European Risk Management Planning

Update of PRAC activities.

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President of the International Society of Pharmacovigilance
Vice President of CIOMS
PRAC Member

Burden of Adverse Drug Reactions in EU

- 5% of all hospital admissions,
- 5% of all hospital patients,
- ADRs are the 5th cause of hospital death,
- 197 000 deaths per year caused by ADRs,
- High percentage of ADRs are preventable,
- Average cost of an ADR : 2 250 €,
- EU Societal cost of ADRs Euro 79 Billion / year.

- Even a small improvement in PV system will have a major impact on public health and society.

Objectives of Pharmacovigilance

- Protect and promote public health
- Post-marketing surveillance of products
  - Reduces uncertainty regarding known risks
  - Generates new information regarding unknown risks
- Health effects of pharmacovigilance are achieved through (regulatory) actions informed by newly generated information in the post-marketing setting

Why do we need Pharmacovigilance?

Preclinical studies are difficult to extrapolate to humans because:

- Small number of animals and limited duration of the observation,
- Pharmacokinetic differences between animals and humans,
- Some events can not be observed with animals (hallucinations…),
- Difficulty to reproduce human disease on animals.

Why do we need Pharmacovigilance?

In clinical trials:

- Main purpose: Therapeutic efficacy of the drug in the targeted indication,
- Administration to a standardized population (not representative of the overall population),
- Small size of the study population (Difficult to observe rare effects),
- Very few or no data on long term usage (cancer, dementia…),

Right drug at the right dose at the right regimen to the right patient

Number of subjects per Clinical Trials (CT)

Medicines:	Number of subjects per CT:
Chemical drugs	1000-5000
Biologic products	100-1000
Biosimilars	100-500

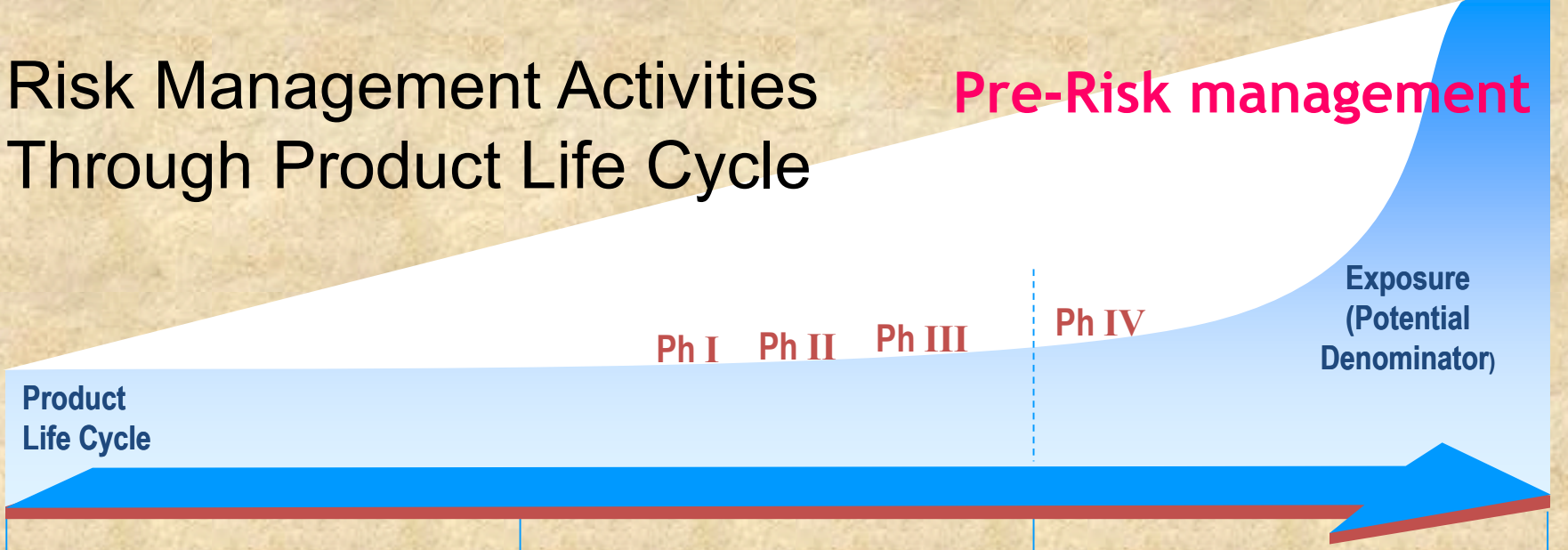
Drug information journal

Why do we need Pharmacovigilance?

In the post-marketing:

- The product will be used in different conditions, at different doses and with different regimen,
- Large number of individuals,
- New safety data on long term usage,
- Be used in patients with multiple concurrent conditions and on multiple concurrent medications.

Risk Management Activities Through Product Life Cycle



Pre-Approval

- Efficacy
- Potential Safety Signals
- Development of target label (LAD)
- Epidemiological studies (indication)

Approval

Passive Pharmacovigilance

- Signal detection
- Alert
- Post-hoc Investigation
- Post Approval Labeling Revision

Consequences

- To rely solely on spontaneous reporting may lead to extreme regulatory decisions and reduces benefits to target population
  - Product withdrawal
  - Delay or refusal of marketing

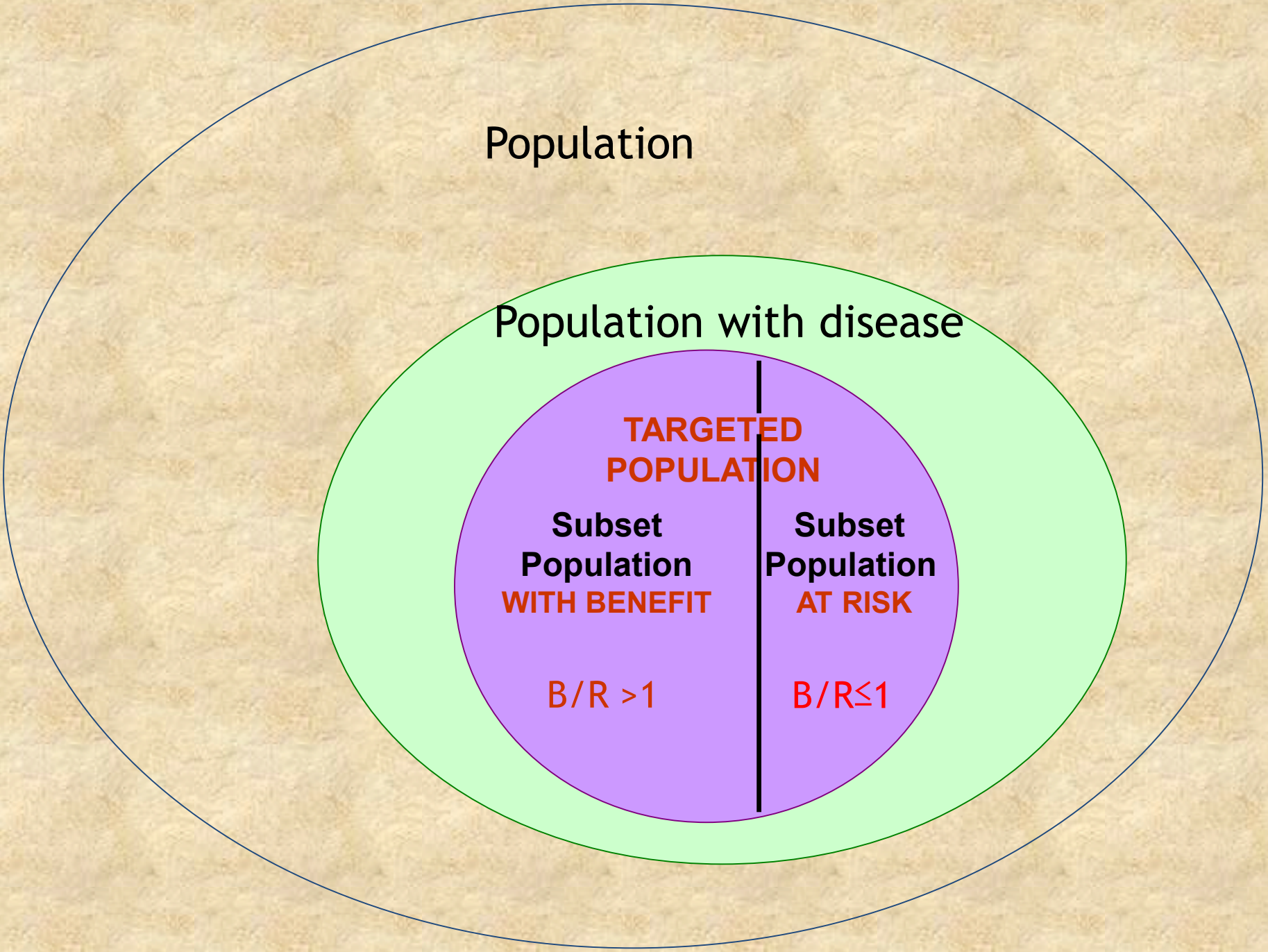
- These extreme actions should only be used when the benefit/risk ratio is either unacceptable or non-manageable

