DEUTSCHE GESELLSCHAFT FÜR REGULATORY AFFAIRS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance Referrals

June M Raine
Chair, PRAC

17th DGRA Annual Congress
7-8 May 2015

Outline of presentation

- Why did EU Pharmacovigilance legislation clarify and strengthen referrals, a key public health tool?
- What has been PRAC's experience of the first 3 years of operation of pharmacovigilance referrals?
- What are main challenges and current activities to improve referral procedures?
- What is coming next? - moving forward to optimise operation of referrals

History of EU Pharmacovigilance

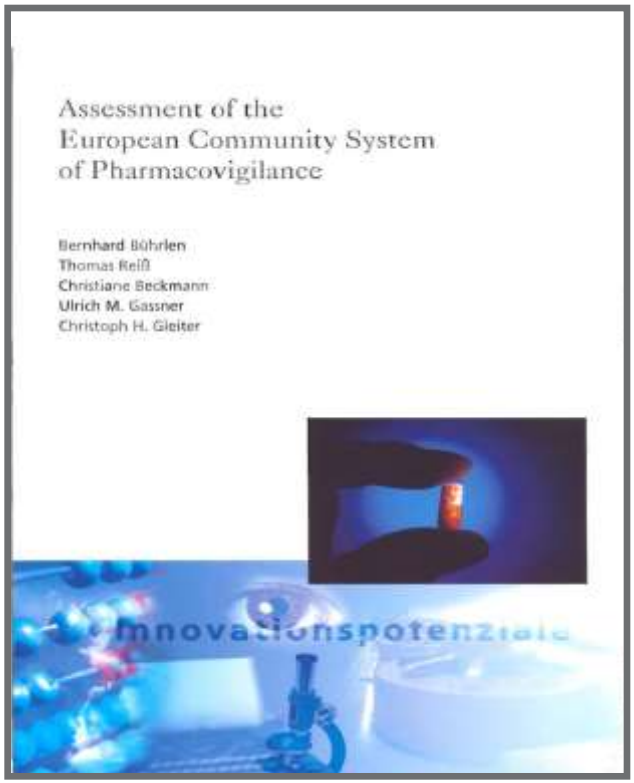
Drug safety crises – combined hormonal contraceptives, cerivastatin, HRT, SSRIs, rofecoxib…..

Variable timeframes for response and inconsistent implementation of safety action by member states

Studies in EU member states estimated that 20% to 70% of ADRs preventable

Pirmohamed et al 2004 BMJ 329; 15-19
Rottenkolber 2011, PDS; 20: 626–634

European Commission review



Independent assessment of European system of pharmacovigilance 2006

- Lack of clear roles and responsibilities
- Lack of proactive and proportionate monitoring
- Duplicative AR reporting rules
- Lack of inclusiveness of stakeholders
- Slow decision-making
- Low levels of transparency

Impact of adverse drug reactions

5% of all hospital admissions due to ADRs

5% of all hospital patients experience an ADR

ADRs 5th commonest cause of hospital death

197,000 deaths per year in EU due to ADRs

5910 lives per year
€237m could be saved

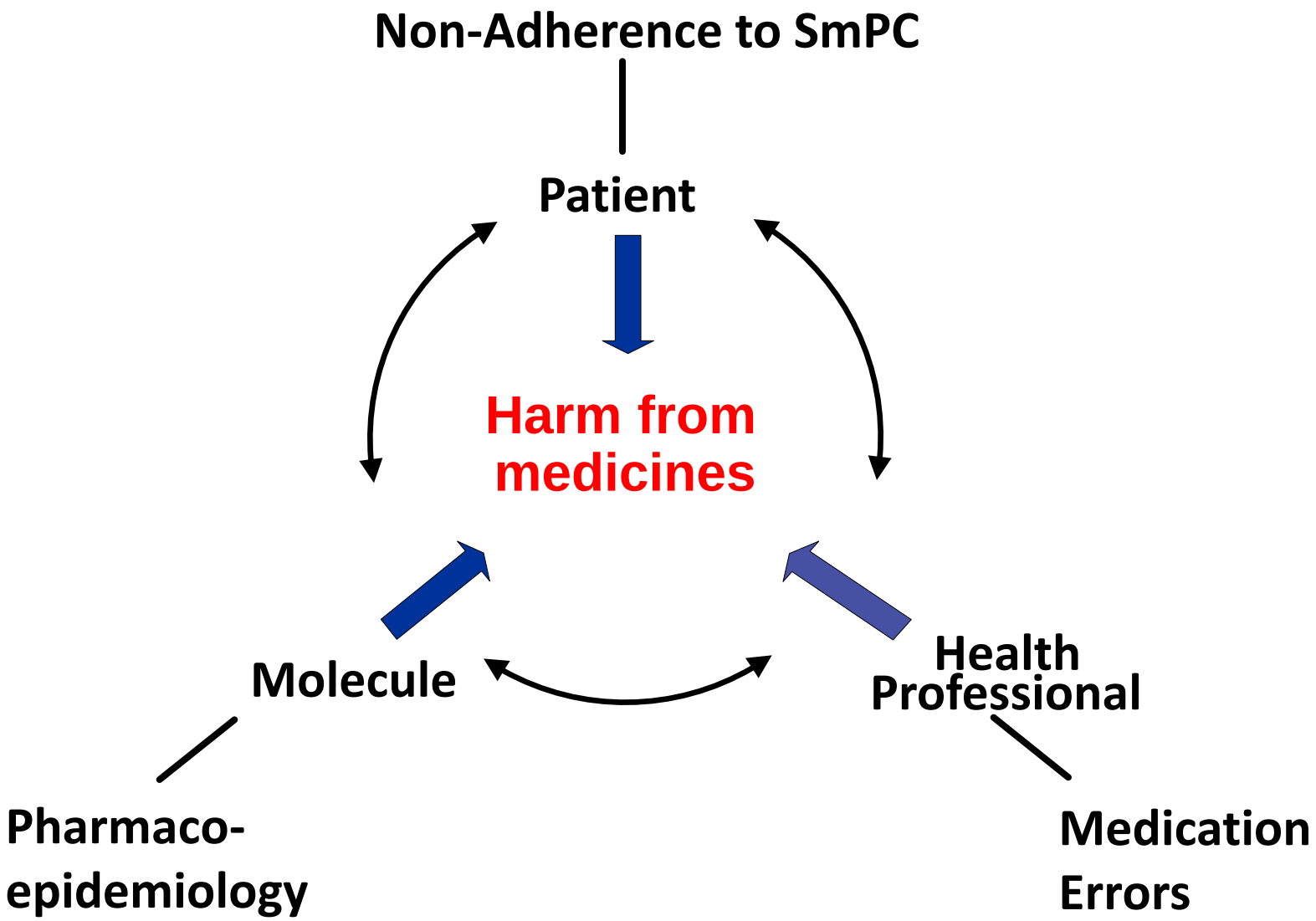
Pharmacovigilance legislative aims

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** – proportional to risk

Directive 2010/84/EU

*For the sake of clarity, the **definition of the term 'adverse reaction'** should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from*

