EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRAC's perspective on implementation: strengthening public health protection

June M Raine
Chair, PRAC

7th Stakeholders' Forum
27 September 2013

Scope of presentation

- Establishing PRAC as public health focussed
- Using the new public health protection tools –PRAC's perspective on implementation
- Looking ahead – what is still to come

L 348/74 EN Official Journal of the European Union 31.12.2010

DIRECTIVES

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 December 2010

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

(2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

The EU public health challenge

5% of all hospital admissions due to ADRs

5% of all hospital patients experience an ADR

ADRs 5th most common cause of hospital death

197,000 deaths per year in EU caused by ADRs

Total societal cost €79 billion

5910 lives per year and €237m could be saved

Pharmacovigilance legislative aims

1. **Clarity** on roles and responsibilities

2. **Proactive** & proportionate safety monitoring

3. **Robust and timely** decision-making leading to consistent action on safety issues

4. **Greater inclusiveness** for patients, healthcare professionals

5. **High levels** of **transparency**

6. **Best use of resources** – avoid duplication

EUROPEAN MEDICINES AGENCY

Establishing the Pharmacovigilance Risk Assessment Committee

Inaugural meeting

Brussels July 19-20th 2012

Membership of PRAC

Appointed by each Member State:

1 member + alternate

28 + EEA countries non voting members

Appointed by European Commission:

6 members - relevant expertise including clinical pharmacology and pharmacoepidemiology

1 member / alternate representing patient organisations

1 member / alternate representing healthcare professionals

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.

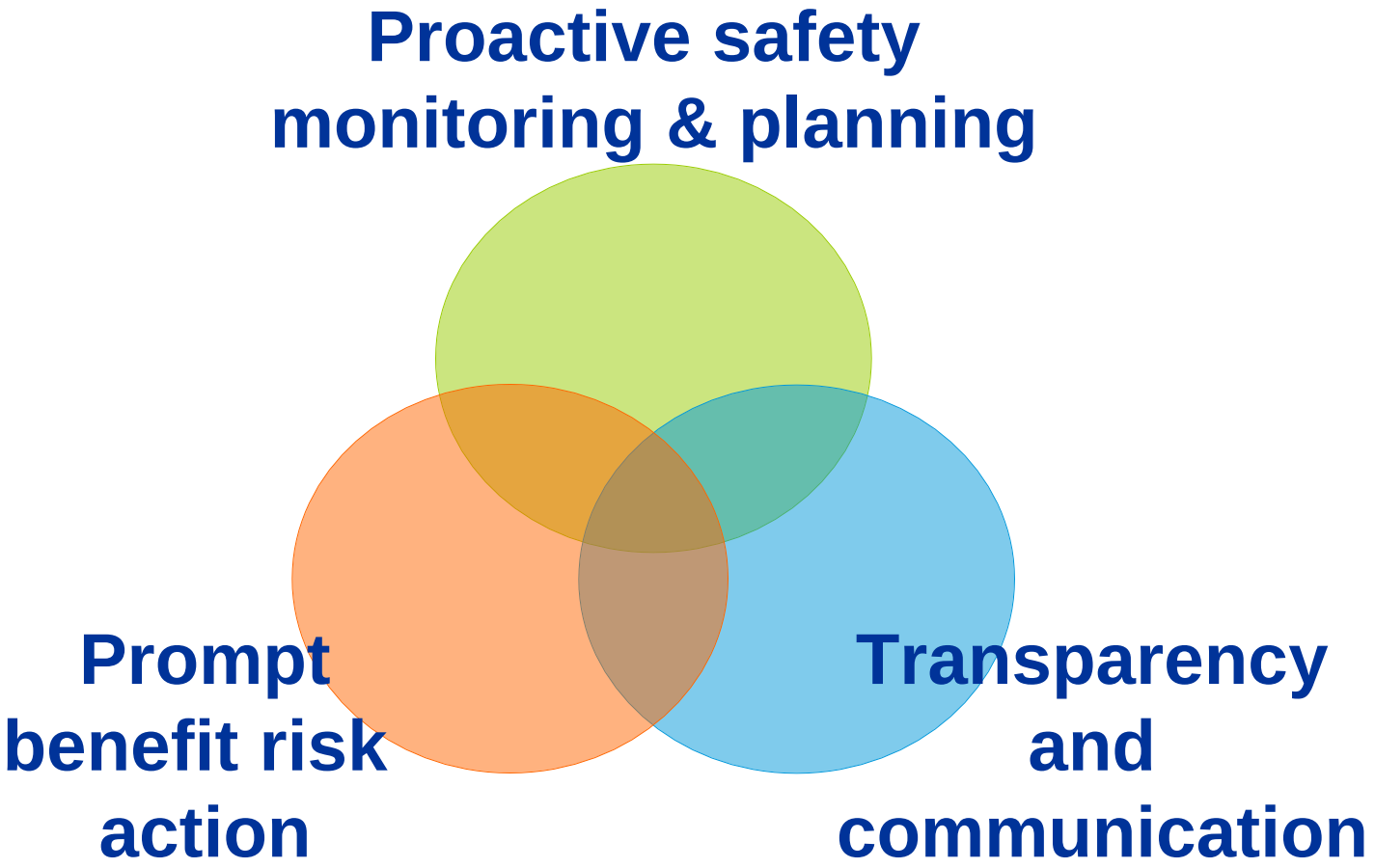
Done at Brussels, 28 February 2013.

