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Post-marketing surveillance of drug safety in 2012: The EU Regulatory network

Benefit-Risk Assessment Methodology Workshop

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Overview

- What is pharmacovigilance?
- The European network for approval and surveillance of medicinal products
- New European pharmacovigilance legislation
- EU network opportunities
- New legislation – major achievements

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New Public Institution….

- 1 March 2012 The National Board of Health and the Danish Medicines Agency merged and became…

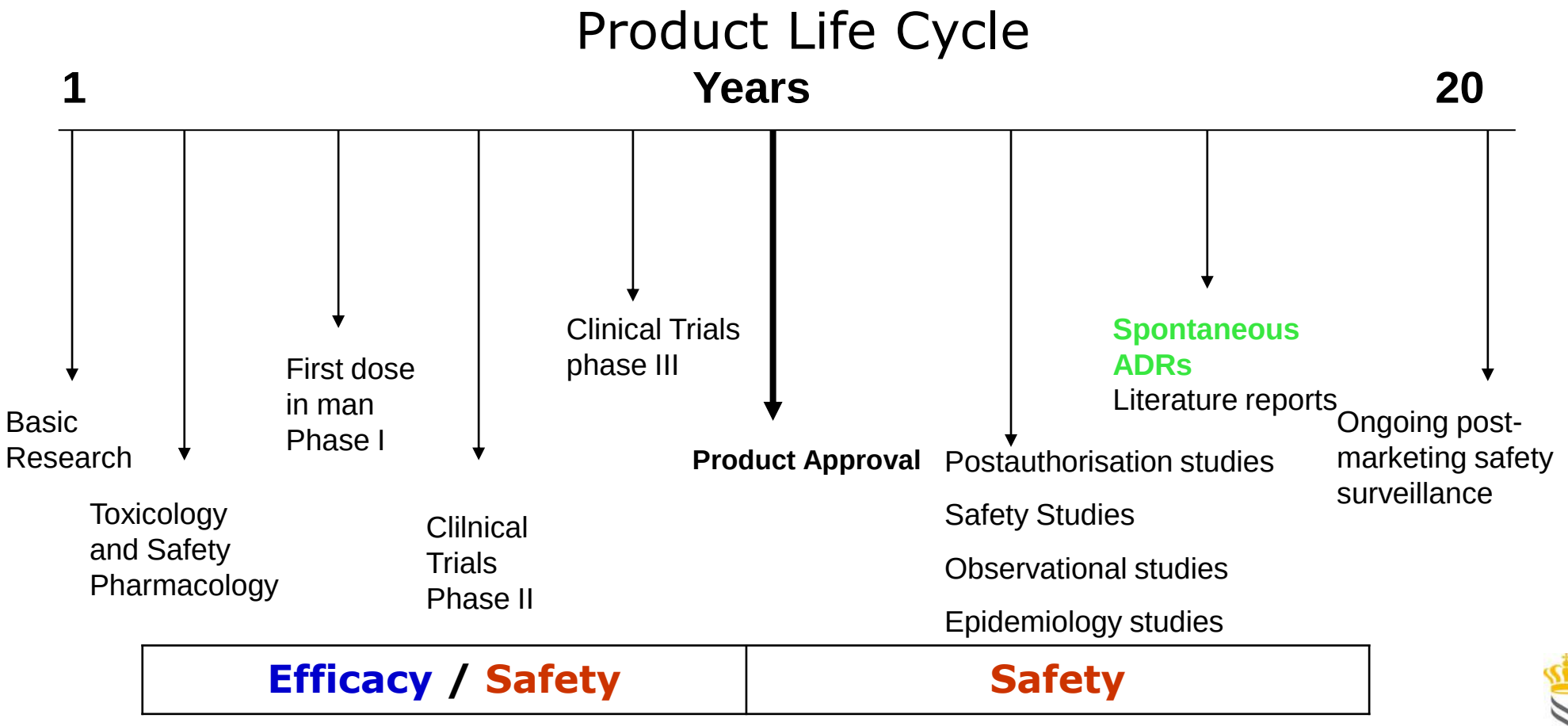
- The Danish Health and Medicines Authority

What is Pharmacovigilance?