- *Medication errors*
- *Uses outside terms of marketing authorisation (includes misuse)*



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

EUROPEAN MEDICINES AGENCY

The Pharmacovigilance Risk Assessment Committee

Inaugural meeting

Brussels July 19-20th 2012

European Commission experts

Pharmacoepidemiology

Marieke de Bruin

Stephen Evans

Pharmacovigilance

Hervé Le Louët

Signal detection

Lennart Waldenlind

Biologicals and vaccines

Brigitte Keller Stanislawski

Risk Communication

Jane Ahlqvist Rastad

PRAC's main goals

- **Proactively investigating drug safety -** filling knowledge gaps via post-authorisation studies, continuous signal detection - wider definition of ADR
- **Responding to safety and benefit risk issues –** risk-proportionate decisions to rigorous timescales, effectiveness of risk minimisation
- **Driving forward the new era in transparency -** real time access to information on PRAC activities
- **Increasing involvement of stakeholders -** health professionals, patients and public

Progress in first 2 years…

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

32 meetings

Over 600 risk management plans

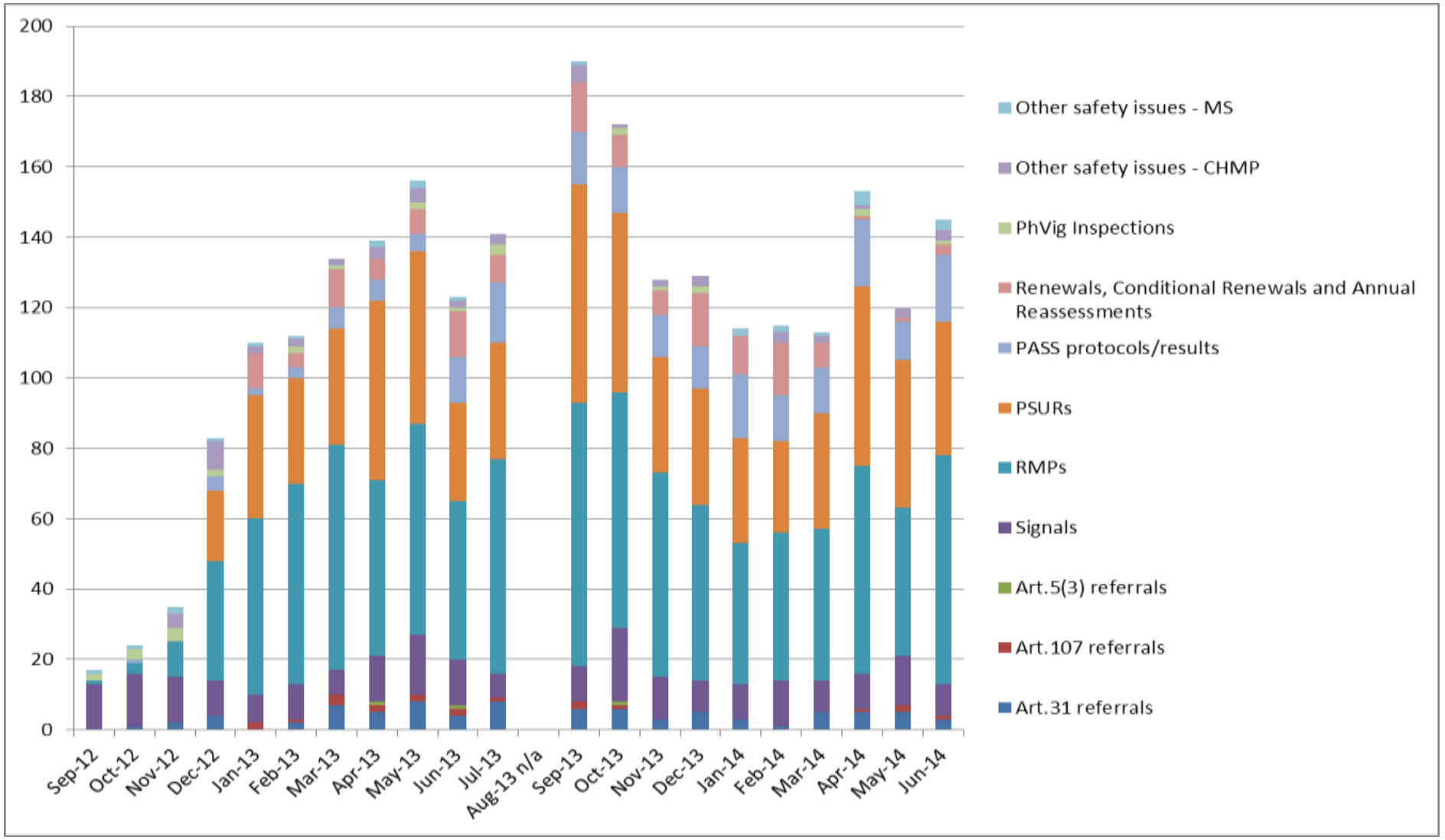
Over 150 protocol reviews

33 safety referrals

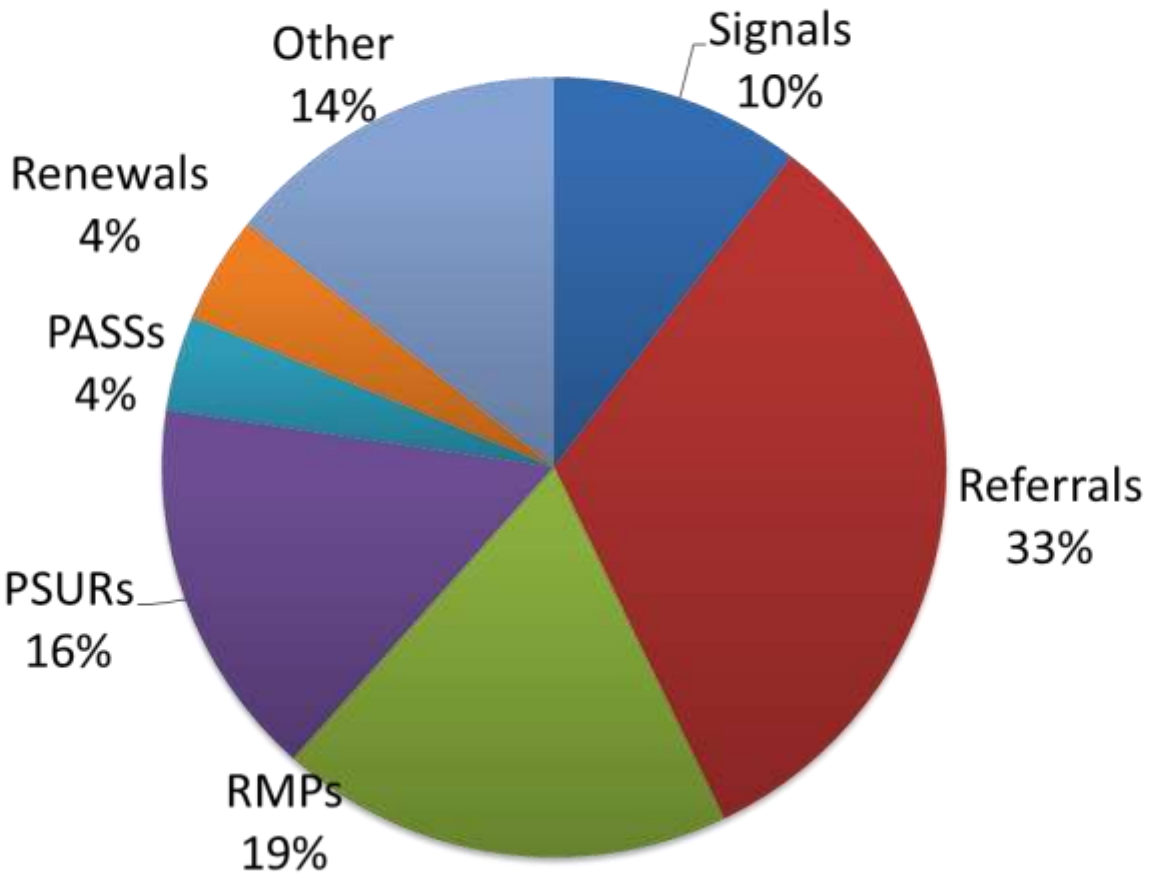
Over 1000 PSURs

Over 300 signals

PRAC monthly activities



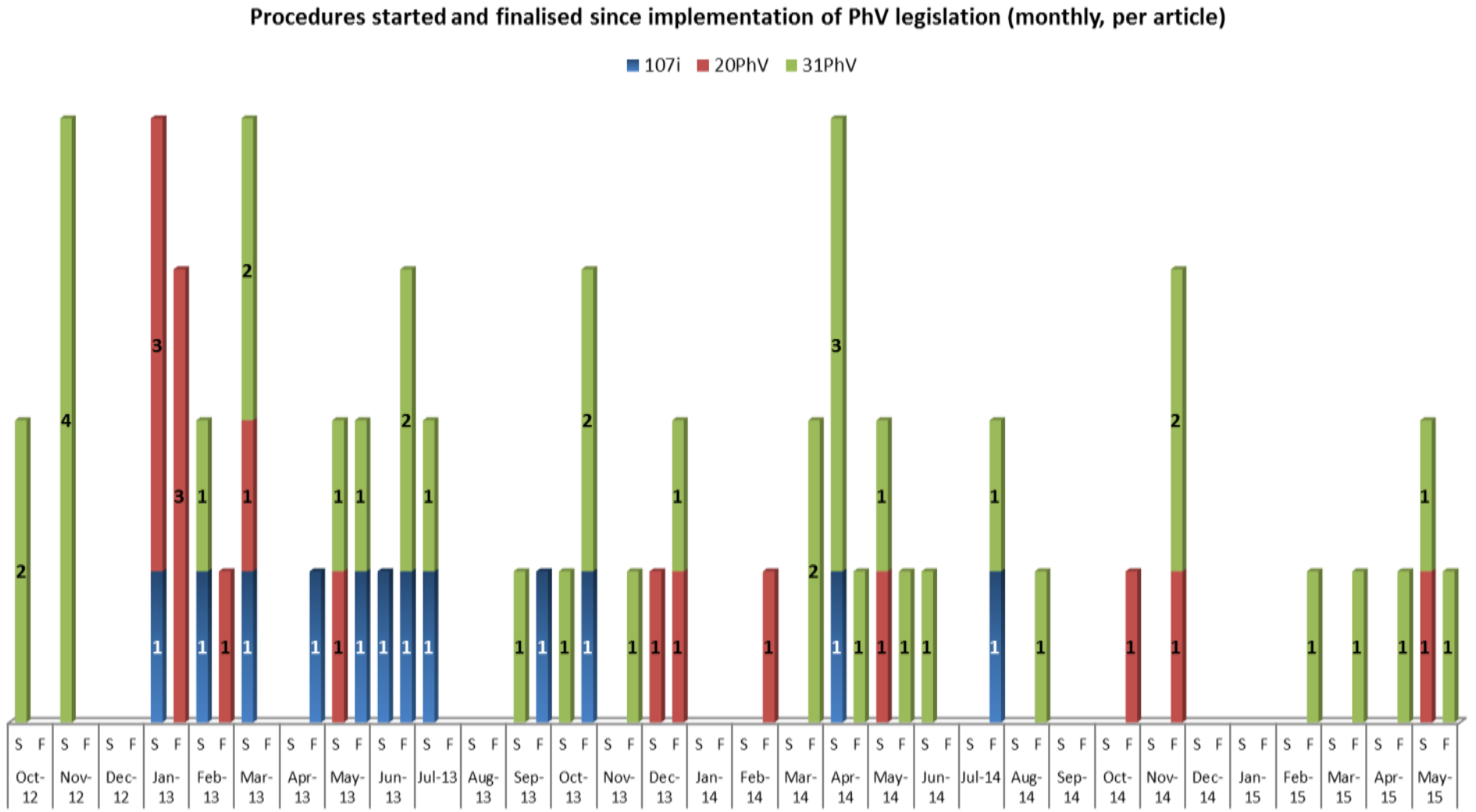
% of PRAC plenary discussion time 2013, based on total hours