Mandate of the 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

Using new public health protection tools - PRAC's perspective on implementation

PRAC's three public health pillars



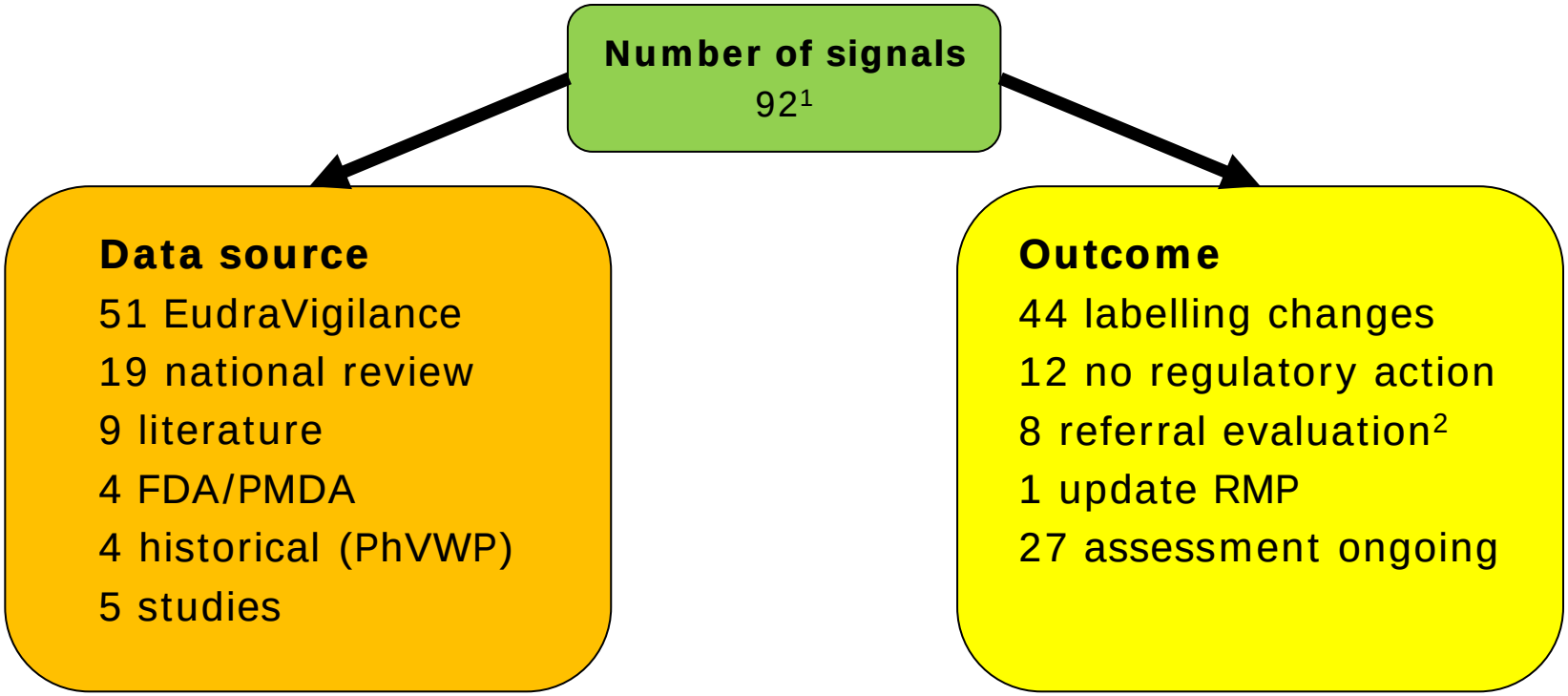
Proactive & planned pharmacovigilance

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

- Tools and processes
- Methodological guidance
- Signal detection methods

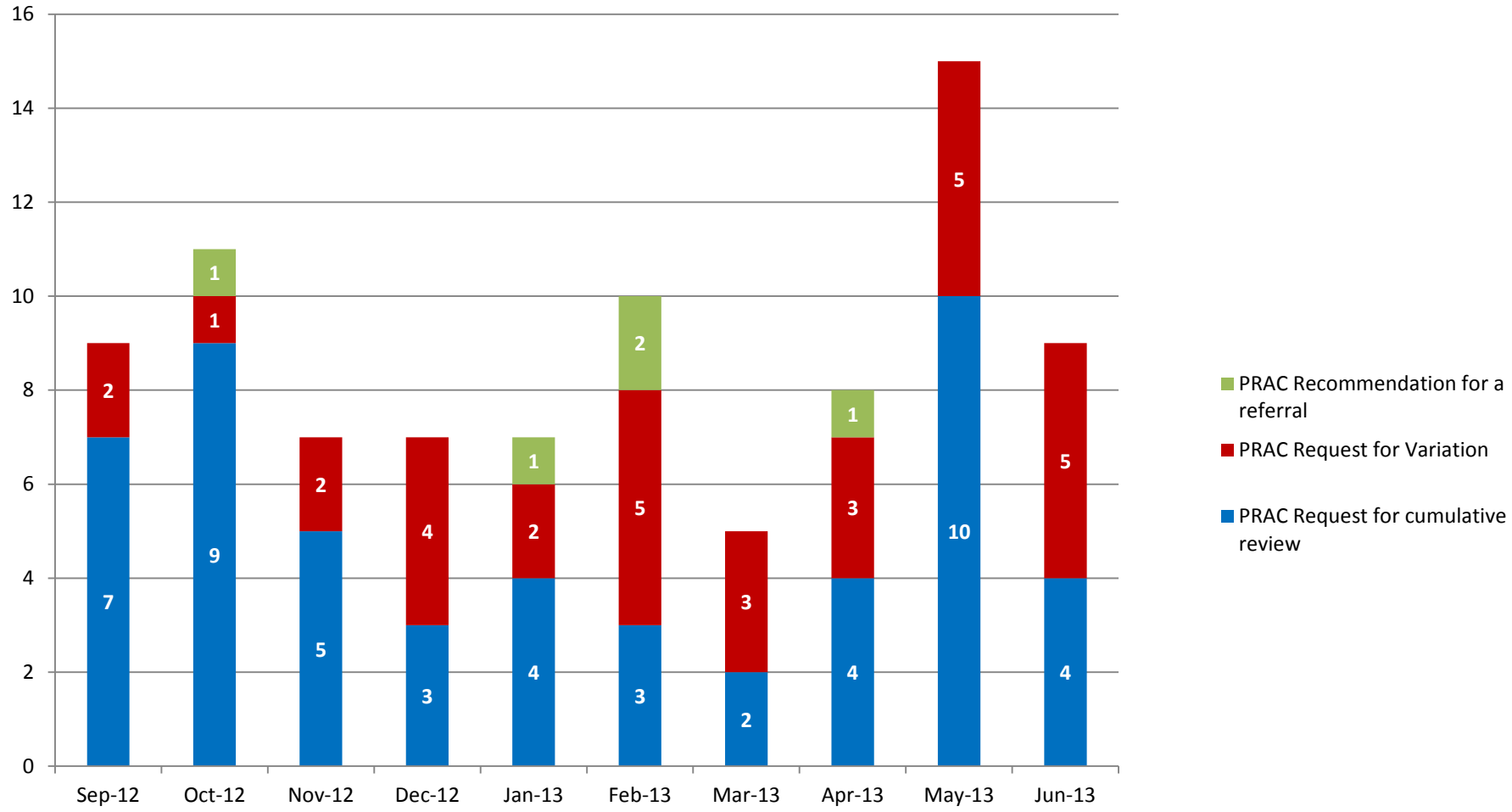
Implementing Regulation 520/2012 "the Pharmacovigilance Risk Assessment Committee shall regularly review the methodology(ies) used and publish recommendations, as appropriate" [Art 20(3)]

Signals – summary *Sept 2012 - Aug 2013*



- [1] 54 for CAPs (59%), 29 for NAPs (31%), 9 for both (10%)
- [2] 6 referrals ongoing, 2 concluded: restriction of use (codeine) and suspension of MA (HES)

