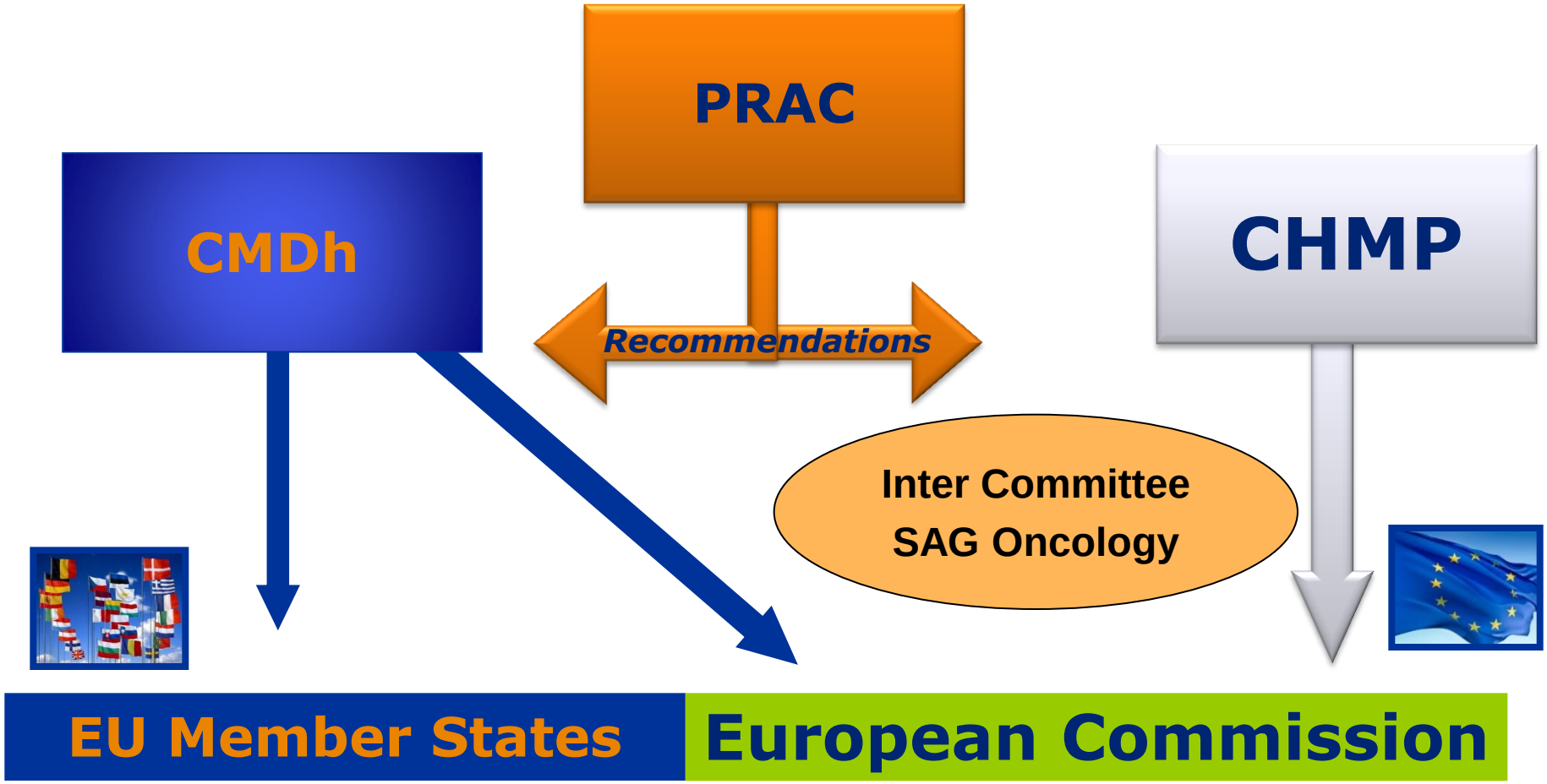
*2 procedures have multiple co-rapporteurs (SABA-HU, BE, CS, IT; RAS - UK, IT, SV, DE, NL, PT, SK, IE, ES)