PRAC safety referrals

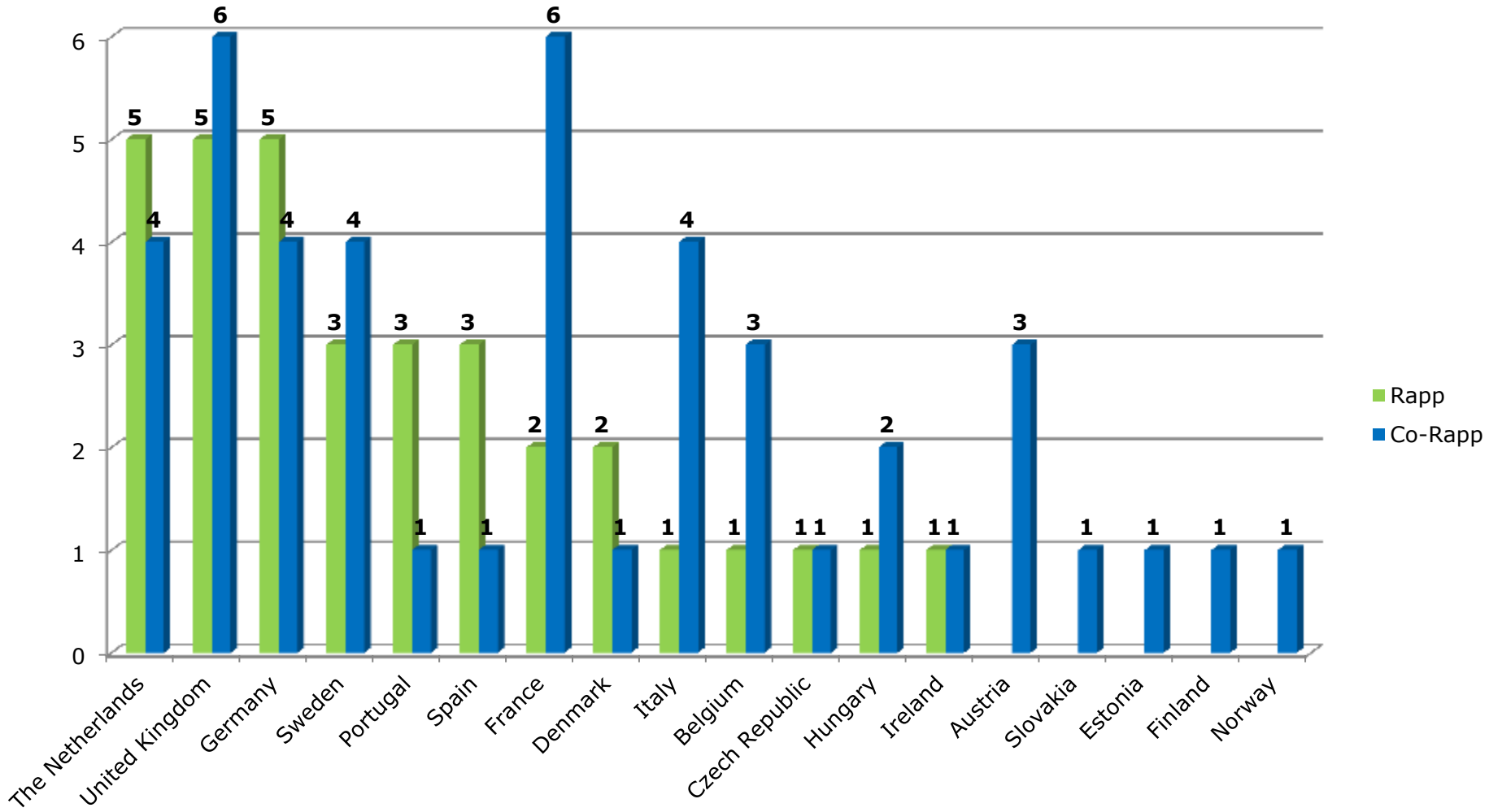
Referrals started and finalised since July 2012

*Ibuprofen/dexibuprofen is included in number of finalised procedures, CMDh is expected in May 2015 CMDh Plenary Meeting

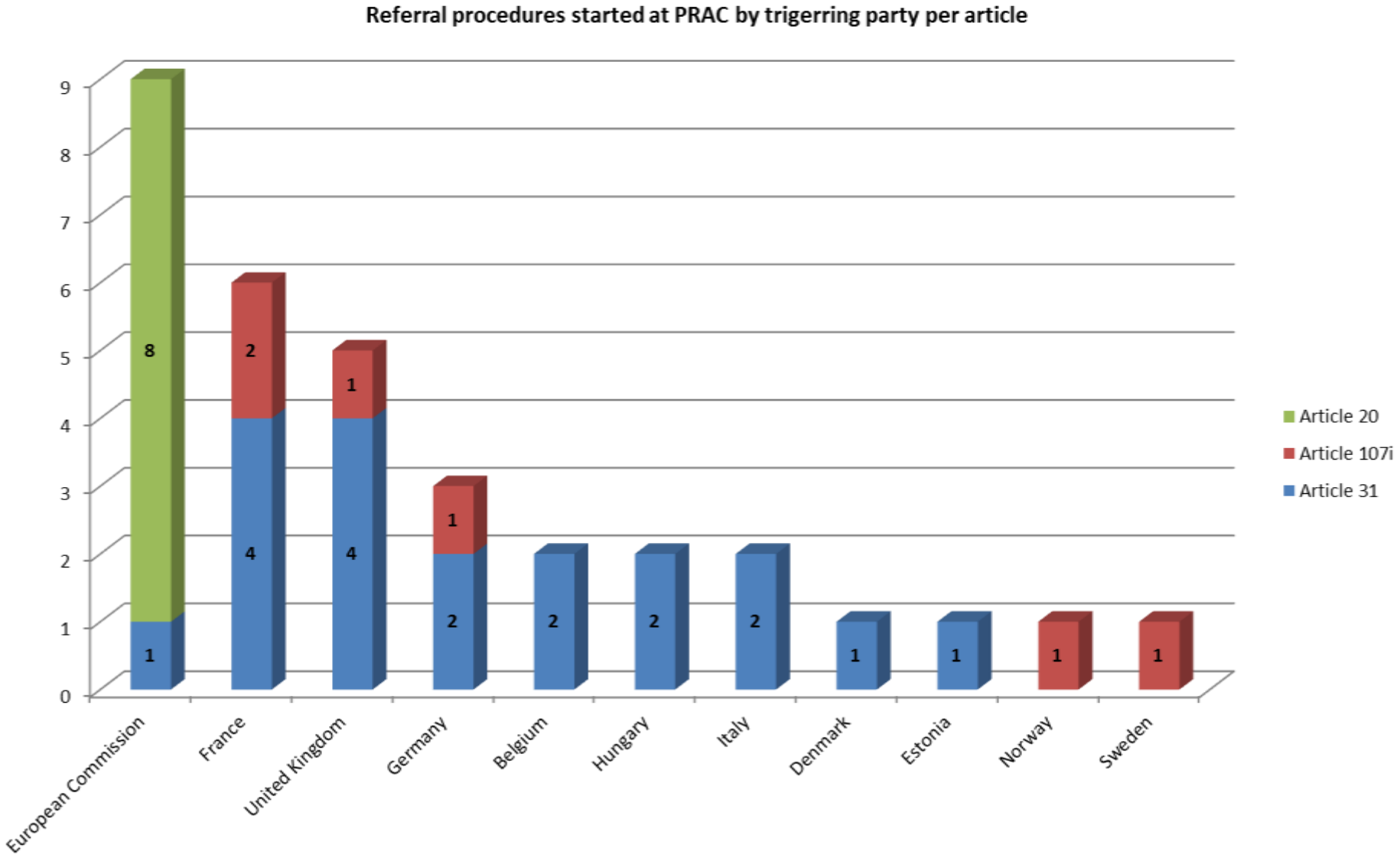


(Co) Rapporteurship for referral procedures

(Co) Rapporteurship per Member State
***3 procedures have multiple co-rapporteurs (SABA**-HU, BE, CS, IT**; RAS** - UK, IT, SV, DE, NL, PT, SK**,** IE, ES, **Ambroxol/Bromhexine** – PT, AT, BE**)**



Referral procedures by triggering party



Article 107i - Urgent Union Procedures

- Tetrazepam (FR)
- Cyproterone (FR)
- Flupirtine (DE)
- Numeta (SE)
- Hydroxyethyl starch (UK)
- Methadone (NO)

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 concluded advice in September 2013 to suspend Numeta 13%, introduce risk management for Numeta 16% for 0-2 year olds

Example 107i procedure – *methadone containing povidone and renal failure*

Povidone containing oral solution - to minimise risk of injection by addicts on therapy