Scope of Pharmacovigilance

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO)

Pharmacovigilance in this presentation goes beyond this

Management of the benefits and risks of medicines on the market


Population
Population with disease
TARGETED POPULATION
Subset Population WITH BENEFIT
Subset Population AT RISK
B/R >1
B/R≤1

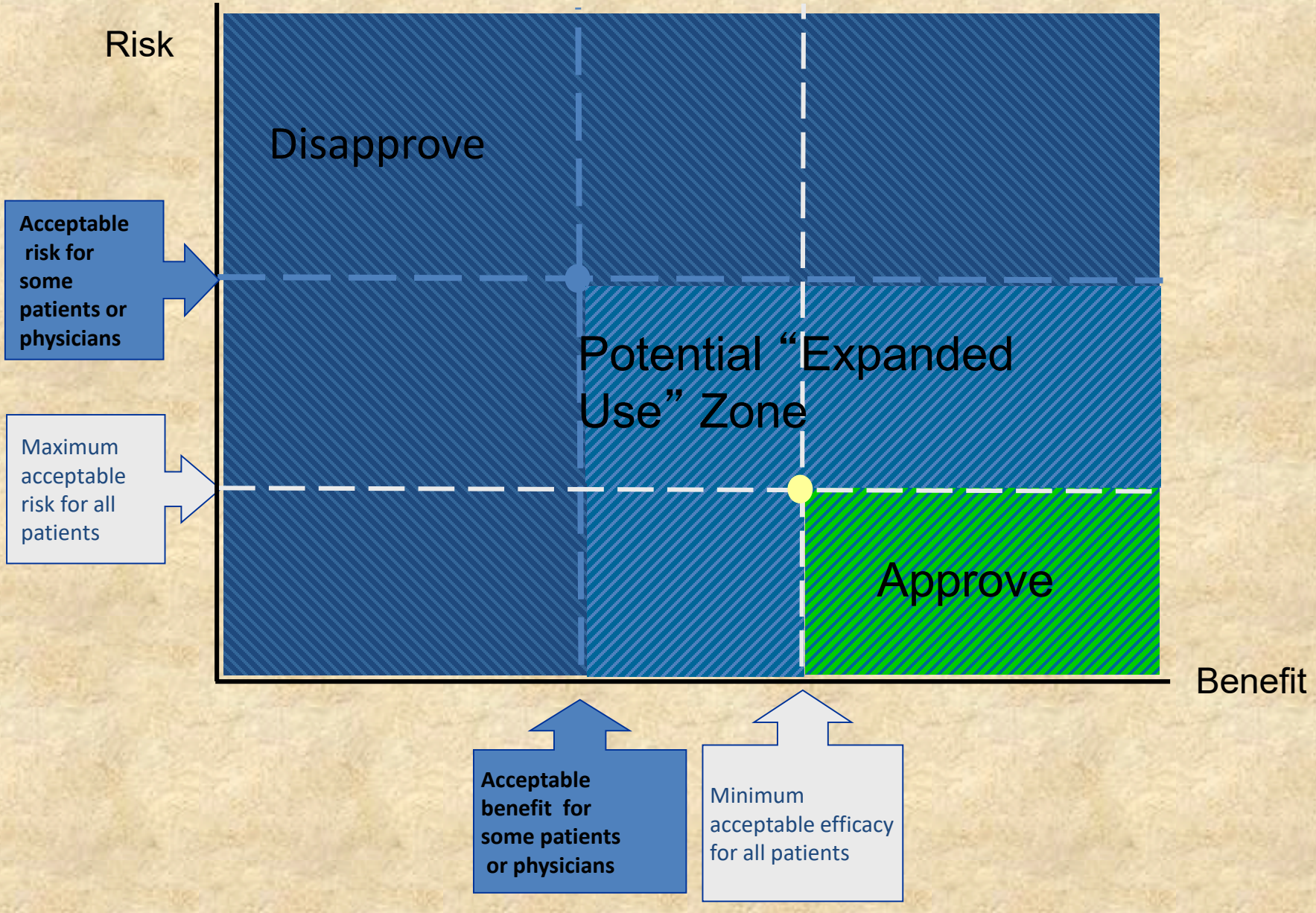
Risk management perspective

Efficacy for all patients
with acceptable risk for all patients

Risk management

Efficacy for a subset population of patients

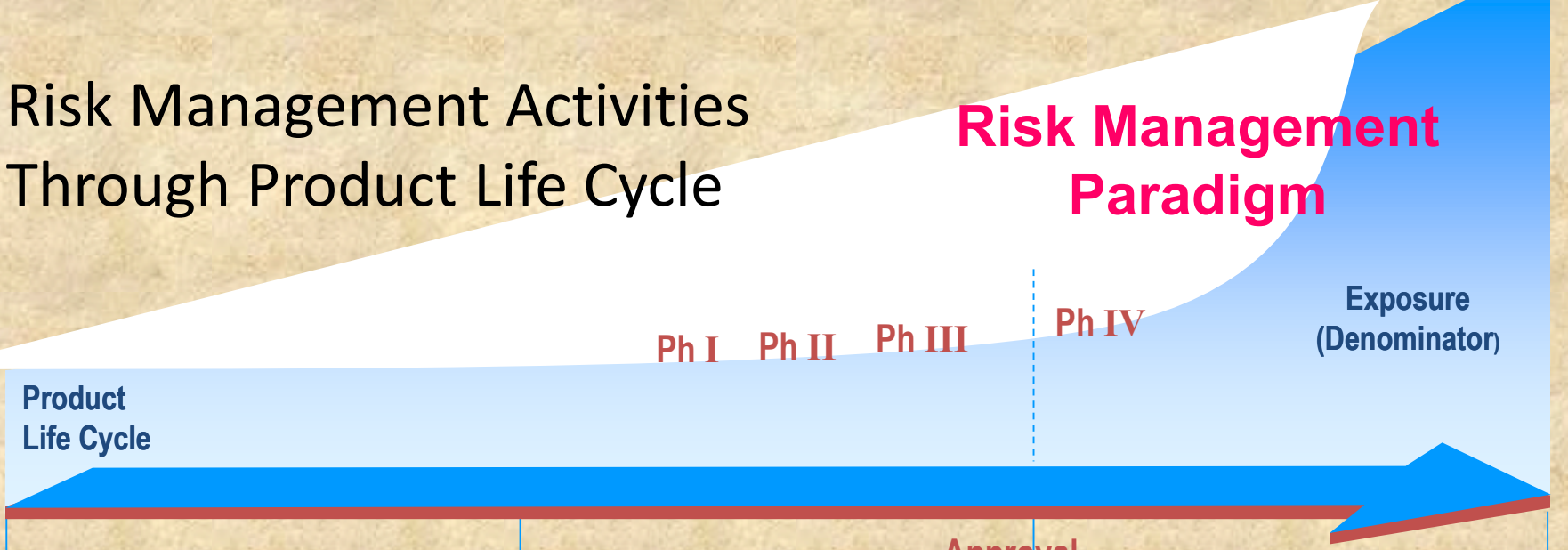
with acceptable risk for this subset population


Risk
Disapprove
Acceptable risk for some patients or physicians
Potential "Expanded Use" Zone
Maximum acceptable risk for all patients
Approve
Benefit
Acceptable benefit for some patients or physicians
Minimum acceptable efficacy for all patients

Strategy

- Proactivity
- Risk AND benefit assessment in real life
- Proportionality (an action should not be more severe than is necessary)
- Impact measure

Risk Management Activities Through Product Life Cycle



Approval

Pre-Approval

- Efficacy
- Potential Safety Signals
- Development of target label (LAD)
- **Develop RM strategies**
- **Epidemiological studies**

Post Marketing PV

- Passive PV
- **Pro-active PV**
  - **Risk Management Plan**
  - **Observational Studies**
  - **Built-in Signal Detection**
  - **Risk Communication**
  - **Post Approval Commitment Studies**

The EU Risk Management Plan

Part I Product(s) Overview

Part II Safety Specification

- **Module SI: Epidemiology of the indication(s) and target population(s)**
- **Module SII: Non-clinical part of the Safety Specification**
- **Module SIII: Clinical trial exposure**
- **Module SIV: Populations not studied in clinical trials**
- **Module SV: Post-Authorisation Experience**
- **Module SVI: Additional EU requirements for the Safety Specification**
- **Module SVII: Identified and potential risks**
- **Module SVIII: Summary of the safety concerns**

Part III Pharmacovigilance Plan

Part IV Plans for post-authorisation efficacy studies

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)

Part VI Summary of the RMP

Part VII Annexes

Part I Product(s) Overview

Part II

Important Identified Risk
Important potential Risk
Important Missing Information

Module SI: Epidemiology of the indication(s) and target population(s)

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Routine PV and other solutions

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Part III Pharmacovigilance Plan

Following the new ENCePP standards

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)

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Part VII Annexes

Solutions for post-marketing safety monitoring

- **Spontaneous reporting:**
  Main safety net to detect new AEs population-wide,

- **Active pharmacovigilance:**
  For important potential risks,

- **Observational studies, registries, large simple trials:**
  Databases or *ad hoc (evaluation of potential risks).*

Observational studies, Large Simple Trials Registries (1)

- For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power.
- Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000 (except vaccines).