PRAC Signals - outcomes



Some examples of labelled signals

Chloroquine hydroxychloroquine and hypoglycaemia

Clopidogrel and eosinophilic pneumonia

Docetaxel and serious/fatal drug interactions

Duloxetine and interaction with linezolid

Efavirenz and interaction with Ginko biloba

Exenatide/liraglutide and GI obstruction

Fingolimod and haemophagocytic syndrome

Roxithromycin and hearing disorders

Roxithromycin and rhabdomyolysis

Tamsulosin and dry mouth syndrome

Temozolomide and hepatic failure

Ticagrelor and interaction with grapefruit juice

Additional monitoring scheme

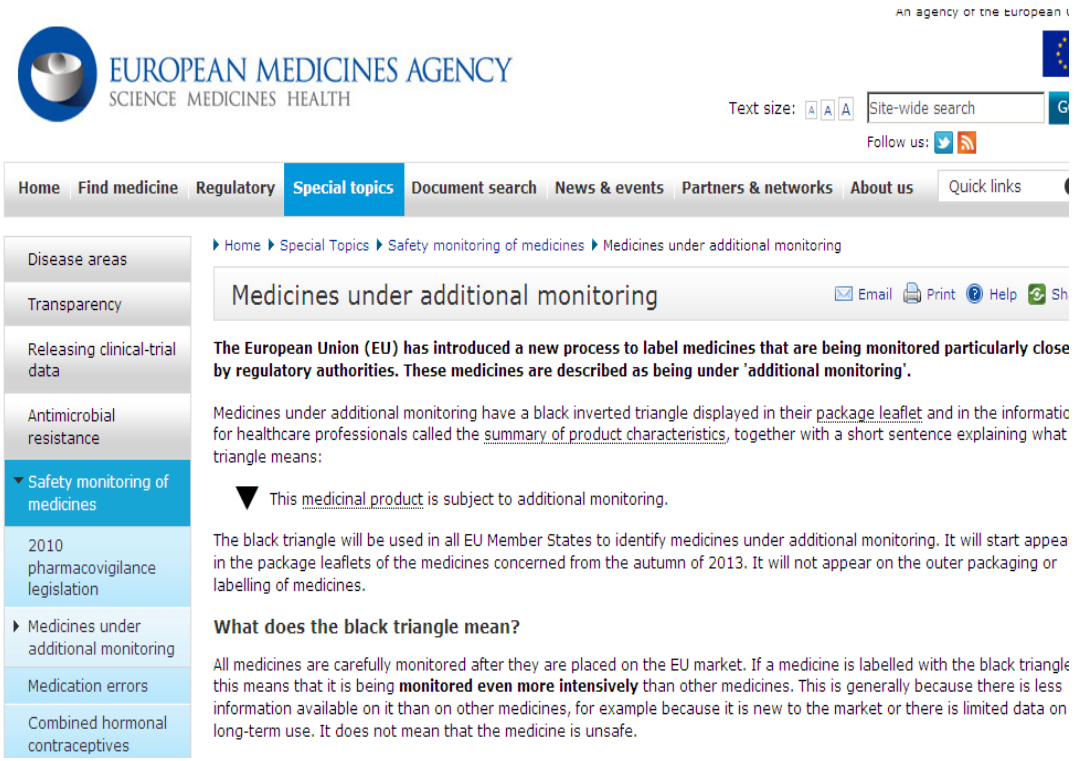
- Views of patient, consumer and healthcare professional organisations were pivotal to choice of inverted black triangle as symbol
- Additional monitoring list now published from April 2013

▼ *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

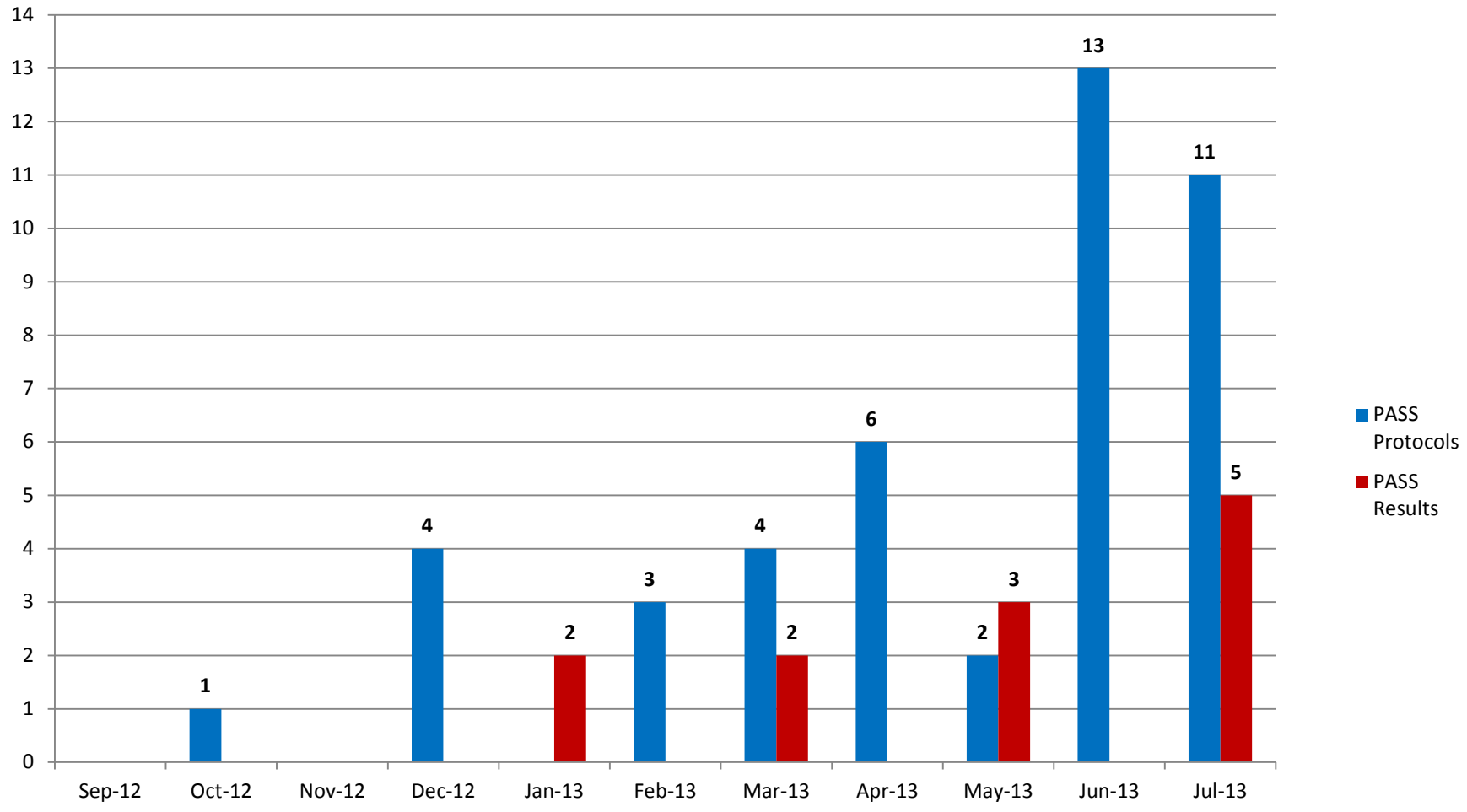
Additional monitoring list



Monthly review by PRAC of proposals for additions to the list

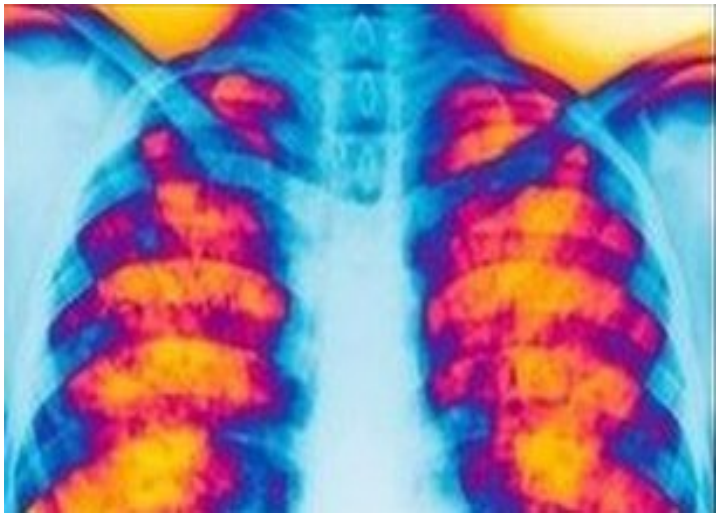
Communications campaign starting 1 October 2012