Reports of renal failure and death from region in Norway

Local pathologists found povidone deposits in specimens

Suspension of high MW products

European Monitoring Centre for Drugs and Drug Addiction

Article 20 PhVig referral procedures

- Tredaptive (nicotinic acid/laropiprant)
- Trevaclyn (nicotinic acid/laropiprant)
- Pelzont (nicotinic acid/laropiprant)
- Kogenate Bayer/Helixate NexGen (octocog alfa)
- Protelos/Osseor (strontium ranelate)
- Corlentor and Procoralan (ivabradine)
- Iclusig (ponatinib)
- Tysabri (natalizumab)

Triggered by European Commission

Example of Art 20 - *Factor VIII*
Kogenate & Helixate inhibitor development

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Factor VIII Products and Inhibitor Development in Severe Hemophilia

Samantha C. Gouw, M.D., Ph.D., Johanna G. van der Bom, M.D., Ph
Rolf Ljung, M.D., Ph.D., Carmen Escuriola, M.D., Ana R. Cid, M.D
Ségolène Claeyssens-Donadel, M.D., Christel van Geet, M.D., Ph.D
Gili Kenet, M.D., Anne Mäkipernaa, M.D., Ph.D., Angelo Claudio Molina
Wolfgang Muntean, M.D., Rainer Kobelt, M.D., George Rivard, M.D
Elena Santagostino, M.D., Ph.D., Angela Thomas, M.D., Ph.D.,
and H. Marijke van den Berg, M.D., Ph.D.,
for the PedNet and RODIN Study Group*

ABSTRACT

BACKGROUND

For previously untreated children with severe hemophilia A, it is unclear the type of factor VIII product administered and switching among produc sociated with the development of clinically relevant inhibitory antibodies development).

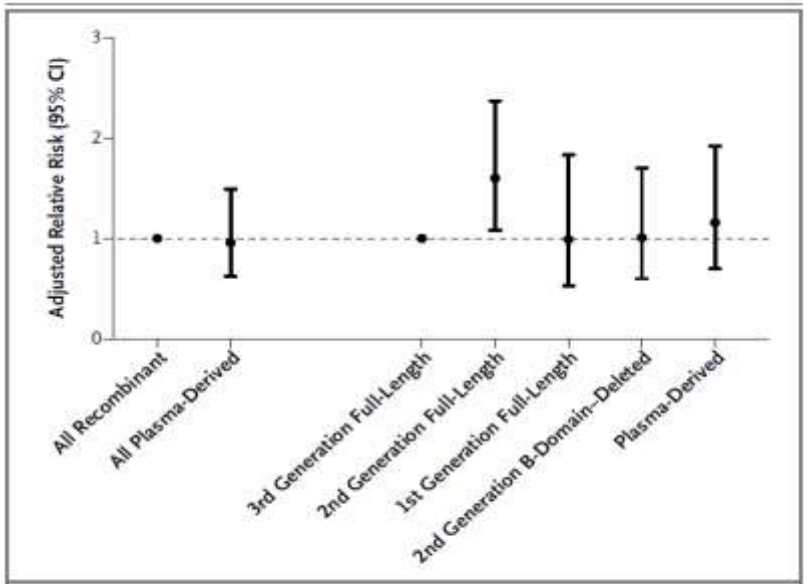


Figure 2. Adjusted Relative Risk of Inhibitor Development, According to the Type of Factor VIII Product.

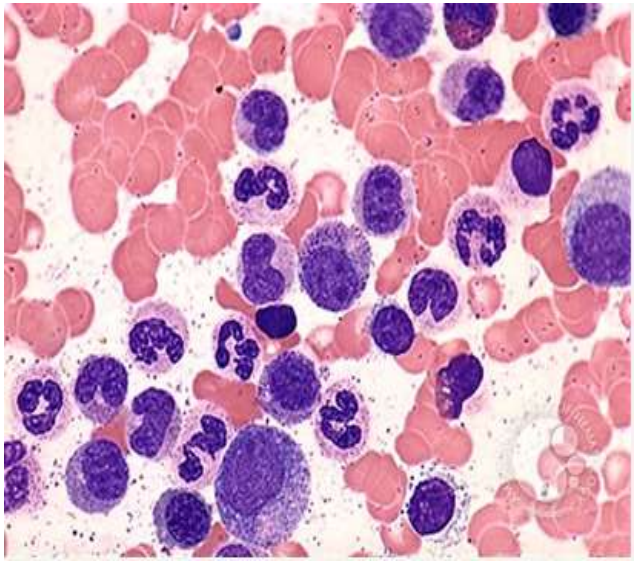
Example of Art 20 - *Ponatinib and cardiovascular risk*

Vaso-occlusive reactions at higher rate than in clinical trials

Product information updated to include warnings about dose-dependent ischaemic CV risk

MAH required to provide prescriber educational material re monitoring and dose adjustments