Observational studies, Large simple trials registries (2)

It may also be difficult to use clinical trials:

- to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications,
- to identify certain risk factors for a particular adverse event.

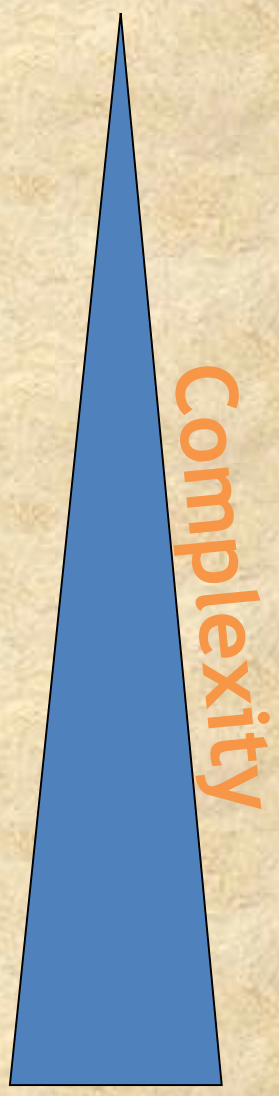
On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials mays be preferable to observational studies.

Registries

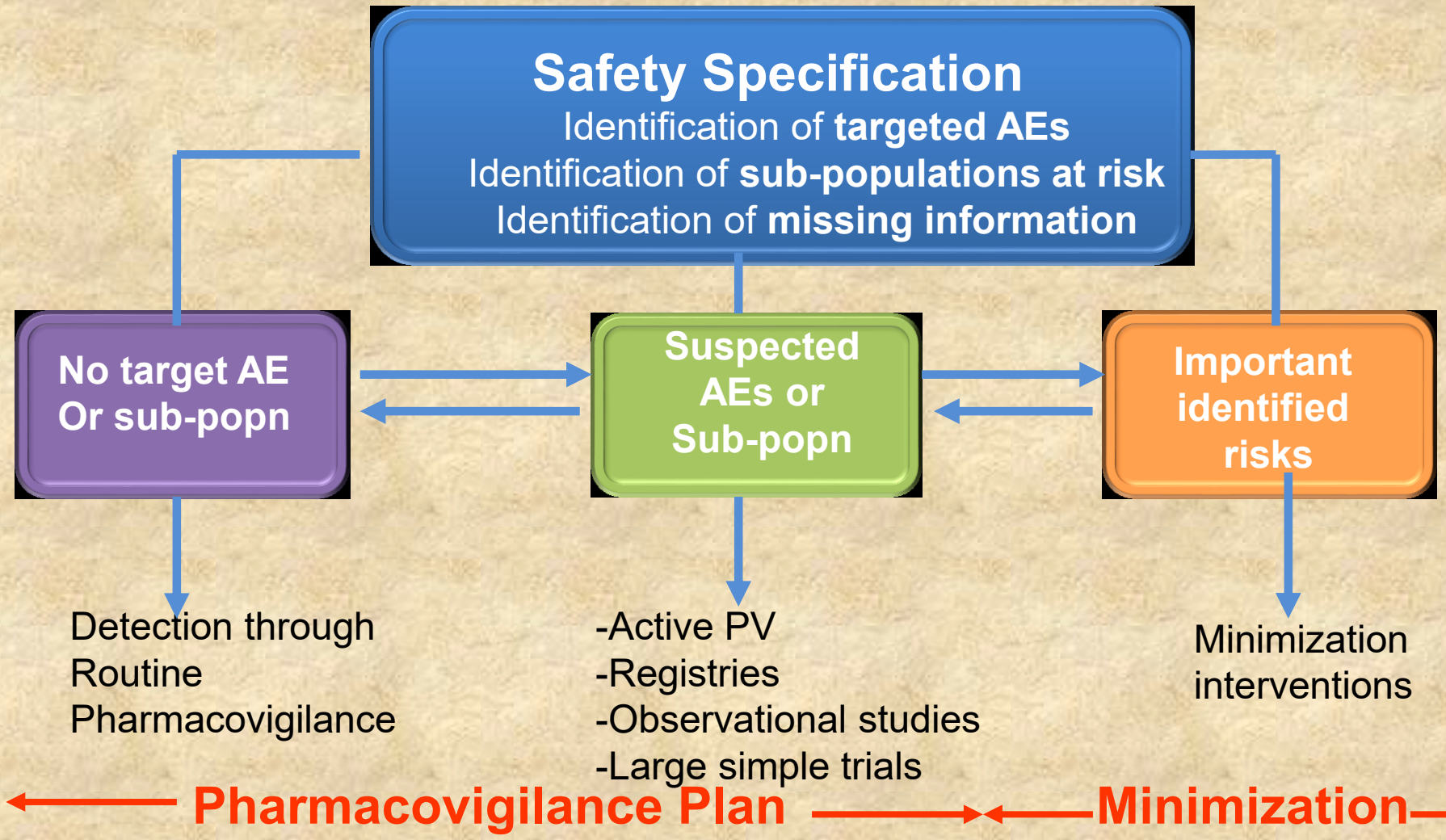
- Small Market, orphan drugs, low prevalence condition, Biologics, etc…
- North America : often associated with controlled prescription program;
- Europe : can be implemented everywhere, especially in country without databases.

Intervention Tools

- Education material to physicians and/or patients
- Medication guide endorsed by health authorities
- Informed consent
- Academic detailing
- Physician authorization (sticker)
  (*e.g. Isotretinoin)*
- Restricted distribution (*e.g. Clozapine)*
- Registries (voluntary or mandatory)



Pharmacoepidemiology Strategy and Tool Box



Key messages

- Working together for continuous improvement of health promotion and protection;
- Delivered:
  - Proactive monitoring
  - Faster safety issue detection
  - Faster warnings to users
  - Increased transparency
  - Engagement of stakeholders
- Renewed focus on: efficiency, process improvement, and simplification

Where we have come from

- Reactive monitoring
- Under-utilisation of structured data collection
- Overlapping roles and responsibilities
- Duplication of effort in efficient use of resource
- Exclusion of patients from safety monitoring
- Low levels of transparency

Example of the EU legislation: the 10 measures.

- ✓ Lists of medicines (29 countries),
- ✓ Authorization requirements,
- ✓ Risk Management Plans,
- ✓ Effectiveness of risk minimization,
- ✓ ADRs reporting,
- ✓ Signal detection,
- ✓ Periodic Safety Update Reports,
- ✓ Decision-making (PRAC),
- ✓ Transparency and communication,
- ✓ Coordination of inspections /Pharmacovigilance Audit.

PRAC

- The Agency has seven scientific committees that carry out the scientific evaluation of applications from pharmaceutical companies.
  - Committee for Medicinal Products for Human Use (CHMP)
  - ***Pharmacovigilance Risk Assessment Committee (PRAC)***
  - Committee for Medicinal Products for Veterinary Use (CVMP)
  - Committee for Orphan Medicinal Products (COMP)
  - Committee on Herbal Medicinal Products (HMPC)
  - Paediatric Committee (PDCO)
  - Committee for Advanced Therapies (CAT)

PRAC mandate

- 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 are the different procedures the PRAC is involved in?

- Assessment of signals relating to medicines marketed in the EU,
- Assessment of any urgent/non urgent safety union procedures (referrals) triggered due to safety concerns identified in medicines authorised in more than one MS,
- Assessment of medicines' risk management plans,
- Assessment of non-interventional safety study protocols and study reports,
- Periodic Safety Update Report (PSUR) single assessment where at least one of the Marketing Authorisations (MAs) has been granted in accordance with the centralised procedure,
- Establishment of a list of EU Reference Dates (EURD) and frequency of submission of PSURs,
- Inspections.

What are referral procedures? (1)

- A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines.
- In a referral, the European Medicines Agency is requested to conduct, on behalf of the European Union, a scientific assessment of a particular medicine or class of medicines.
- The medicine, or the class or medicines, is ‘referred’ to the PRAC, so that the committee can make a recommendation for a harmonised position across the European Union.

What are referral procedures? (2)

- There are a number of reasons why a referral may be started, ranging from concerns over the safety of a class of medicine to disagreements among Member States on the use of the medicine
- At the end of the referral, the Committee makes a recommendation, and the European Commission issues a decision to all Member States reflecting the measures to take to implement the PRAC recommendation.

Safety Issues	
Article 107i procedures	This type of procedure is triggered when a Member State or the European Commission consider that urgent action is necessary because of a **safety issue**. Situations that fall under this procedure include consideration for suspension or revocation of the marketing authorisation for a medicine, the prohibition of supply of a medicine or major changes to the marketing authorisation such as deletion of indications, reduction of the recommended dose or new contraindications. The procedure is also applicable in case of a safety issue with a class of medicines.
Safety, quality, manufacturing or efficacy issues	
Article 20 procedures	This type of procedure is triggered for medicines that have been authorised via the centralised procedure in case of **manufacturing or safety** issues.
Article 31 referrals	This type of referral is triggered when the interest of the Community is involved, following concerns relating to the **quality, safety or efficacy** of a medicine or a class of medicines.