PASS Protocols & Results at PRAC



Example of PASS

The applicant should conduct a 5-year long-term observational study with ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP



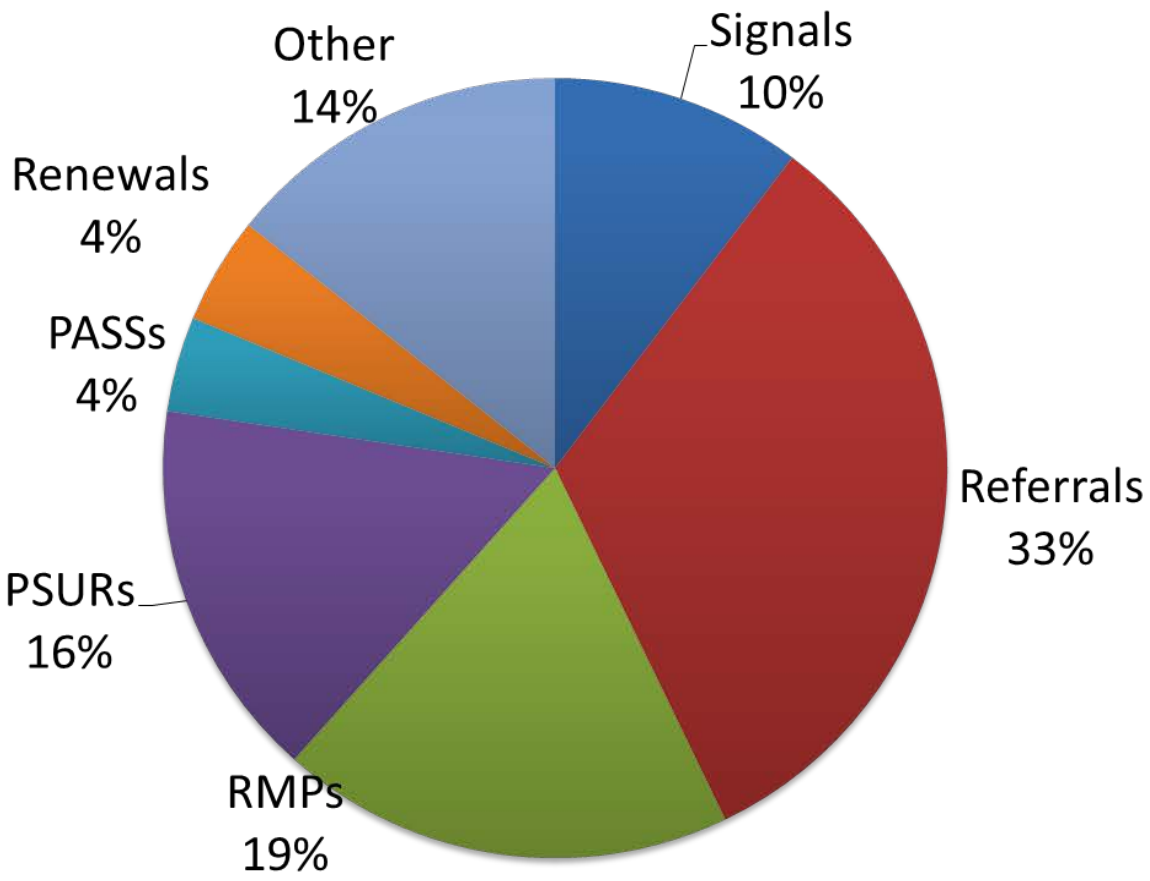
http://clinicaltrials.gov/ct2/show/NCT01117012?term=ivacaftor&rank=22

Prompt benefit risk recommendations

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

PRAC safety referrals

% of PRAC plenary discussion time 2013, based on total hours



Urgent Union Procedure 107i

Nicotinic Acid / laropiprant (CAP Jan 13)	• HPS2-THRIVE study suggesting nicotinic acid was the driver for the observed excess of adverse events.
Cyproterone / ethinylestradiol (NAP Feb 13)	• Risk of venous and arterial thromboembolism, off label use in contraception
Tetrazepam (NAP Jan 13)	• Serious adverse skin reactions
Flupirtine (NAP Mar 13)	• Increased number of reports of idiosyncratic liver toxicity (liver enzyme elevations to fatal liver failure or liver transplant).

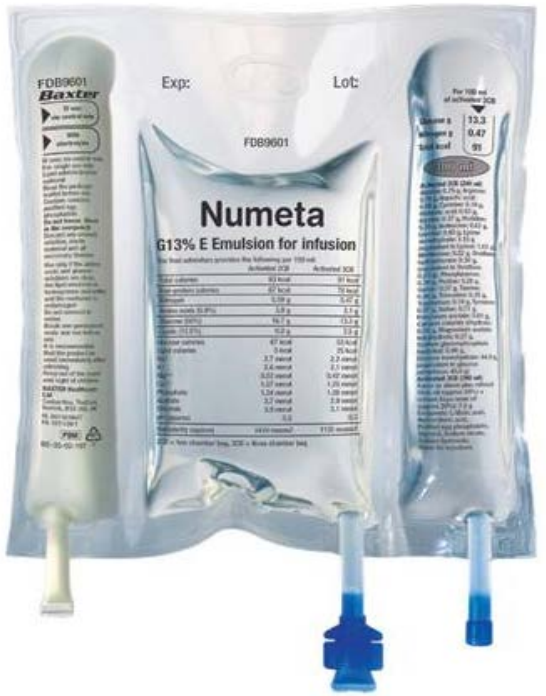
Example 107i procedure – *Numeta 13%*

Numeta 13% parenteral nutrition for preterm babies

Signal of 14 reports of hypermagnesaemia – July 2013

Voluntary recall of Numeta 13%

PRAC concludes advice September 2013 to suspend Numeta 13%, introduce risk management for Numeta 16%



Article 31 procedures

Codeine (NAP Oct 12) OTC	• Increased risk of toxicity, manifesting as fatal or life-threatening respiratory depression when codeine is used in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea.
Diclofenac (NAP Oct 12) OTC	• Cardiovascular safety: increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment.
Short Acting Beta Agonists (NAPs Nov 12)	• Benefit/Risk review in obstetric indications due to serious cardiovascular adverse events in the context of limited benefit in maintenance therapy.
Hydroxyethyl starch solutions (NAP Nov 12)	• Higher risk of mortality in septic patients who were treated with HES and a higher risk of negative effects on renal function in ICU patients.
Almitrine (NAP Nov 12)	• Risk of occurrence of peripheral neuropathy (leading to temporary invalidity with long term recovery) and weight loss (potentially severe) in the context of limited/lack of efficacy.
Diacerein (NAP Nov 12)	• Safety concerns (digestive disorders, including diarrhoea and melanosis, skin reactions sometimes serious, hepatic disorders) in the context of limited benefit in the symptomatic treatment of osteoarthritis.