Further study into benefits and risks at different doses

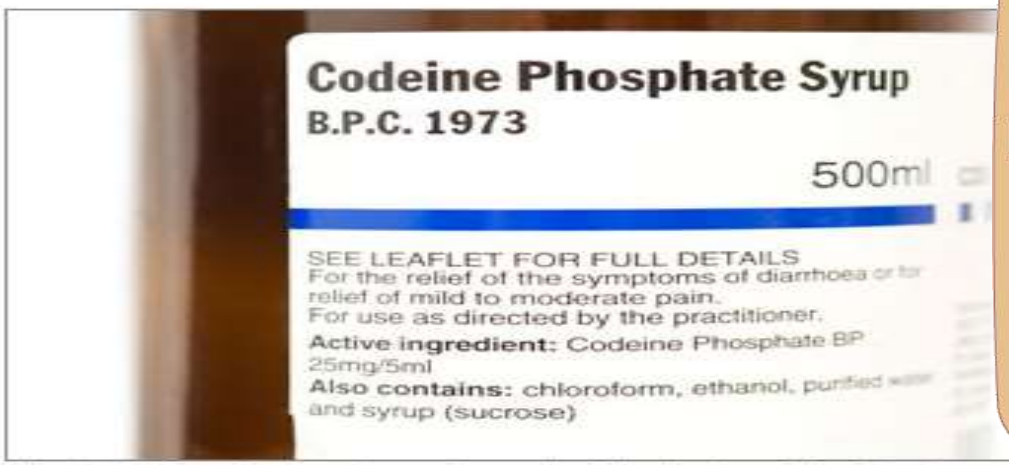


Article 31 PhV referral procedures

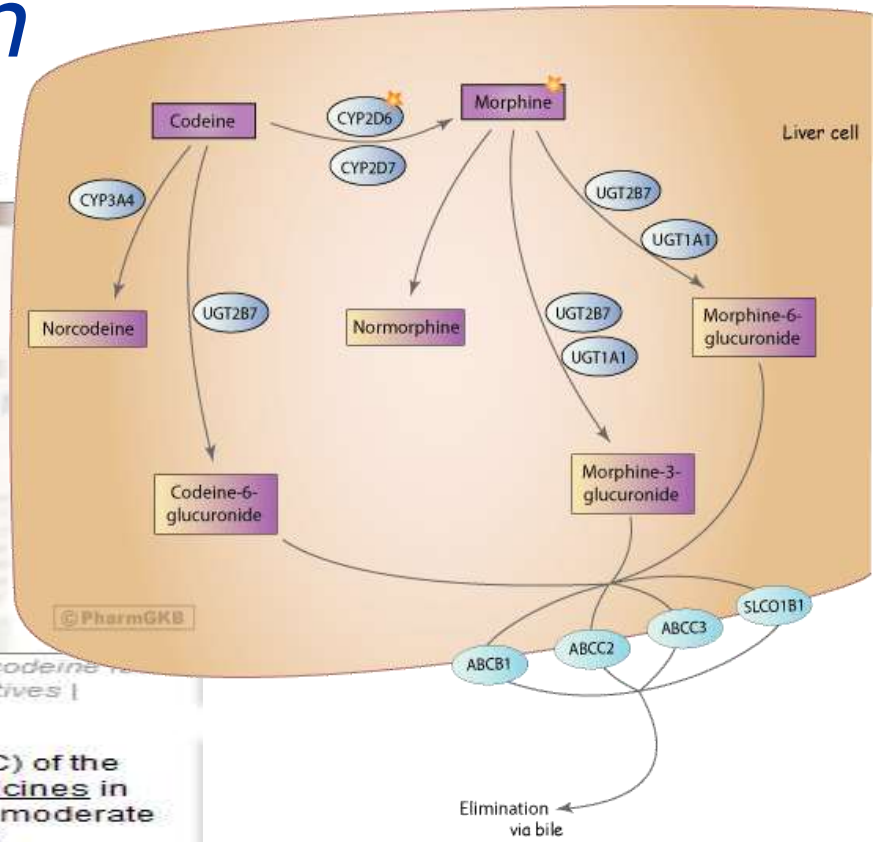
- Almitrine (FR)
- Codeine – analgesia paediatric (UK)
- Diclofenac (UK)
- Hydroxyethyl Starch (DE)
- Short Acting Beta Agonists (HU)
- Combined Hormonal Contraceptives (FR)
- Nicotinic acid (DE)
- Diacerein (FR)
- Zolpidem (IT)

- Domperidone (BE)
- Renin Angiotensin System agents (IT)
- Bromocriptine (FR)
- Sodium valproate (UK)
- Testosterone (ET)
- Ambroxol/bromhexine (BE)
- Codeine – cough paeds (DE)
- Hydroxyzine (HU)
- Ibuprofen/dexibuprofen (UK)
- Inhaled corticosteroids (EC)

Example of Art 31 - *Codeine for analgesia in children*



The risk of respiratory depression outweighs the benefits of using codeine for moderate pain in children under 12 years as there are safer alternatives | SCIENCE PHOTO LIBRARY



The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has recommended that use of codeine-containing medicines in children be restricted to those aged over 12 years with acute moderate pain that cannot be relieved by other analgesics, for example, paracetamol or ibuprofen.

In addition, codeine should never be used for children under 18 years undergoing tonsillectomy or adenoidectomy to treat obstructive sleep apnoea. The prescribing information will also be updated to contraindicate codeine in conditions associated with impaired breathing.

Example of Art 31 *Domperidone and CVS risk*

Cardiac safety reviewed by PRAC after data accrued

Large pharmaco-epdemiological study - increased risk of sudden cardiac death in over 60s

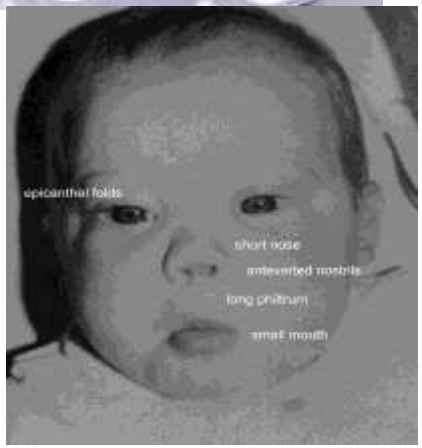
Restriction of indication to nausea and vomiting, dose restriction and duration limit

Data on efficacy in children to be generated

Legal classification a matter for MS

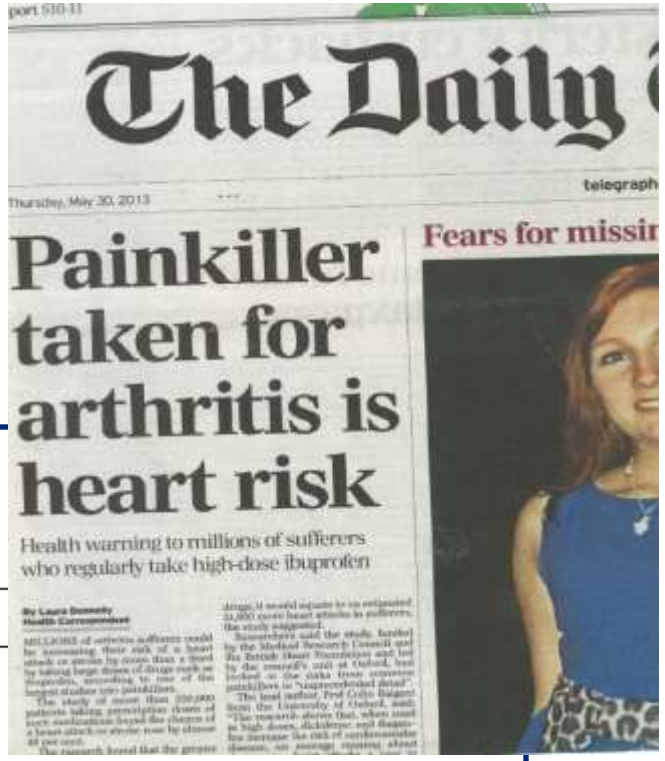
Example of Art 31 - *Sodium valproate in pregnancy and developmental disorders*

- Indications in EU - epilepsy, bipolar disorder & migraine
- Use in women of child-bearing potential varies across Europe
- New evidence of persistent developmental risk following exposure in pregnancy
- Patient representatives contributed to design of risk minimisation measures



Example of Art 31

Diclofenac & CVS risk



The Daily

telegraph

Thursday, May 30, 2013

Painkiller taken for arthritis is heart risk

Health warning to millions of sufferers who regularly take high-dose ibuprofen

Fears for missi

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]