PRAC members

Appointed by each Member State:

- 1 member + 1 alternate
- **28** + EEA countries non voting members

Appointed by the European Commission following a public call for expressions of interest:

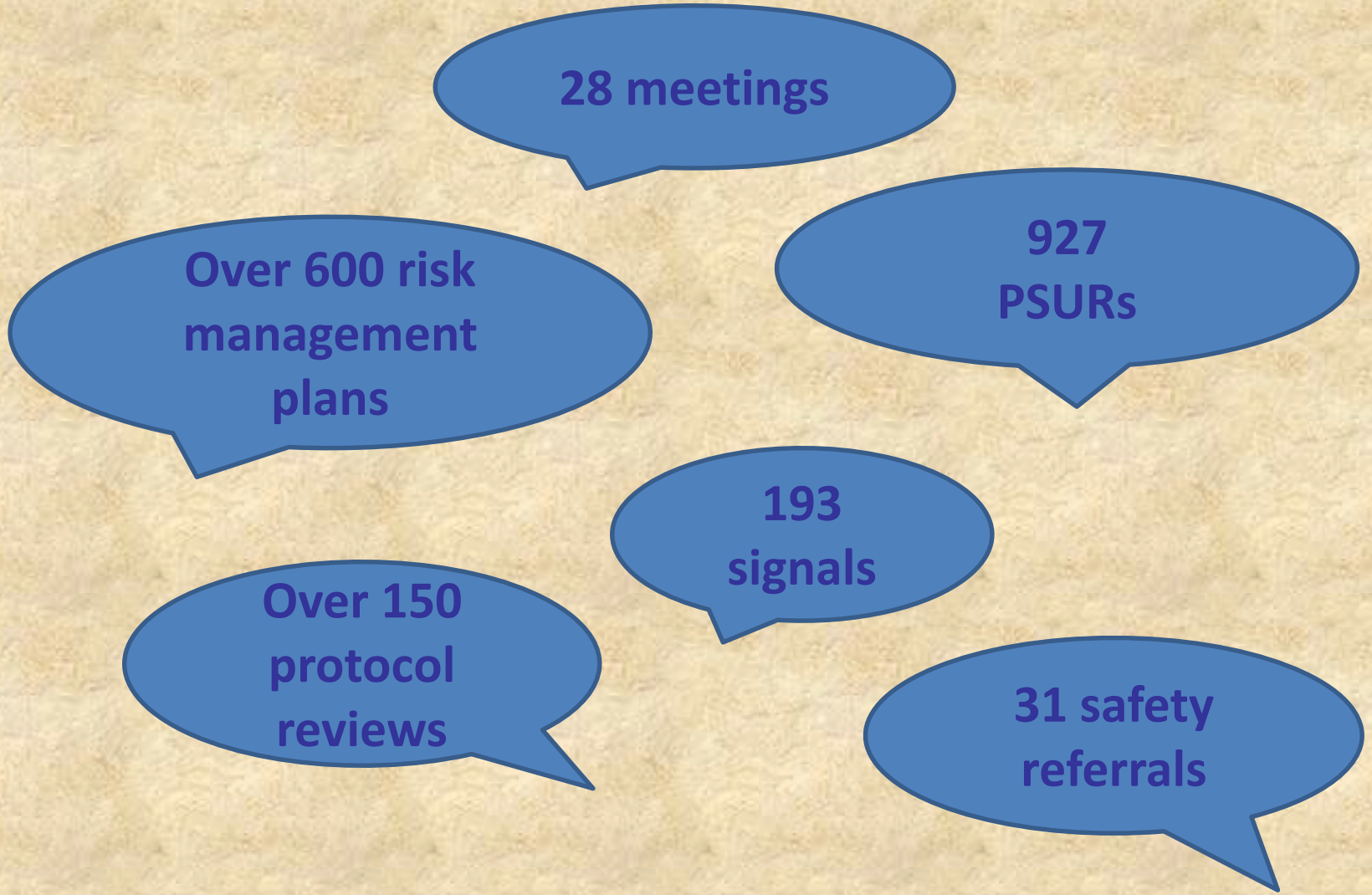
- *1 patient organisations[1] rep + alternate*
- *1 healthcare professionals[1] rep + alternate*
- 6 members to ensure relevant expertise available