- Pharmacovigilance is the ongoing surveillance of product safety and repetitive assessment of the benefit-risk balance throughout the product life cycle

- A product safety profile evolves over time and it necessitates a continuous safety surveillance in order to identify new safety issues which may change the benefit-risk balance of a product

Focus on safety throughout the entire lifecycle!



What is Pharmacovigilance?
The 4 main steps

- Risk **detection**
  - Multiple sources and methods; evidence hierarchy
- Risk **assessment**
  - Joint assessment industry/regulators, national/EU
- Risk **minimization**
  - Regulatory initiatives, scientific initiatives
- Risk **communication NEW!**
  - Medical literature, mass media

Basic tools in pharmacovigilance

- Adverse drug reaction (ADR) reports / Individual Case Safety Reports (ICSRs)
- Signal detection
- Periodic Safety Update Report (PSUR)
- Risk Management Plans (RMP)
- Post-authorisation Safety Studies (PASS)

Pharmacovigilance in a non-transparent, non-involving environment

- 20th century strategy – build national institutions capable of collecting and evaluating ADR data
- Decision making based on national experience
- Scope – national, healthcare professionals
- Communication - None

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Crucial societal developments with impact on pharmacovigilance

21th century strategy needs to cover….

- Internet era → rapid data exchange → cross-border transparency
- Internationalisation → decision making based on international experience → cross-border harmonisation
- Empowerment of patients / citizens → active involvement of a new stakeholder → cross-border engagement of the public

European Medicines Agency
EMA – Docklands, London, since 1995

EU Committees / procedures

- Pharmacovigilance Working Party → Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Human Medicinal Products (CHMP); Central procedure for granting of marketing authorisations; rapporteur / co-rapporteur
- Coordination Group for Mutual and Decentral Procedure (CMD(h)); reference member state
- European Risk Management Strategy Facilitation Group (ERMS) → Project Oversight Committee

Internationalisation in decision-making process – Example

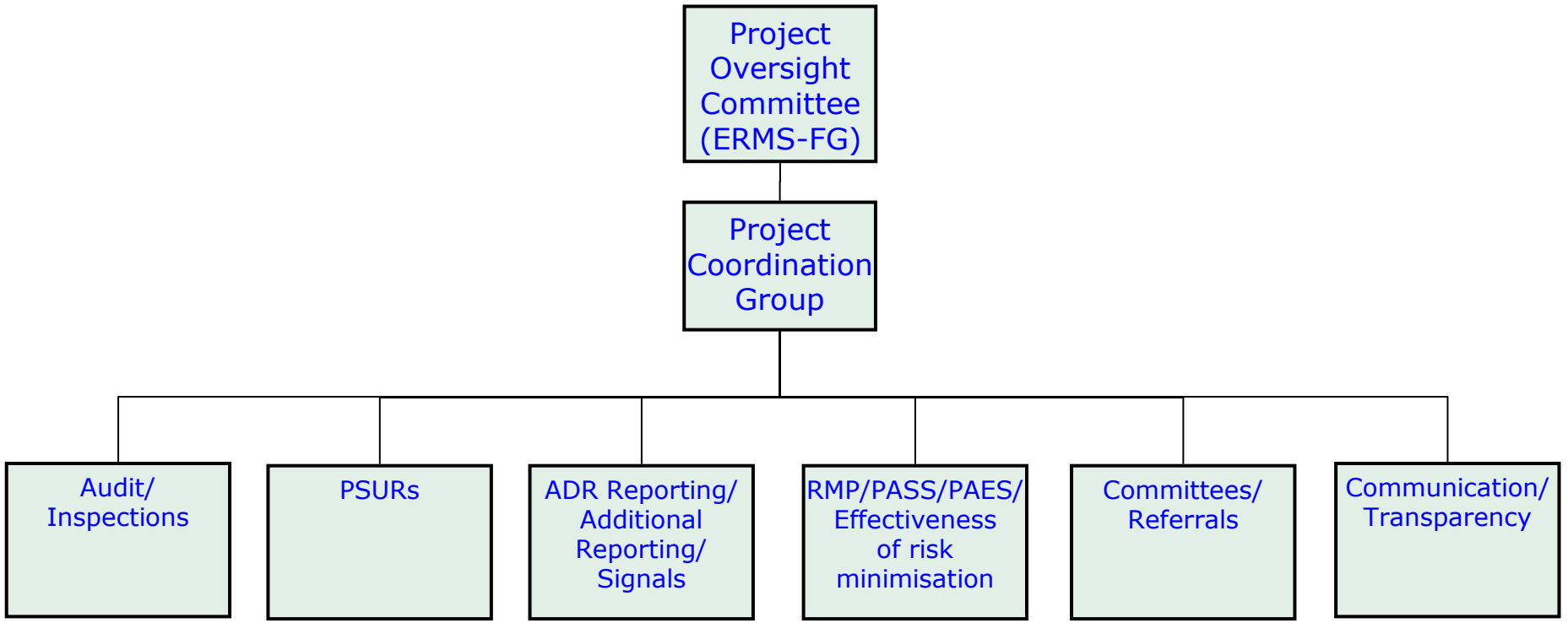
- The H1N1 flu pandemic in 2009
- Total number of vaccinated
  - In DK 420.000; in the EU 36.5 mio.
- Total number of ADR reports
  - In DK < 600, in the EU > 13.000
- Pandemrix® and narcolepsy
  - In Finland significant increase in cases of narcolepsy
  - In the EU only sporadic cases → B/R unchanged