Availability of more robust evidence

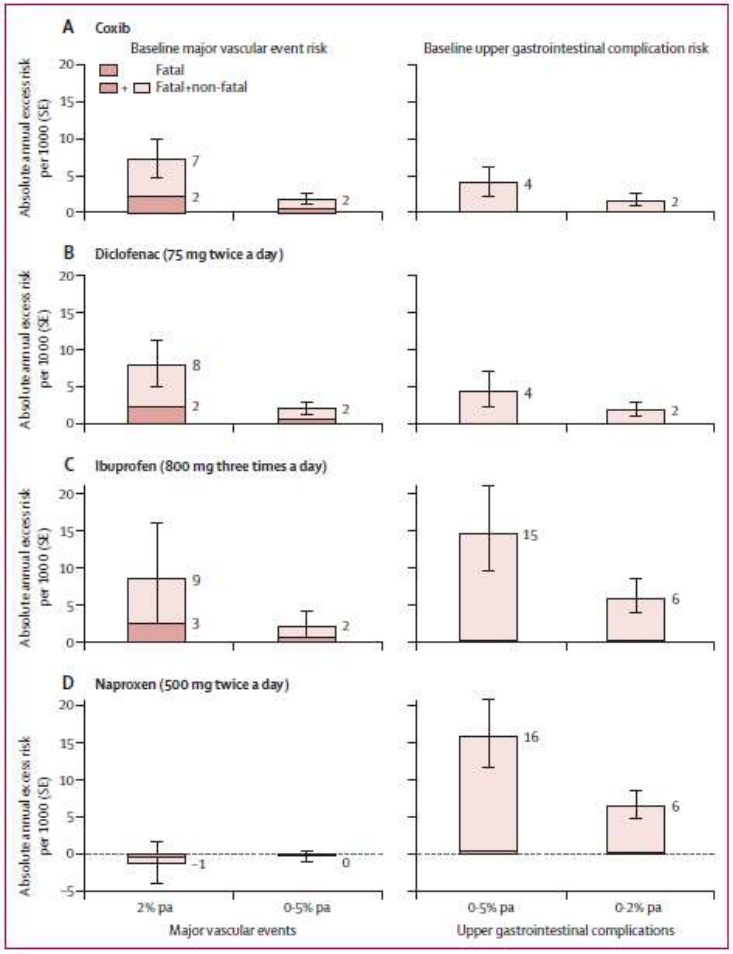
Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

*Coxib and traditional NSAID Trialists' (CNT) Collaboration**

Summary

Background The vascular and gastrointestinal effects of non-steroidal anti-inflammatory drugs (NS selective COX-2 inhibitors (coxibs) and traditional non-steroidal anti-inflammatory drugs (tNSAI characterised, particularly in patients at increased risk of vascular disease. We aimed to provide through meta-analyses of randomised trials.

Methods We undertook meta-analyses of 280 trials of NSAIDs versus placebo (124 513 participant years) and 474 trials of one NSAID versus another NSAID (229 296 participants, 165 456 person- outcomes were major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascu coronary events (non-fatal myocardial infarction or coronary death); stroke; mortality; heart fa gastrointestinal complications (perforation, obstruction, or bleed).



Ibuprofen- and dexibuprofen-containing medicines

Summary | Key facts | All documents

PRAC recommends updating advice on use of high-dose ibuprofen

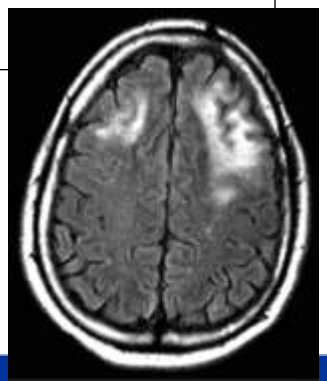
Review confirms small increased cardiovascular risk with daily doses at or above 2,400 mg

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review confirming a small increase in the risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2,400 mg per day). The review clarifies that the risk with high-dose ibuprofen is similar to the risk seen with some other non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors and diclofenac.

No increase in cardiovascular risk is seen with ibuprofen at doses up to 1,200 mg per day, which is the highest dose generally used for over-the-counter (OTC) preparations taken by mouth in the European Union (EU).

Ongoing referral procedures

Procedure name	Article	Started	Issue
Inhaled corticosteroids in COPD	31PhV	May-15	Risk of pneumonia
Tysabri (natalizumab)	20PhV	May-15	Accumulating data on risk of PML



Reflection on PhVig referrals

Use of a wide range of evidence sources

Range of actions proportionate to risk, taking into account therapeutic context

Prompt decisions- from 1 to 16 months, average 7 months

Referrals involving established medicines prominent

Patient engagement adds important value

Effective committee interfaces

Communication and transparency

PRAC considers risk of severe allergic reactions with ambroxol- and bromhexine-containing medicines to be small

Press release

12/01/2015

PRAC considers risk of severe allergic reactions with ambroxol- and bromhexine-containing medicines to be small

Update of product information is recommended

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of medicines containing ambroxol or bromhexine. This follows concerns over the risk of allergic reactions with these medicines, which are widely used as expectorants (to help clear mucus from the airways).

The PRAC considers that the risk of allergic reactions is small, but has recommended that the product information for these medicines should be updated with further

Related information

- Ambroxol and bromhexine-containing medicines
- Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 6 -9 January 2015 (12/01/2015)

Contact point:

Monika Benstetter
Tel. +44 (0)20 3660 8427
E-mail: press@ema.europa.eu

Stakeholder involvement - Patients and Healthcare Professionals

- Interaction with patient and healthcare professional organisations during formal reviews
- Contribute to drafting of communications
- Input to setting goals for risk minimisation measures and decisions on effectiveness of RMMs

Communicating safety messages

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

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

Categories

All Headlines
Lifestyle/exercise (729)
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Genetics/stem cells (303)
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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

Key referral challenges for PRAC

- Optimising Committee interfaces
- Timely access to best evidence
- Collaboration with stakeholders including academia
- Monitoring effectiveness of risk minimisation

Optimising committee interfaces

Resourceful use of tools
Early dialogue

Use of Inter-Committee
Scientific Advisory groups

PRAC

CMDh

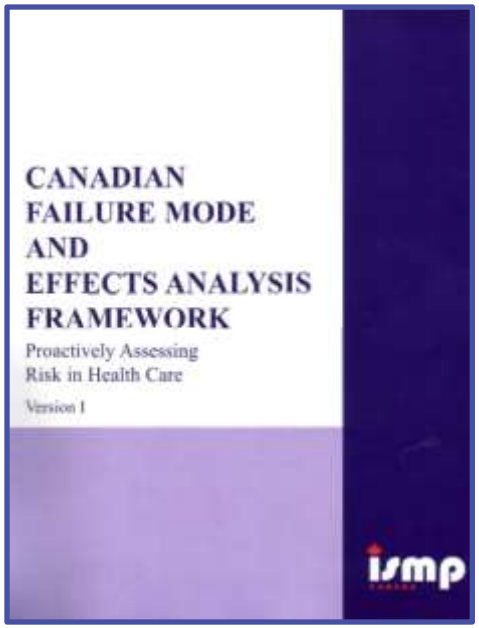
CHMP

Recommendations

EU Member States | **European Commission**

Incorporating new methodologies & best evidence

PROTECT



imi

European network of centres to promote access to European pharmacoepidemiological resources

Improve research standards

Increase independence and transparency in research

Stimulate collaboration and exchange of information and experience

Monitoring effectiveness of RMMs

- Systematic approach making best use of latest available guidance and methodologies
- Routine application in scientific advice to marketing authorisation holders, PBRERs, benefit risk reviews
- Greater transparency on results of evaluation of RMMs effectiveness to healthcare professionals & organisations

Moving forward

Opportunities identified by EMA from experience:

- ✓ ***Support to stakeholders*** *from the outset*
- ✓ ***Support to network***
  - ✓ *(co-)rapporteurs and Committee members*
- ✓ ***Focused reviews*** *(clear and targeted scopes)*
- ✓ ***Streamlined templates***