[1] *Criteria for involvement in EMA activities*

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

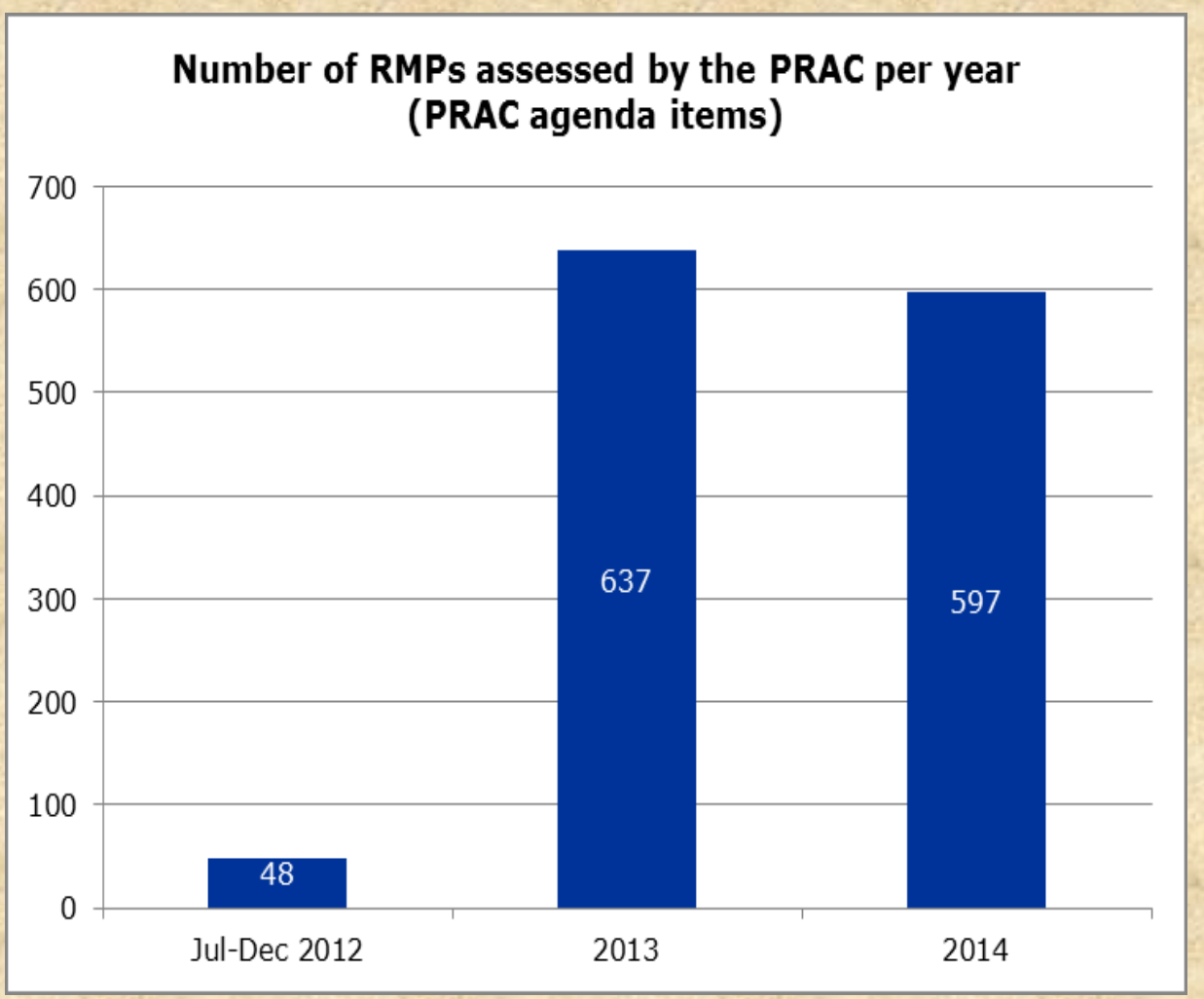
Overall PRAC activities



Risk Management planning

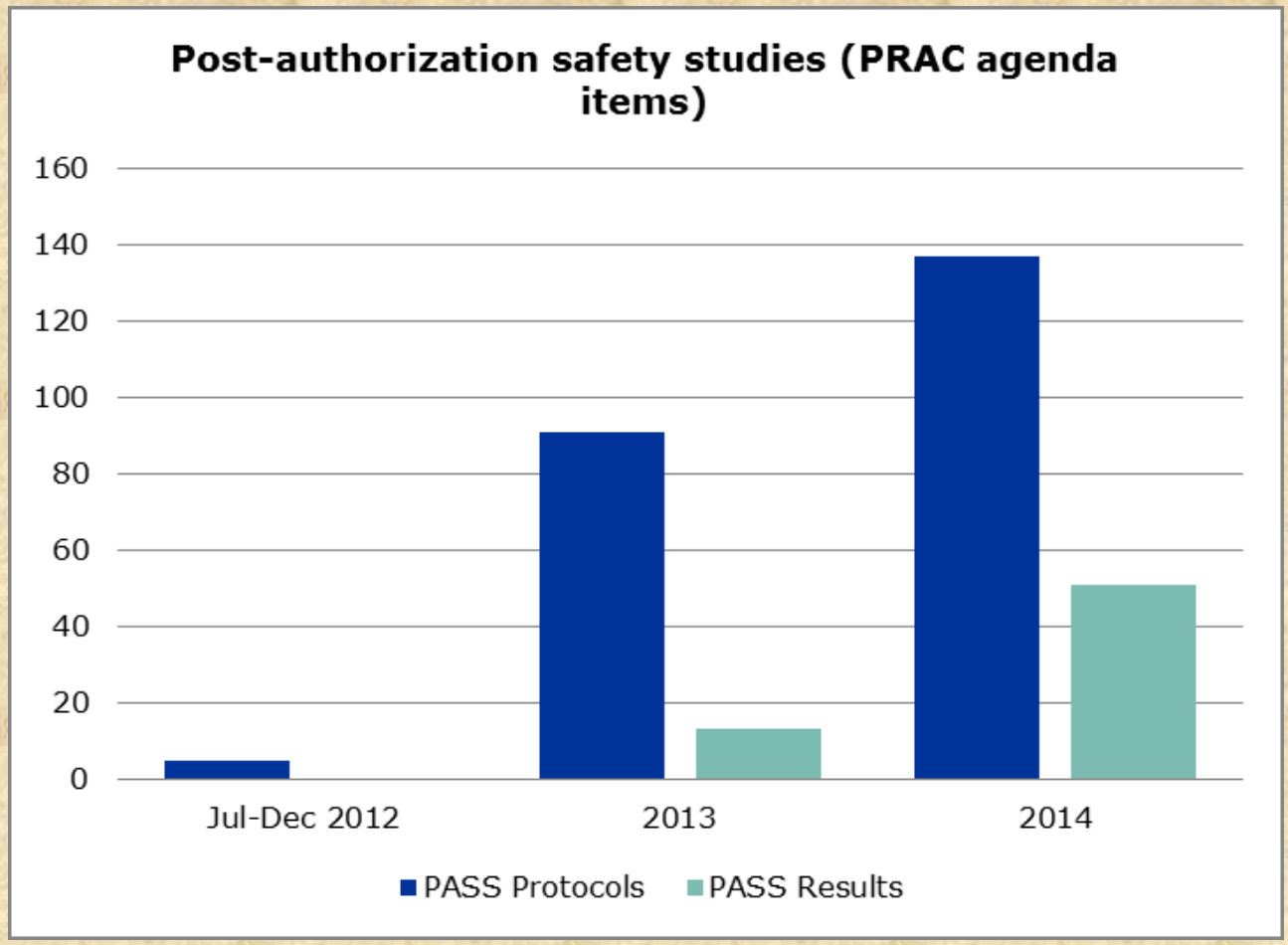
Planning of data collection and risk minimisation