New EU Pharmacovigilance Legislation

- Regulation (EU) no. 1235/2010 of 15 Dec 2010
  - Amends, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) 726/2004
  - Applies from 2 July 2012

- Directive 2010/84/EU of 15 Dec 2010
  - Amends, as regards pharmacovigilance, directive 2001/83/EC relating to medicinal products for human use
  - National law to apply from 21 July 2012

Governance and Organisation



PRAC membership

Appointed by each Member State:

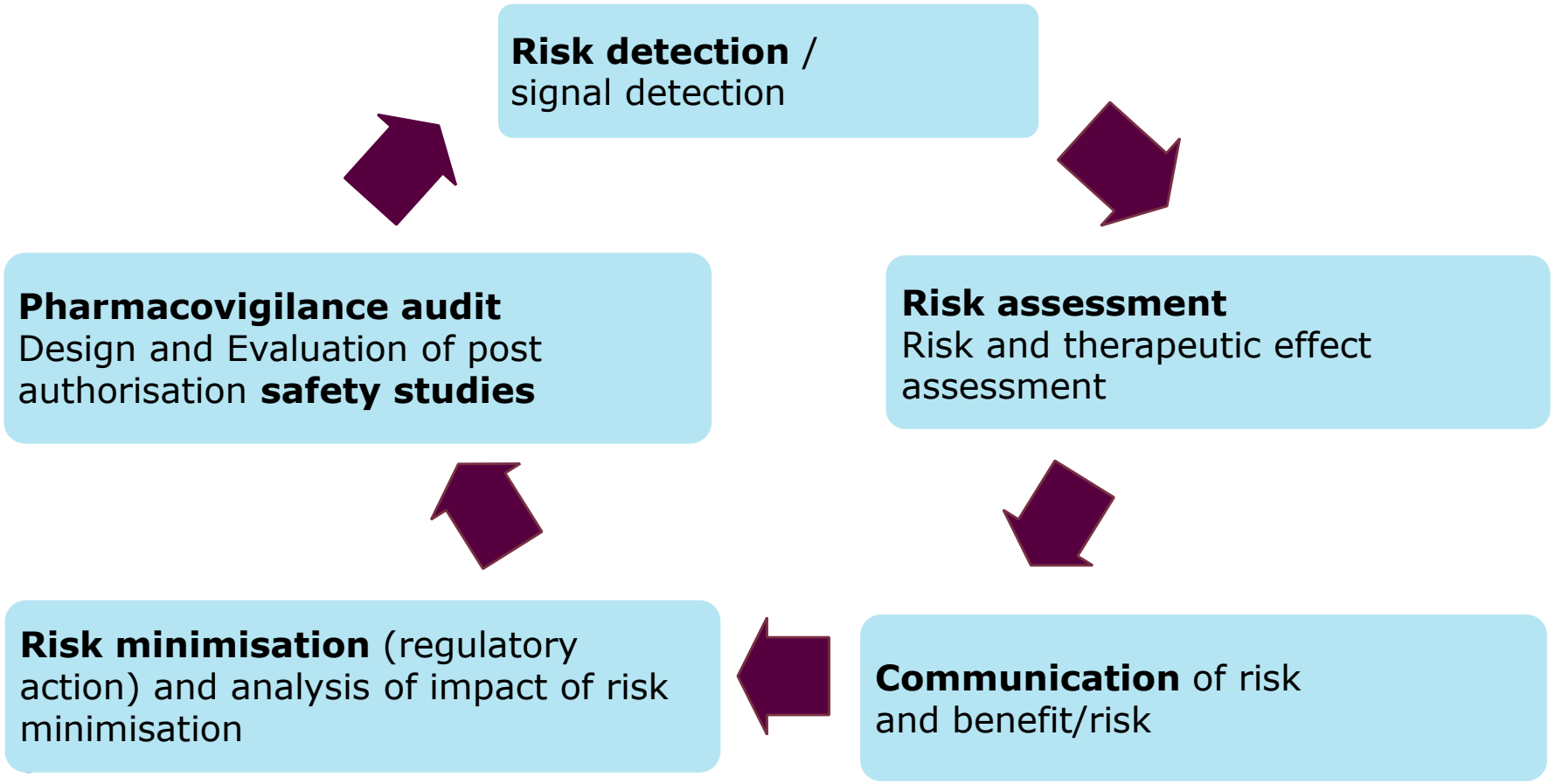
- 1 member + 1 alternate
- 27 + EEA countries non voting members