Referral procedures started at PRAC by trigerring party per article



Building inter committee collaboration



Collaborating with Paediatric Committee

Report of PDCO / PRAC Workshop published on 18th August 2014

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SCIENCE MEDICINES HEALTH

18 August 2014
EMA/288486/2014
Human Medicines Research & Development Support Division

Report on the EMA workshop of pharmacovigilance in the paediatric population

28 April 2014

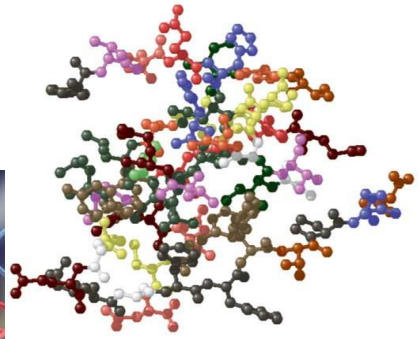
Introduction

On 28 April 2014, the European Medicines Agency (EMA) convened a first one day workshop on the needs and priorities for pharmacovigilance in the paediatric population.

The objectives of the workshop were to outline the current work performed at the EMA with regards to paediatric safety, and to discuss the potential for improvement in terms of active paediatric pharmacovigilance, and proactive planning with regards to surveying medicines when they come to the Marketing Authorisation phase.

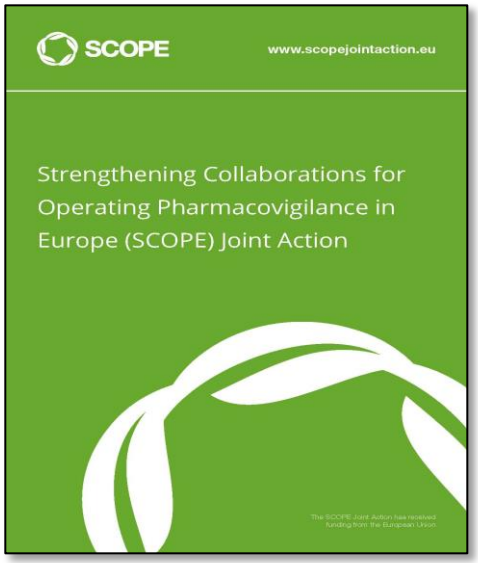
Contributing to Guideline development

- Revision of paediatric pharmacovigilance guideline
- GVP Population Modules
  - Pharmacovigilance in elderly
- GVP Product modules
  - Biologic medicines
- Pharmacogenetics and pharmacovigilance



Incorporating new methodologies & building on the best practices

PROTECT



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Did you know?

You can report side effects yourself

As a patient, you have the right to report unwanted side effects of medicines directly to the authorities. You can also report a side effect on behalf of someone in your care, such as a child or relative.

Remember to speak to your doctor or pharmacist if you are worried about any suspected side effects.

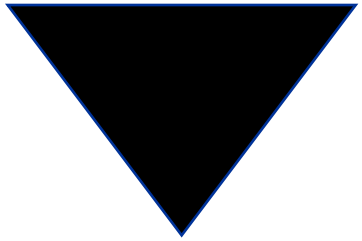
Why report a side effect?

We are always learning more about medicines.

Although they are tested extensively in clinical trials before they are authorised, not everything can be known about their side

How do I report a side effect?

If you think a medicine has caused a side effect, please check the package leaflet that comes with the medicine for information on how to report it.



¿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.

A Road Map for PRAC

- Generating best evidence, and using all data available – pharmacoepidemiology, pharmacogenomics
- Optimal use of new methodologies and tools – PAES, quantifying benefit risk, data integration
- Building capacity, sustainability - SCOPE
- Stakeholder engagement in benefit risk, and in implementation of risk minimisation
- Evaluating impact of new legislation - process indicators and public health outcome measures

Summary

- Establishment of PRAC is central to implementation of EU Pharmacovigilance legislation
- Over the first two years delivering the public health objectives has been the PRAC's key focus
- Experience demonstrates capability for robust scientific decision making to rigorous timescales
- Major strides forward in transparency and stakeholder involvement
- Now we are moving from compliance to optimisation

We are ready!