supports protection and innovation



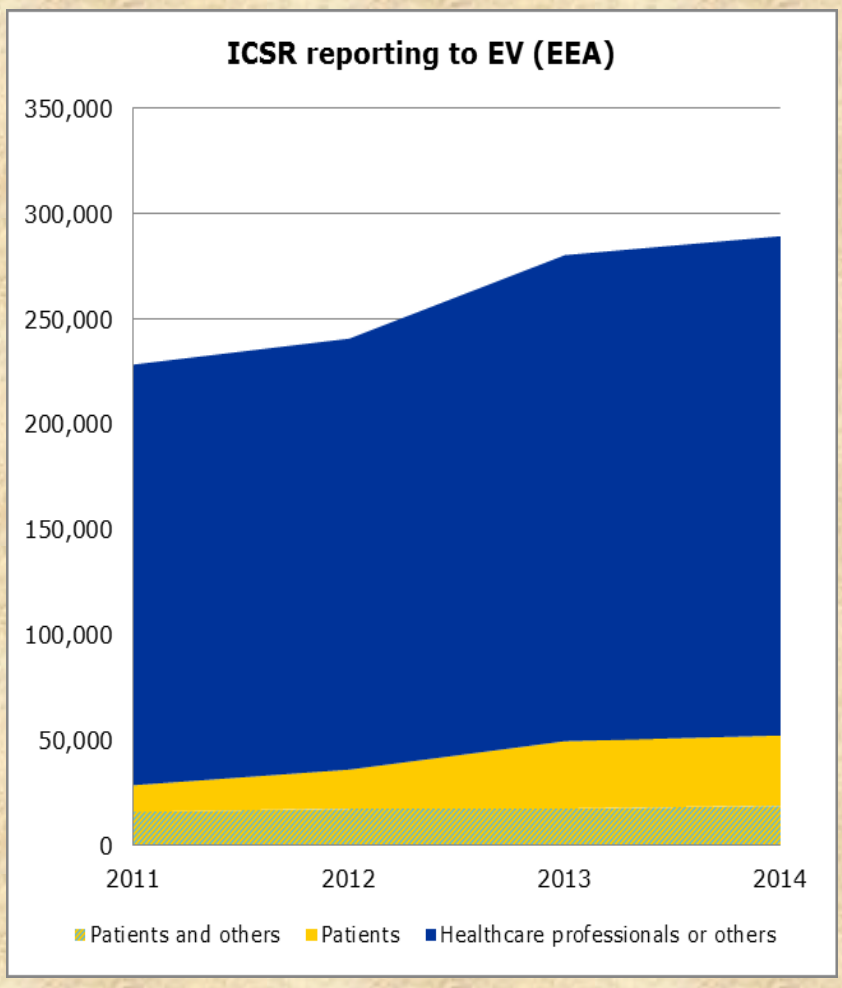
Post-authorisation studies

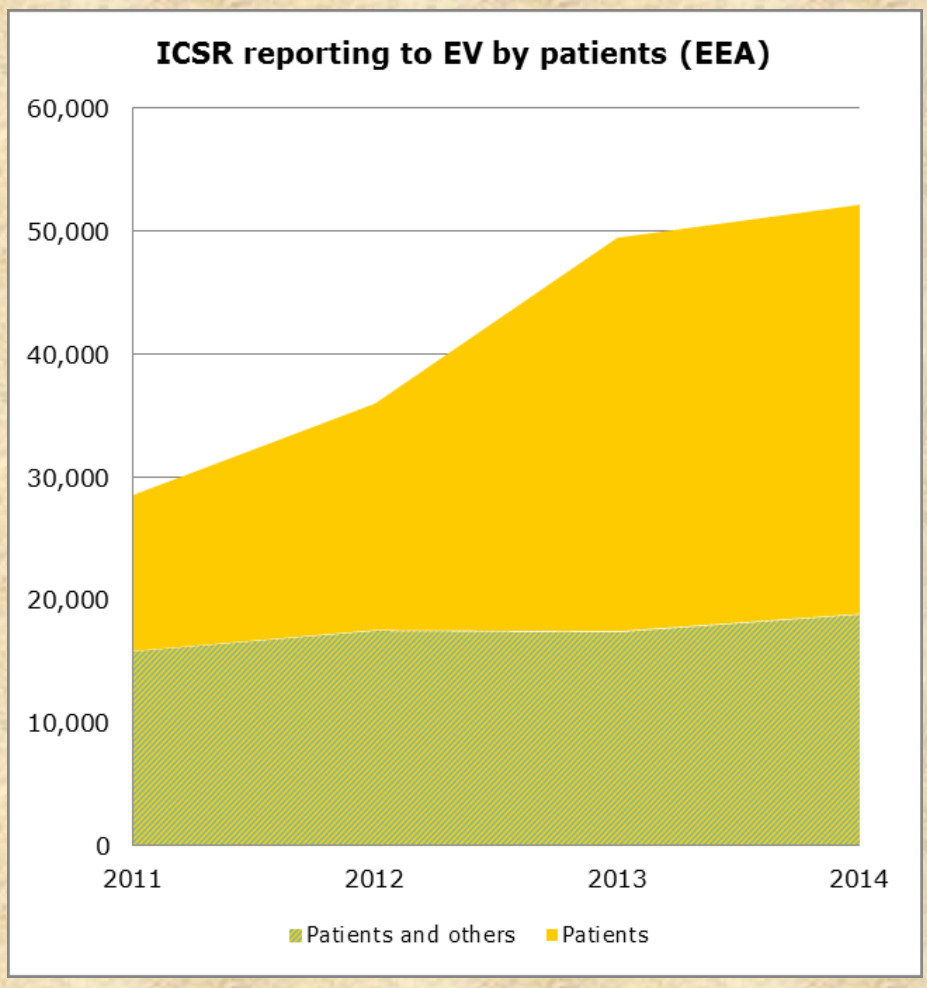
better planned and better scrutinised



Reporting of suspected side effects

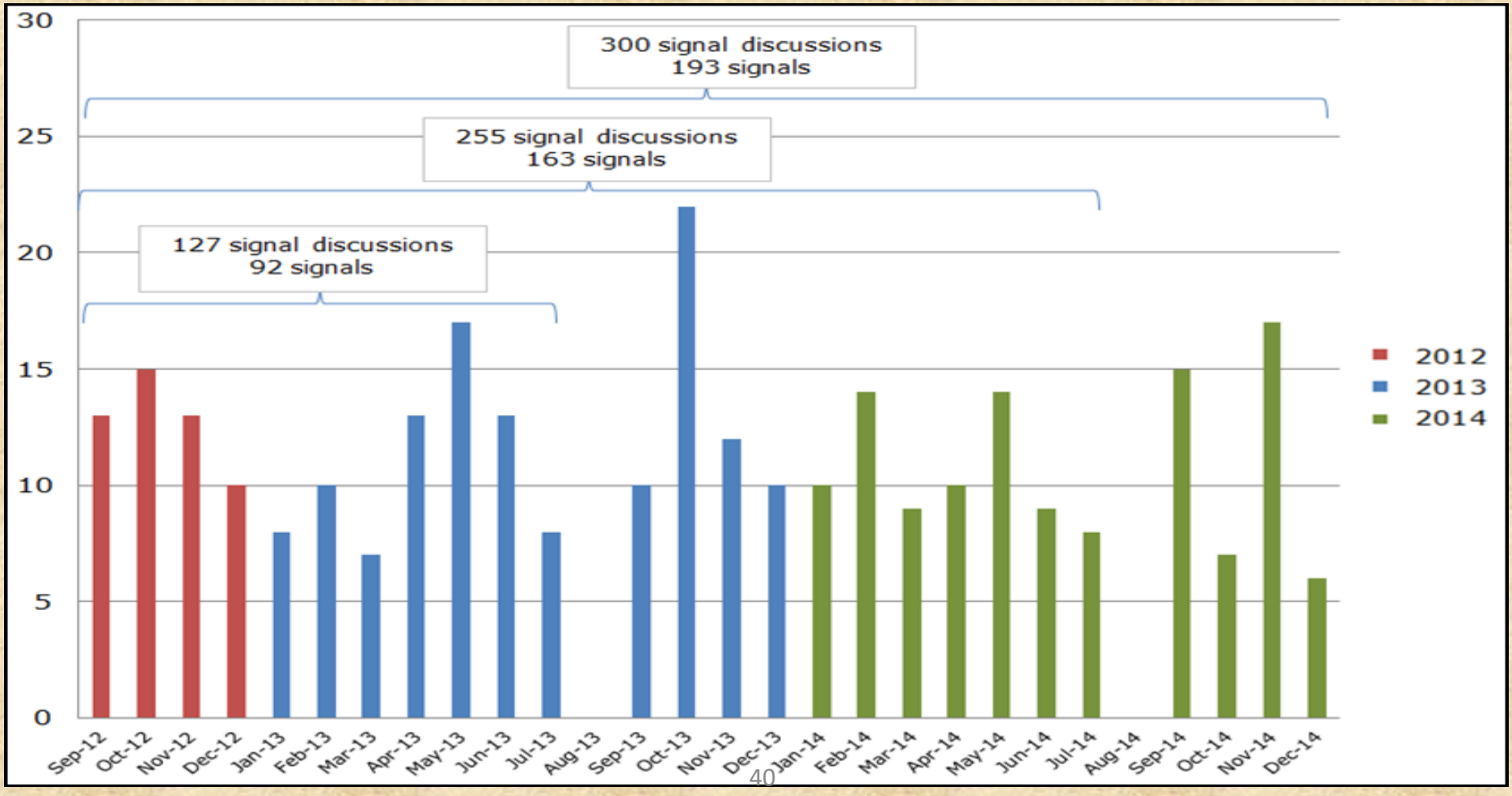
PRAC advice on additional monitoring and reporting forms





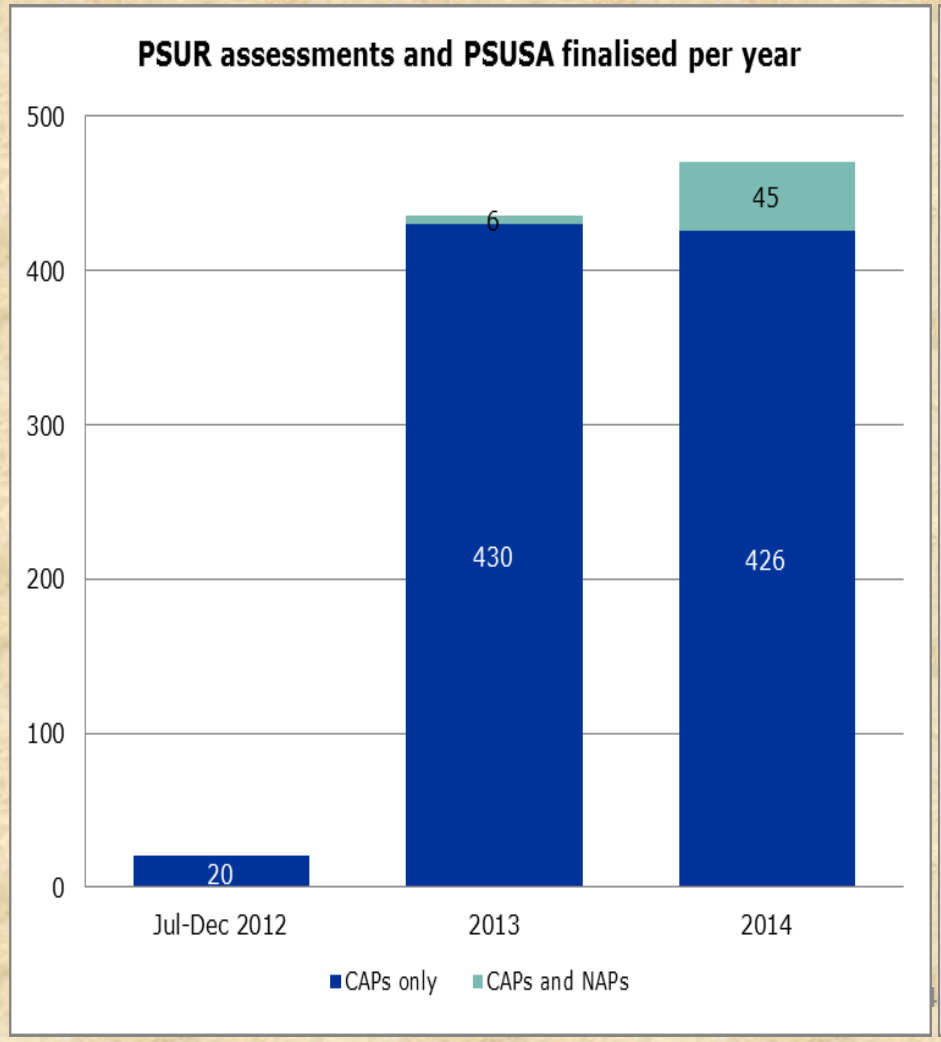
Safety signals at PRAC

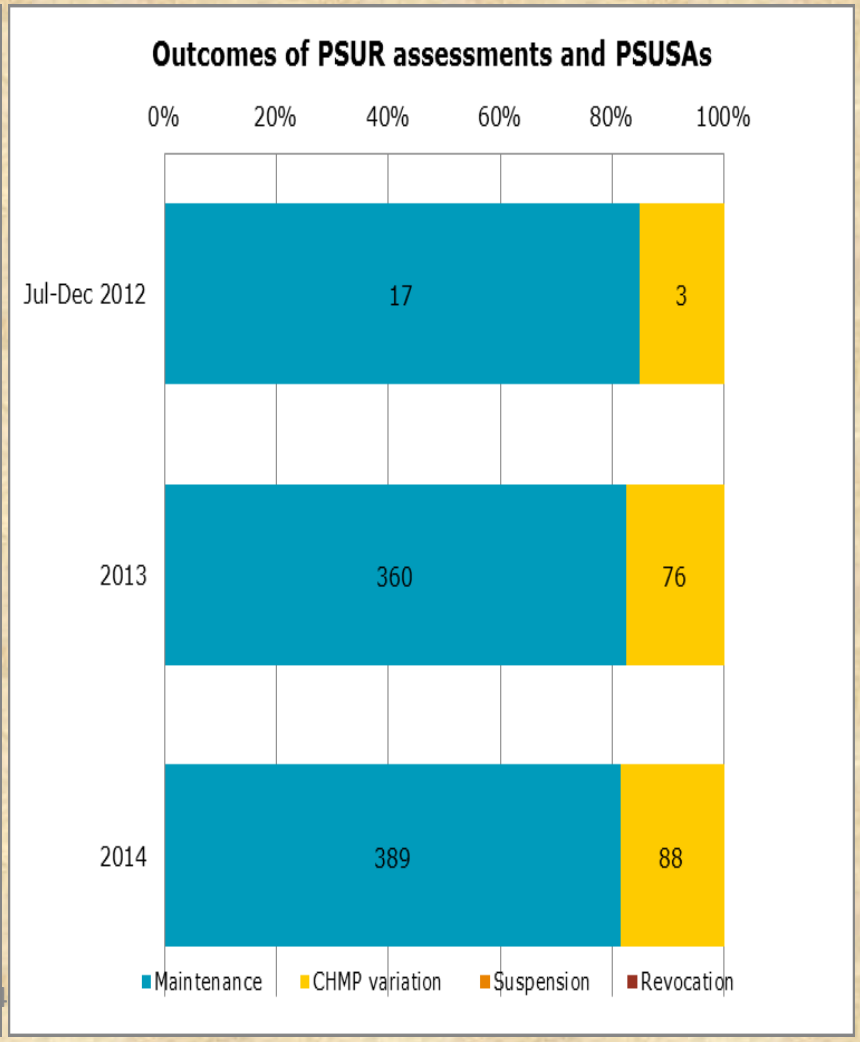
Faster detection and management of new and changing safety issues