Article 31 procedures

Combined hormone contraceptives (NAP – CAPs Feb 13)	• Risk of venous thromboembolism
Domperidone (NAP Mar 13) OTC	• Review of the benefit-risk in view of cardiovascular risk (QT-prolongation, arrhythmia, sudden death)
Nicotinic acid and related substances (NAP Mar 13)	• HPS2-THRIVE study suggesting nicotinic acid was the driver for the observed excess of adverse events.
Octocog alfa (CAP Mar 13)	• Review of the B/R balance in view of increased risk of inhibitor development as compared to third generation full-length recombinant factor VIII products.
Renin-angiotensin system acting agents (NAPs May 13)	• Review of the risks of combining certain medicines to block separate stages of the renin-angiotensin system (RAS) in the treatment of hypertension and congestive heart failure

BMJ

BMJ 2013;346:f1464 doi: 10.1136/bmj.f1464 (Published 7 March 2013)

EDITORIALS

Is an EMA review on hormonal contraception and thrombosis needed?

Sufficient evidence exists to recommend the second generation pill with the lowest tolerable oestrogen dose for all indications

...ber 11, 2013

Girl, 18, suffers stroke after two years on the Pill

Shocked: Georgie with mum Kim

A TEENAGER has been left partially blind after suffering a stroke linked to the contraceptive pill.

Georgie Holland, 18, collapsed after being sent home from college and spent two days in bed before her parents took her to hospital, where a scan revealed a blood clot in her brain that was affecting the flow of blood.

Doctors linked the stroke to her taking the contraceptive

Daily Mail Reporter

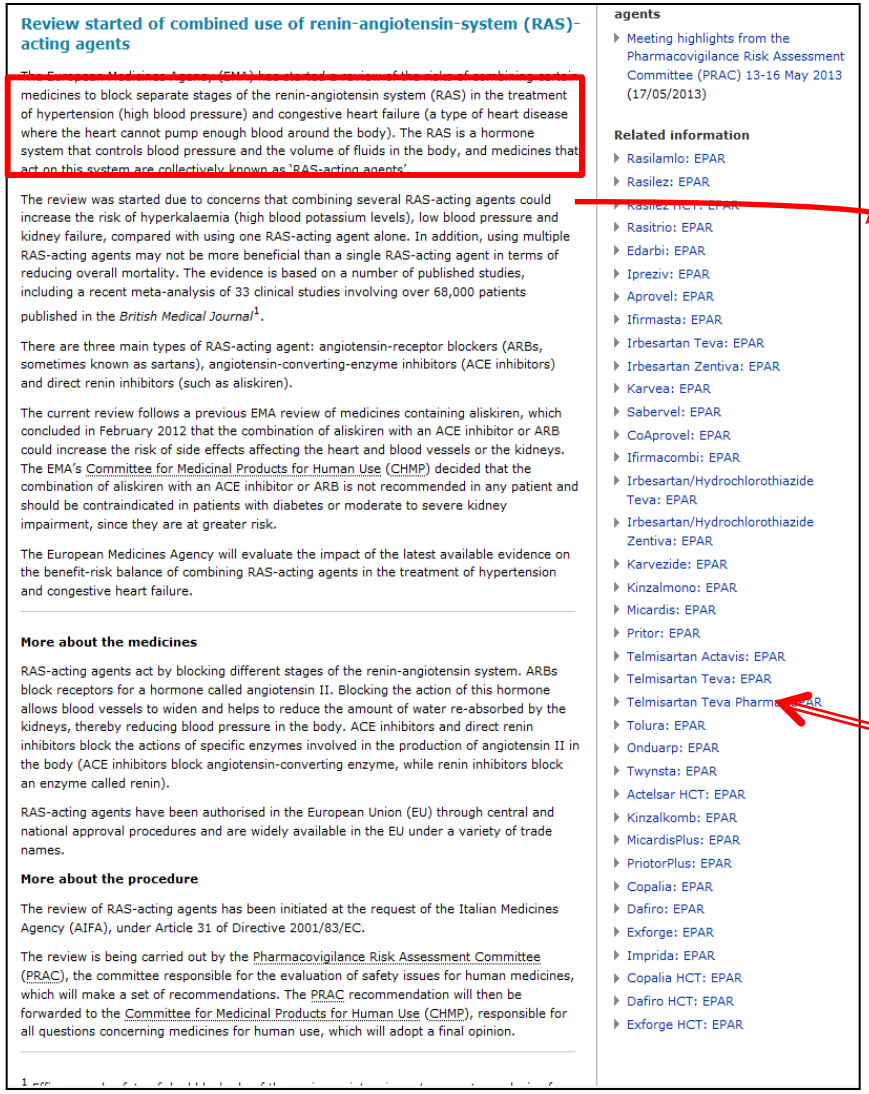
was allowed to leave, but I couldn't think clearly. I ended up walking out of the school and down the road.

'My dad was passing, on his way to get me, and saw me collapsed in a bush. I didn't know why I had decided to walk out of the school.'

She spent two days at home but remained so ill that she knew what I was thinking but I was unable to speak without slurring.'

She was taken to hospital for tests. 'When I saw the scan I was shocked – there was a black clot in the middle of my brain which had stopped the blood from flowing,' she said.

The cause of the stoke has been linked to the contraceptive pill as there are no other contributing factors. It is



Review started of combined use of renin-angiotensin-system (RAS)-acting agents

The European Medicines Agency (EMA) has started a review of the risks of combining certain medicines to block separate stages of the renin-angiotensin system (RAS) in the treatment of hypertension (high blood pressure) and congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body). The RAS is a hormone system that controls blood pressure and the volume of fluids in the body, and medicines that act on this system are collectively known as 'RAS-acting agents'.

The review was started due to concerns that combining several RAS-acting agents could increase the risk of hyperkalaemia (high blood potassium levels), low blood pressure and kidney failure, compared with using one RAS-acting agent alone. In addition, using multiple RAS-acting agents may not be more beneficial than a single RAS-acting agent in terms of reducing overall mortality. The evidence is based on a number of published studies, including a recent meta-analysis of 33 clinical studies involving over 68,000 patients published in the *British Medical Journal*[1].

There are three main types of RAS-acting agent: angiotensin-receptor blockers (ARBs, sometimes known as sartans), angiotensin-converting-enzyme inhibitors (ACE inhibitors) and direct renin inhibitors (such as aliskiren).