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 activities and expertise needed



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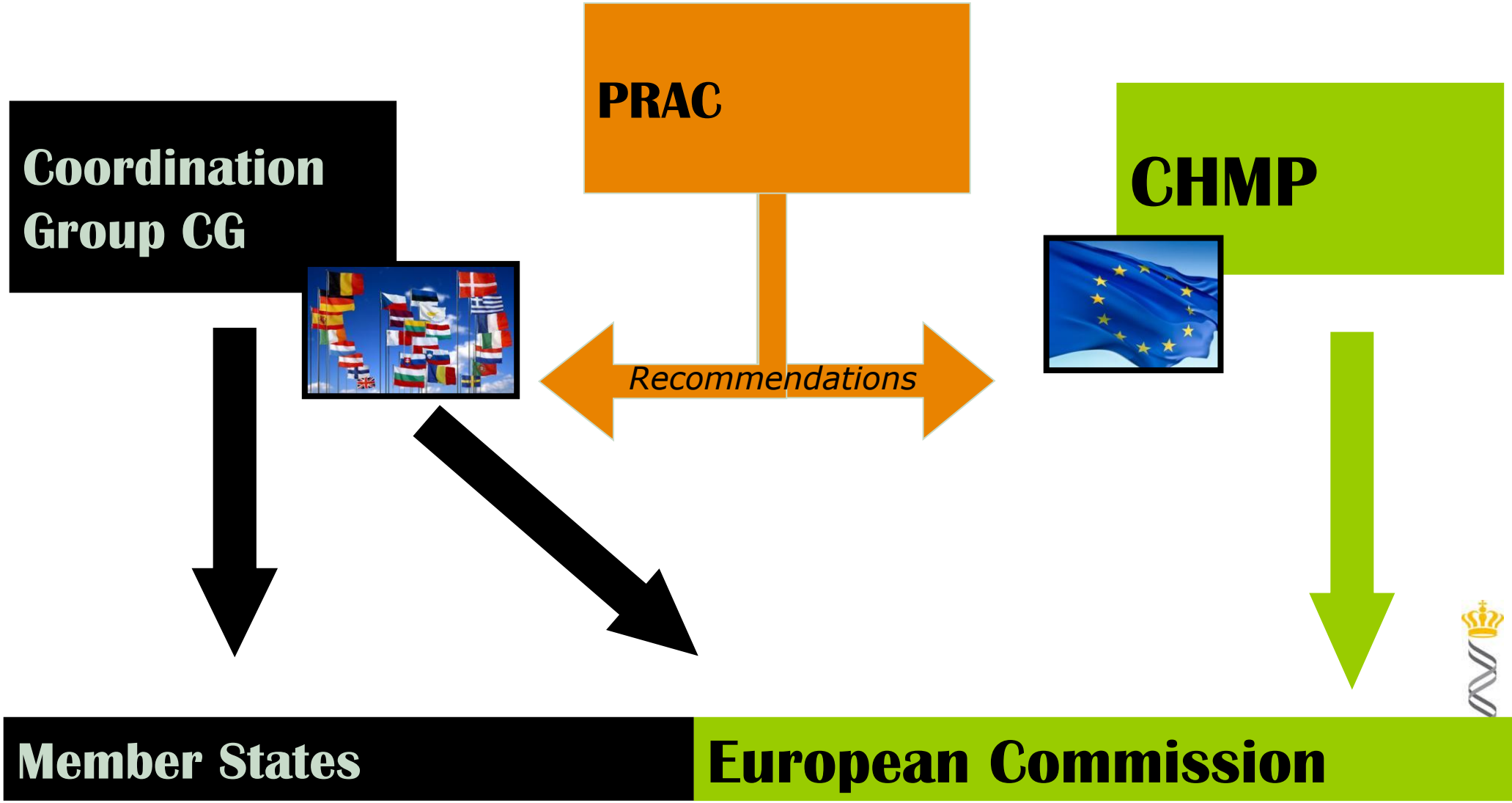
PRAC and the other Groups/Committees