Periodic Safety Update Reports

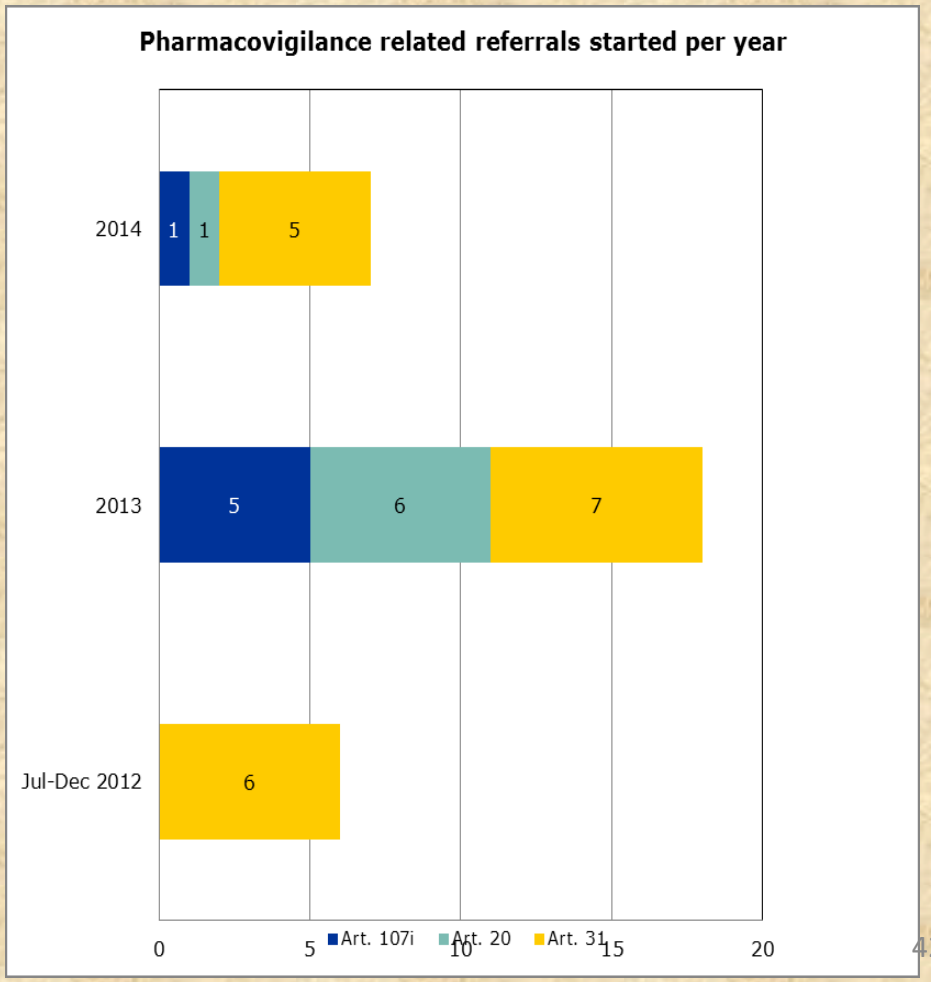
integration of benefit and risk and direct application of new labelling (faster impact)





Referrals to PRAC

major assessments delivering labelling for safe and effective use of medicines



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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 be given the choice.

A study, **published in the Lancet**, showed the drugs posed even greater risks for smokers and the overweight.

The risks have been reported before, but a team of researchers at the University of Oxford analysed the issue in unprecedented detail in order to help patients make an informed choice.

Related Stories

Drug 'overused' despite heart risk

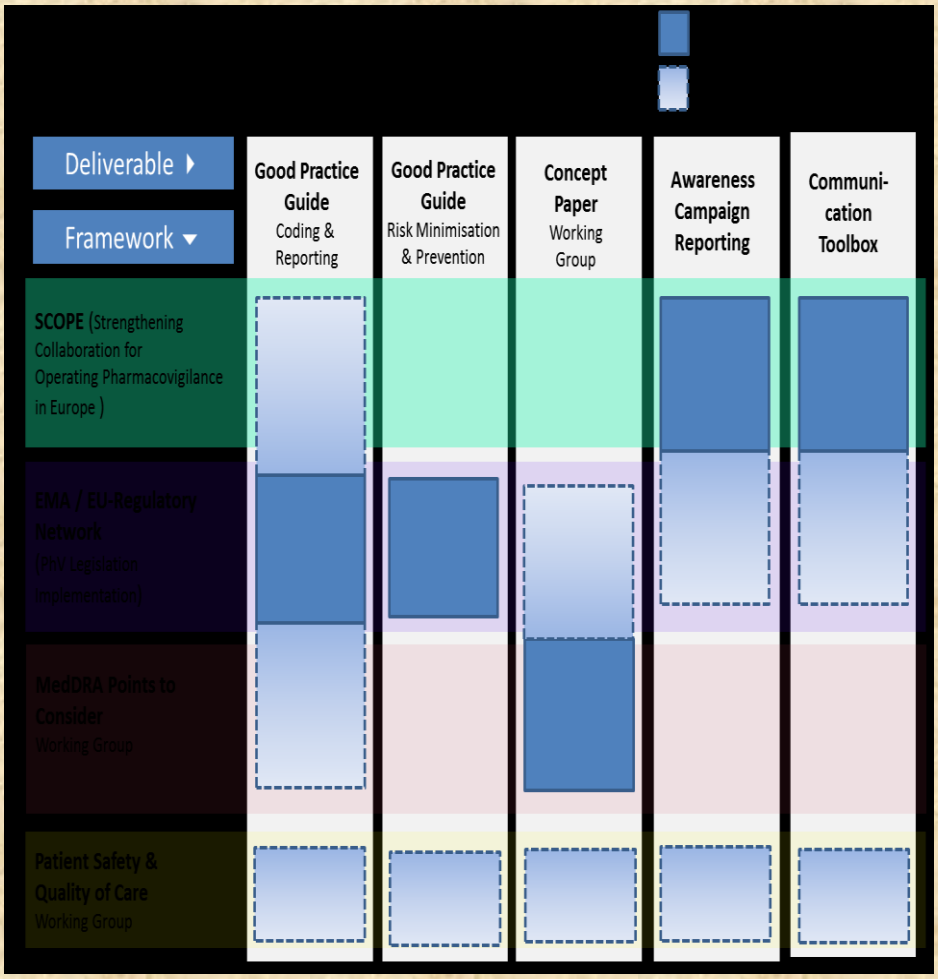
Painkillers linked to heart risk

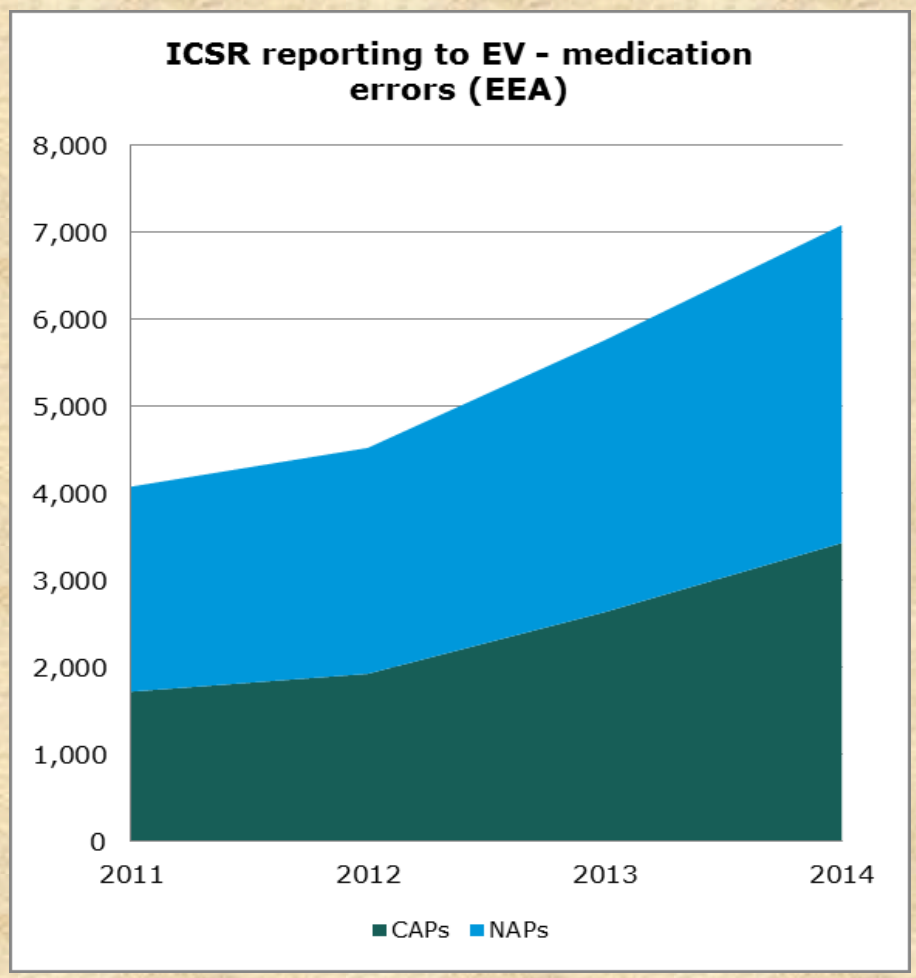
Q&A: Vioxx lawsuit

Medication errors:

improvements to reduce the burden of harm

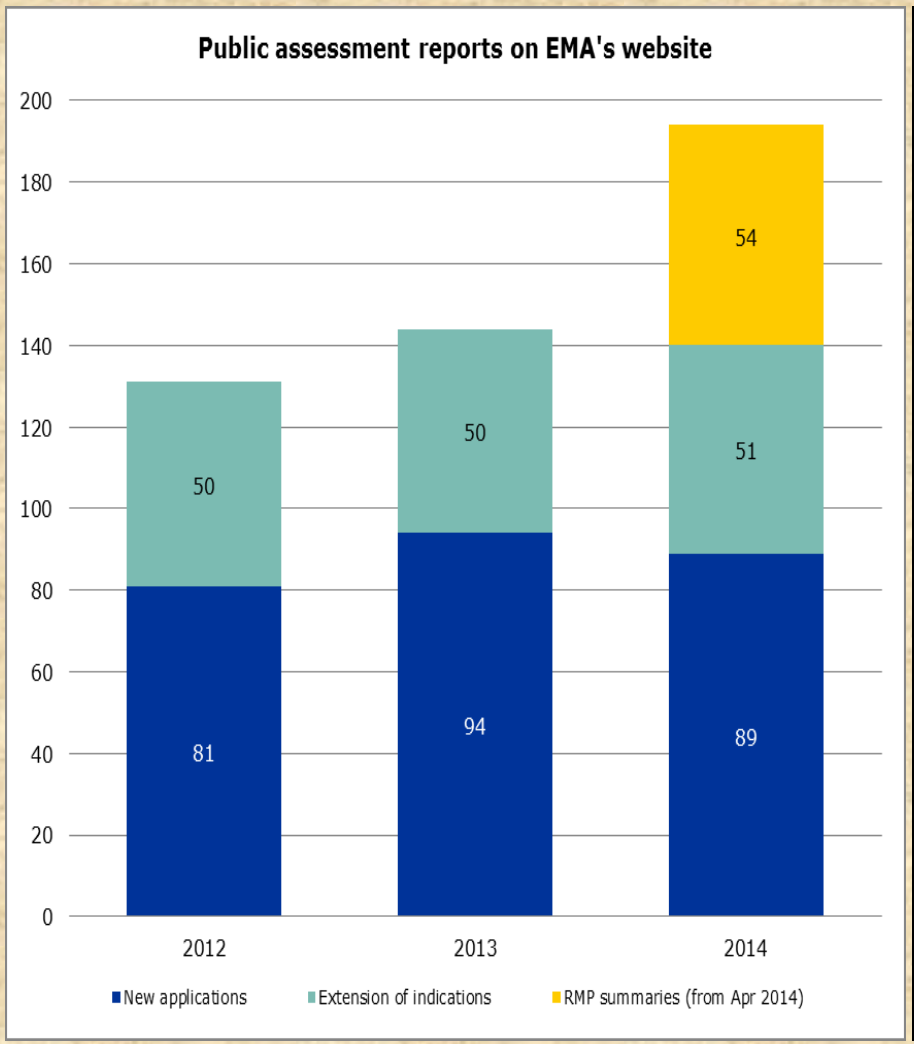
PRAC adoption of good practice guides



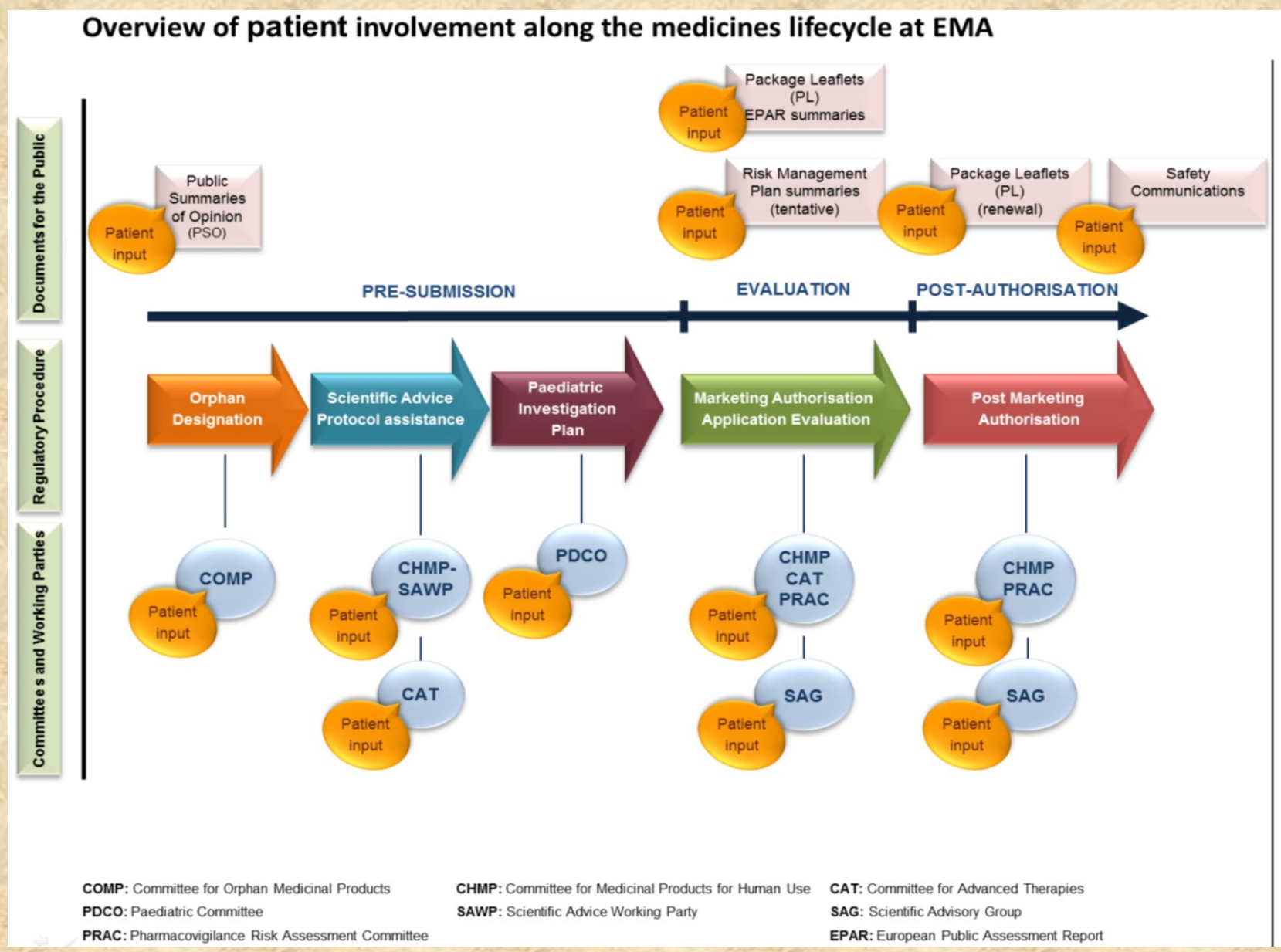


Major increase in transparency

committee proceedings, side effect data, RMP summaries, PSUR assessment conclusions



Engagement of stakeholders



Success factors

- **Working together** for continuous improvement of health promotion and protection
- Renewed focus on: **efficiency**, process improvement, and simplification
- Harness the opportunities of **new technology** and
- Harness the opportunities of **real-world evidence**
- Ensuring system improvements and product decisions are **evidence based**
- Focus on making a **positive impact**

Ongoing challenges

- **Complexity**
- **Access** to data and EU-wide real-world evidence
- **Quality** of data
- Greater **patient** engagement
- Best use of **resources**
- **Globalisation**

Conclusions

- Working together for continuous improvement of health promotion and protection
- Delivered:
  - Proactive monitoring
  - Faster safety issue detection
  - Faster warnings to users
  - Increased transparency
  - Engagement of stakeholders
- Renewed focus on: efficiency, process improvement, and simplification