The current review follows a previous EMA review of medicines containing aliskiren, which concluded in February 2012 that the combination of aliskiren with an ACE inhibitor or ARB could increase the risk of side effects affecting the heart and blood vessels or the kidneys. The EMA's Committee for Medicinal Products for Human Use (CHMP) decided that the combination of aliskiren with an ACE inhibitor or ARB is not recommended in any patient and should be contraindicated in patients with diabetes or moderate to severe kidney impairment, since they are at greater risk.

The European Medicines Agency will evaluate the impact of the latest available evidence on the benefit-risk balance of combining RAS-acting agents in the treatment of hypertension and congestive heart failure.

More about the medicines

RAS-acting agents act by blocking different stages of the renin-angiotensin system. ARBs block receptors for a hormone called angiotensin II. Blocking the action of this hormone allows blood vessels to widen and helps to reduce the amount of water re-absorbed by the kidneys, thereby reducing blood pressure in the body. ACE inhibitors and direct renin inhibitors block the actions of specific enzymes involved in the production of angiotensin II in the body (ACE inhibitors block angiotensin-converting enzyme, while renin inhibitors block an enzyme called renin).

RAS-acting agents have been authorised in the European Union (EU) through central and national approval procedures and are widely available in the EU under a variety of trade names.

More about the procedure

The review of RAS-acting agents has been initiated at the request of the Italian Medicines Agency (AIFA), under Article 31 of Directive 2001/83/EC.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations. The PRAC recommendation will then be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for all questions concerning medicines for human use, which will adopt a final opinion.

1 Eff...

agents

- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 13-16 May 2013 (17/05/2013)

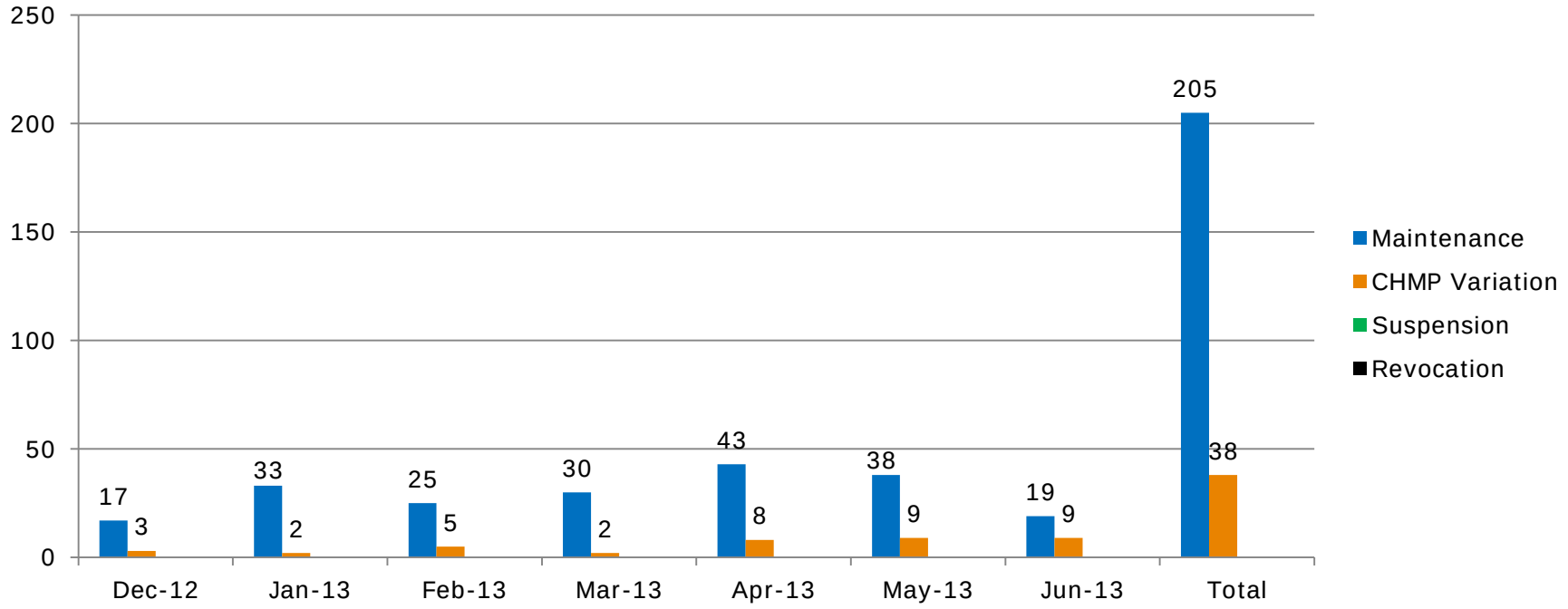
Related information

- Rasilamlo: EPAR
- Rasilez: EPAR
- Rasilez HCT: EPAR
- Rasitrio: EPAR
- Edarbi: EPAR
- Ipreziv: EPAR
- Aprovel: EPAR
- Ifirmasta: EPAR
- Irbesartan Teva: EPAR
- Irbesartan Zentiva: EPAR
- Karvea: EPAR
- Sabervel: EPAR
- CoAprovel: EPAR
- Ifirmacombi: EPAR
- Irbesartan/Hydrochlorothiazide Teva: EPAR
- Irbesartan/Hydrochlorothiazide Zentiva: EPAR
- Karvezide: EPAR
- Kinzalmono: EPAR
- Micardis: EPAR
- Pritor: EPAR
- Telmisartan Actavis: EPAR
- Telmisartan Teva: EPAR
- Telmisartan Teva Pharma...EPAR
- Tolura: EPAR
- Onduarp: EPAR
- Twynsta: EPAR
- Actelsar HCT: EPAR
- Kinzalkomb: EPAR
- MicardisPlus: EPAR
- PriotorPlus: EPAR
- Copalia: EPAR
- Dafiro: EPAR
- Exforge: EPAR
- Imprida: EPAR
- Copalia HCT: EPAR
- Dafiro HCT: EPAR
- Exforge HCT: EPAR

"EMA has started a review of the risks of combining certain medicines to block separate stages of the renin-angiotensin system (RAS) in the treatment of hypertension and congestive heart failure"

- 24 substances
- 37 CAPs
- > 16,000 NAPs
- 9 Rapporteurs
- Number of companies involved unknown

PSURs Outcomes at PRAC



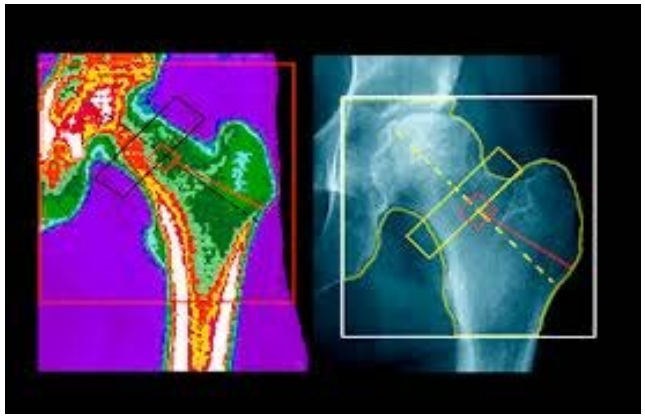
- 243 PSUR PRAC recommendations (single CAPs) from Dec 2012 till June 2013
- 38 (16%) PRAC recommendations to vary MA
- No suspensions, no revocations

Example –*Strontium ranelate*

Periodic safety update report identified increased risk of cardiac disorders including MI

PRAC advised variation to restrict MA on safety grounds

CHMP started referral under Art 31



heartwire

PREVENTION

CV risks prompt recommendations for EU strontium ranelate restrictions

APRIL 15, 2013 Deborah Flapan

London, UK - The Pharmacovigilance Risk Assessment Committee (PRAC) of the **European Medicines Agency** (EMA) has recommended restrictions in the use of **strontium ranelate** (Protelos/Osseor, Servier) to reduce the risk for adverse cardiovascular events in postmenopausal women [1].