Support to stakeholders from outset -1

- EMA team appointed from the start
- Earlier notification
  - To **QPPVs** identified in the **Article 57 database** of the start of pharmacovigilance referral procedures referred to the PRAC
  - **Process improvement step** following interaction with stakeholders - see also http://www.ema.europa.eu/docs/en_GB/document_library/Annex_to_CHMP_highlights/2015/04/WC500185350.pdf
  - Notifications provided **by Wednesday** before the PRAC meeting if **available**, for **information** only
  - Keep **Article 57** database up-to-date

Support to stakeholders from outset -2

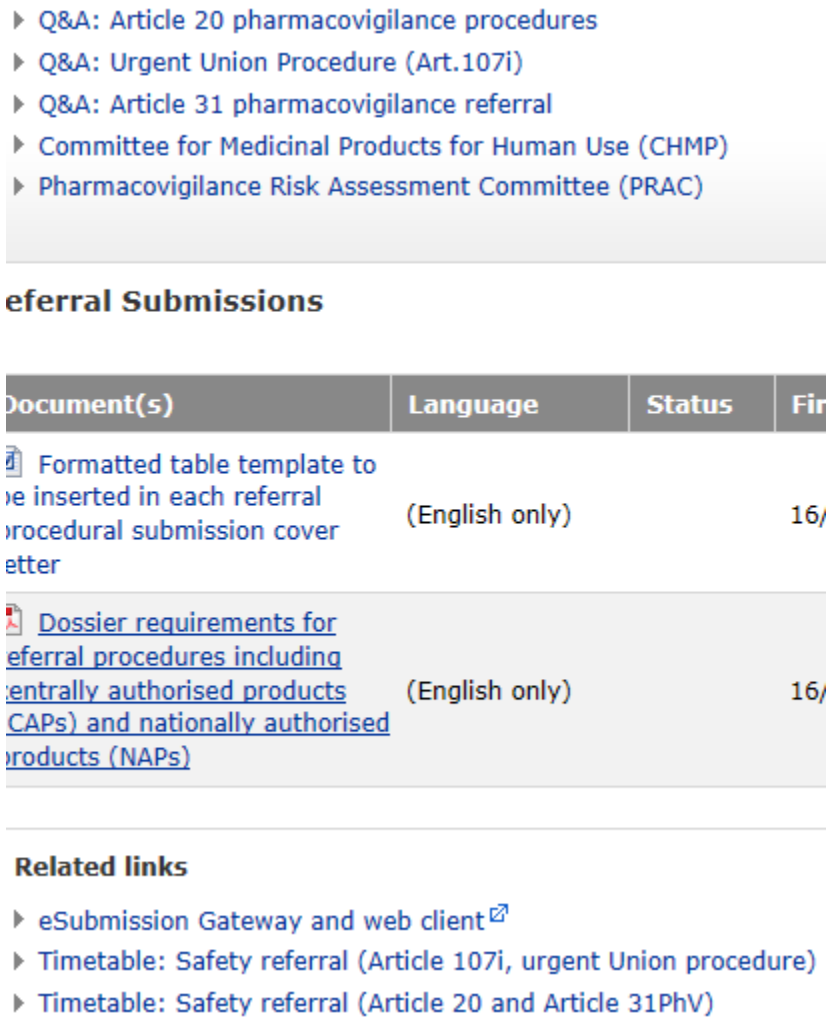
Updated advice on EMA website

Q&As for all different PhV procedures (Articles 20, 31, 107i)

eSubmissions via gateway in modular format, e.g. M1-M5

Dedicated contact from referral team and for technical support

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0



- Q&A: Article 20 pharmacovigilance procedures
- Q&A: Urgent Union Procedure (Art.107i)
- Q&A: Article 31 pharmacovigilance referral
- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)

eferral Submissions

Document(s)	Language	Status	Fi
Formatted table template to e inserted in each referral rocedural submission cover etter	(English only)		16/
Dossier requirements for eferral procedures including entrally authorised products CAPs) and nationally authorised roducts (NAPs)	(English only)		16/

Related links

- eSubmission Gateway and web client
- Timetable: Safety referral (Article 107i, urgent Union procedure)
- Timetable: Safety referral (Article 20 and Article 31PhV)

Support to network (Co)rapporteurs & Committee members -1

- Early dialogue
- Scope of referral defined/confirmed at PRAC
- New process for rapporteur appointment

Article	Rapporteur	Co-rapporteur
Article 20 of Regulation (EC) No 726/2004	Priority given to the PRAC rapporteur already identified for the CAP(s)[1]	Priority given to the PRAC co-rapporteur already identified for the CAP(s)1
Article 31 of Directive 2001/83/EC	Open to all PRAC members[2]	Open to all PRAC members
Article 107i of Directive 2001/83/EC	Open to all PRAC members[2]	Open to all PRAC members

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004163.pdf

[1] If more than one CAP is involved, the PRAC referral (co-) rapporteur shall be appointed from amongst the PRAC (co-) rapporteurs for the CAPs involved in the referral.
Note: In case the referral procedure is not product specific, the PRAC Chairman may advise to open Rapporteurship to all PRAC members

[2] The rapporteurship is not open to the Member State who triggered the referral. The triggering Member State may bid for Co-Rapporteurship but will not be appointed by default.

Support to network (Co)rapporteurs Committee members -2

- Regular support to ensure procedural excellence
- Regulatory/procedural advice as needed
- Additional data sources to enrich the review
- Interactions with working parties, other Committees
- Early consideration of consultations (e.g. patients, public health professionals, healthcare organisations, other experts)

Focused reviews

- Focused list of questions (LoQ)/list of outstanding issues (LoOI)
- Explore alternatives to gathering administrative data from stakeholders
- Explore data from other sources available to Committees
- Best use of expertise available, consultations and timing
- Timetable to strike a balance between data needed, timelines for responses and urgency of the matter

Streamlined templates

- Simplify process
- Concept of 'living document' for rapporteurs' assessment report
  - Improve communication with stakeholders
  - Improve predictability and visibility of changes with updated reports
- Strengthening output => quality guidance and documentation supporting the output

Upcoming initiatives

- Building on increase in "know-how" of the process from experience with the revised process and feedback from stakeholders and the EU network
- Encouraging marketing authorisation holders to work together eg DHPCs, PASS studies
- Public hearings
  - Introduced by PhV legislation, held by PRAC where the urgency of the matter permits
  - Public consultation on rules of procedure document took place in 2014 and revisions under discussion

Stakeholder collaboration - Industry
Article 22a of Directive 2010/84/EU

"If the same concerns apply to more than one medicinal product, the national competent authority shall, after consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct ***a joint post-authorisation safety study****"*

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 information public
- Part of overall assessment
- Declaration of Interests
- Recorded / video streamed
- Language a challenge

ORGANISATION

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

Summary

- Over the first 3 years the PRAC's key focus has been delivering the public health objectives
- PRAC's scientific work on referrals is central to implementation of EU Pharmacovigilance legislation
- Experience demonstrates PRAC's capability for robust decisions made to rigorous timescales
- Major strides forward in transparency and stakeholder involvement
- Now we are moving from compliance to optimisation with initiatives based on engagement, effectiveness, and efficiency

Dankeschön!

Questions