An agency of the European Union

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Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 2-5 September 2013

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News

06/09/2013

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 2-5 September 2013

PRAC highlights

The Pharmacovigilance Risk Assessment Committee (PRAC) gave recommendations on two medicines and started one new safety review at its September 2013 meeting.

PRAC recommends restriction to the use of short-acting beta-agonists in obstetric indications

The PRAC recommended that medicines called 'short-acting beta-agonists' should no longer be used in oral or suppository forms in obstetric indications (for the care of pregnant women), such as for suppressing premature labour or excessive labour contractions. However, injectable forms of these medicines should remain authorised for short-term obstetric use under specific conditions.

More information on this, and all other PRAC recommendations, is included in the table below.

PRAC recommends suspension and reformulation for Numeta G13%E and risk minimisation measures for Numeta G16%E

The PRAC recommended suspending the marketing authorisation of Numeta G13%E, an intravenous nutrition preparation given to premature babies for nutritional support, until a reformulated preparation has been approved.

For Numeta G16%E, another intravenous nutrition preparation used in full-term newborns and children up to two years of age, the PRAC considered the benefit-risk balance to be positive, provided that a number of risk-minimisation measures are implemented.

New review for bromocriptine started

The PRAC started a new review procedure for bromocriptine-containing medicines when used orally for preventing or suppressing lactation (milk production) in women following childbirth. The PRAC will assess whether the benefits of these medicines outweigh the risk of rare but potentially serious (including fatal) cardiovascular, neurological and psychiatric side effects.

Related information

- Oral bromocriptine-containing medicines indicated in the prevention or suppression of physiological lactation post-partum: Article-31 procedure
- Numeta G13%E and Numeta G16%E emulsion for infusion: Article-107i procedure
- Short-acting beta-agonists: Article-31 procedure
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Pharmacovigilance Risk Assessment Committee (PRAC): 2-5 September 2013

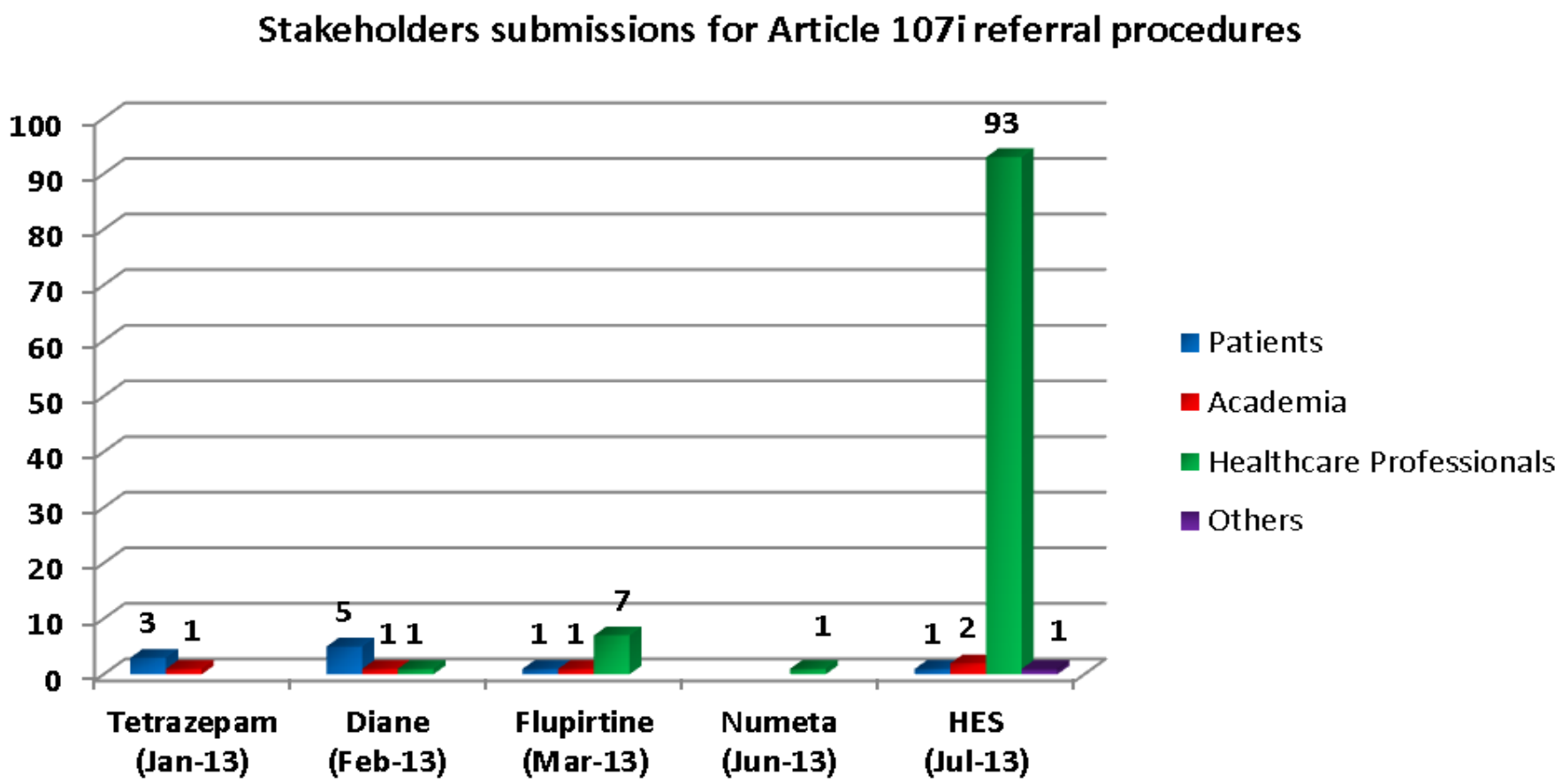
Acronyms and abbreviations used in PRAC minutes (05/10/2012)

Contact point:

Monika Benstetter
Tel. +44 (0)20 7418 8427
E-mail: press@ema.europa.eu

Highlights from 2-5 September PRAC meeting, published 6th September

Stakeholder involvement



Looking ahead -

what is still to come?

Current PRAC priorities

- Increasing stakeholder involvement
- Strengthening the science base for benefit risk decision-making
- Optimising use of regulatory tools for public health
- Measuring the public health impact of activities

Public Hearings

DEFINITION

- Public invited
- Stakeholders views and concerns
- Specific questions

OBJECTIVES

- Increased transparency
- Empower EU citizens
- Add value and increase understanding

WHEN TO HOLD?

- Level of risk acceptance
- Define balance B/R

LEGAL BASIS

- Urgency matter permits
- Extent and seriousness safety concerns
- Art. 107 and Art. 31

OPENESS AND TRANSPARENCY

- All info public
- Part of overall assessment
- Declaration of Interests
- Recorded / video streamed
- Language challenge

ORGANISATION

- Website
- Specific questions
- Priority representatives of groups / organisations
- Time allocation

Strengthening the science base

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 January 2013
EMA/14946/2013
Patient Health Protection

European Medicines Agency process for engaging in external regulatory sciences and process improvement research activities for public and animal health

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Further legislation…

Ref. Ares(2013)1034784 - 13/05/2013

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products — authorisations, EMA

Brussels,
SANCO/D5/FS D(2013) 1126143

DELEGATED ACT ON POST-AUTHORISATION EFFICACY STUDIES

(ARTICLE 10B OF REGULATION (EC) NO 726/2004 AND ARTICLE 22B OF DIRECTIVE 2001/83/EC)

POST-AUTHORISATION EFFICACY STUDIES

Expert group discussion
4 June 2013

Optimising use of new tools

Referrals –scope, criteria for triggering

Signal roles and responsibilities, methodologies

“EC Joint Action”

Joint Action - SCOPE

Strengthening Collaborations to Operate Pharmacovigilance in Europe

EUROPEAN COMMISSION
EXECUTIVE AGENCY FOR HEALTH AND CONSUMERS

Health Unit

Luxembourg,
EAHC LB/IK Ares (2012)

2013 CALL FOR PROPOSALS FOR JOINT ACTIONS

SECOND PROGRAMME OF COMMUNITY ACTION IN THE FIELD OF HEALTH (2008-2013)

Facilitating collaboration among the Member States for the effective operation of the pharmacovigilance system in the EU

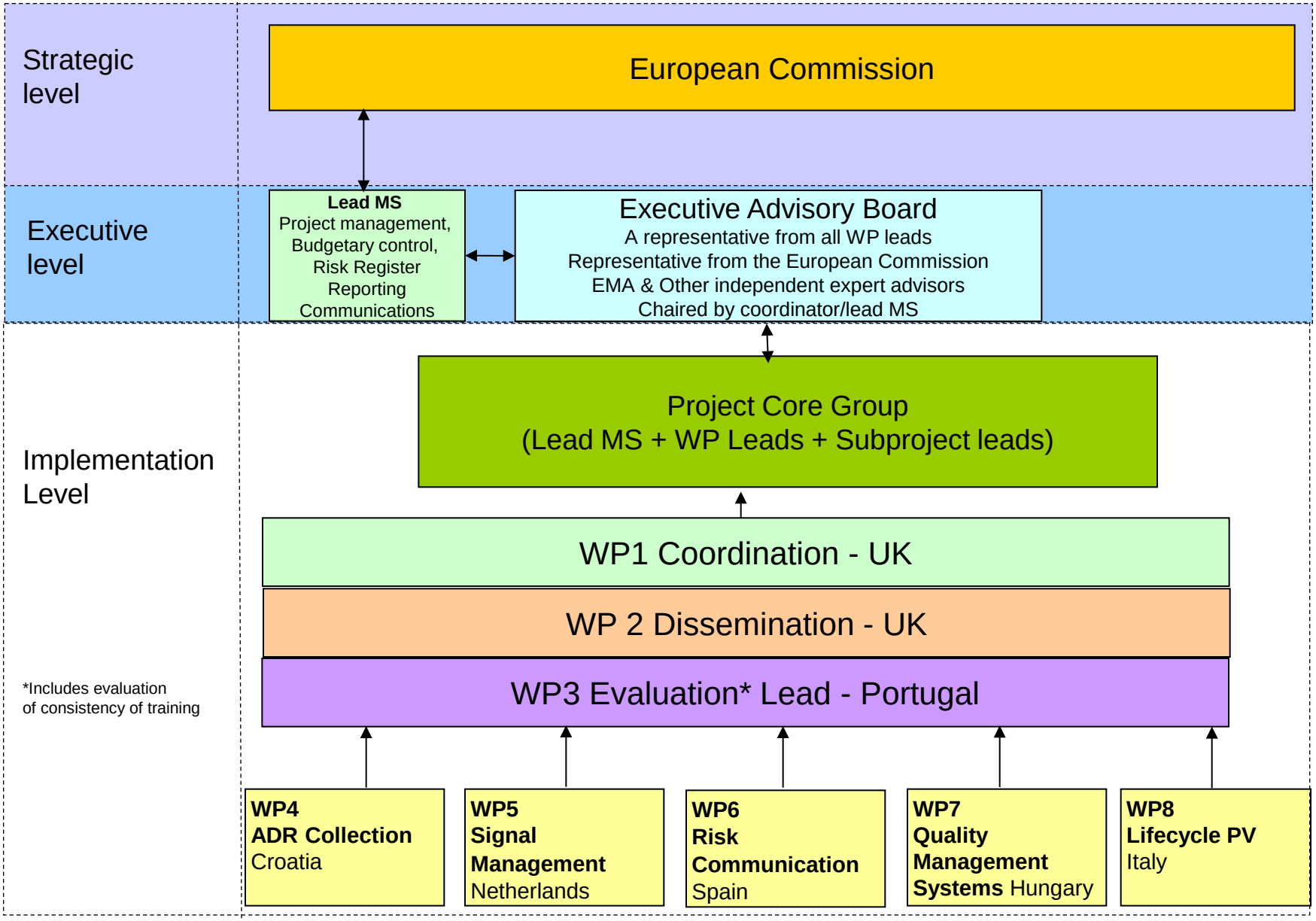
Joint Action - SCOPE

Operate

Comply

Implement

SCOPE - Governance Structure



Innovative Medicines Initiative

IMI-GB-DEC-2013-13
Annex 1

9th Call for Proposals 2013

Innovative Medicines Initiative

Version 2

TABLE OF CONTENTS

Public health outcomes

Demonstrably strengthening protection of public health– what this is all about

Summary

- Establishment of PRAC is central to implementation of EU Pharmacovigilance legislation
- Over the first year 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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 July 2013
EMA/445949/2013
Press Office

Press release

Pharmacovigilance Risk Assessment Committee: one year of public health promotion and protection

"In a busy, exciting and productive first year establishing the new Pharmacovigilance Risk Assessment Committee (PRAC), the Committee has proactively grasped the opportunities of the new pharmacovigilance legislation to strengthen European drug safety. By involving patients and healthcare professionals in our decision-making, strengthening the science base of risk assessment, and working transparently, we have made great strides towards a new era in protecting public health. We look forward to even greater progress in the year to come," explains Dr June Raine, Chair of the PRAC.

Future focus is the PRAC
Three R's

- Rigorous science
- Risk:proportionate decision-making
- Relevance to public health