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PRAC and Transparency

Regulation EU 1235/2010 states that in order to increase transparency as regards as pharmacovigilance issues a European medicines web portal should be created and maintained by the Agency in collaboration with Members States and the Commission

Agenda & Minutes

Assessments

Decisions

Opinions
Agreements
Positions

Recommendations

Available to the public

New transparency tools

- Web portals
- Coordination of safety announcements
- Public hearings
- List of medicinal products subject to additional monitoring

European Medicines Web Portal

- To be created and maintained by EMA – aiming at increasing transparency; links to national web portals

- Publications – examples:
  - List of medicinal products subject to additional monitoring
  - List of literature monitored by EMA for a defined list of active substances
  - Various public assessment reports
  - Information on initiated safety referrals

Coordination of safety announcements

- Lack of co-ordination → suspicion that regulatory authorities deliberately hide data
- EMA has experience with co-ordination of safety announcements for centrally authorised products and referrals (*early notification* procedure)
- For non-centrally authorised products EMA will co-ordinate the safety announcements

List of medicinal products subject to additional monitoring

- Balance in between pre-mature and unnecessarily delayed granting of a market authorisation
- New active substances, biological medicinal products incl. biosimilars, medicinal products for pediatric use, biotech. products being the result of a new manufacturing process…
- At request of the regulatory authorities, e.g. for medicinal products subject to required PASS or to conditions or restrictions to safe and effective use specified in the RMP

Literature monitoring by EMA

- Aim - to decrease duplicate reporting

- Publication of a defined list of literature for a defined list of substances used in medicinal products for which there are several marketing authorisations

New ADR definition

- Adverse reaction:
  - A response to a medicinal product which is noxious and unintended
- Aim:
  - to ensure that the definition not only covers noxious and unintended effects derived from authorised use at normal doses, but also from medication errors and uses outside the authorised SmPC, incl. misuse / abuse

Patient reporting

- Patients considered to be “well placed” to report
- MSs should encourage patients to report
  - Provide not only web-based reporting forms, but also provide other means by which patients can report
  - Involve patient & HCP organisations as appropriate

Eudravigilance

- Single point of receipt of ICSRs
  - MAHs report directly
  - MSs forward ICSRs received at national level incl. consumer reports
- Accessible to MSs, EMA and Commission + to MAH and the public "*to an appropriate extent*"
- Need to consider – examples:
  - Quality assurance at entry
  - Signal management

Periodic Safety Update Reports

- Information on all ICSRs reported from all countries where the medicinal product is marketed, + patient exposure figures, data on studies, regulatory actions…
- To be submitted by the MAH at regular intervals
- Assessed by EU member states on workshare basis
- Hitherto a risk evaluation tool
- Key changes of structure:
- Benefit Evaluation
- Integrated benefit/risk analysis for approved indications – method???

Risk Management Plan (1)

- Format and content: Seven parts
  - Part I – Product(s) overview
  - Part II – Safety specification
    - Module 1 – Epidemiology of indications and target populations
    - Module II – Non-clinical
    - Module III – Clinical trial exposure
    - Module IV – Populations not studied in clinical trials
    - Module V – Post-authorisation experience
    - Module VI – Identified and potential risks
    - Module VII – Additional EU requirements for the safety specification
    - Module VIII – Summary of the safety concerns

Risk Management Plan (2)

- Format and content cont…
  - Part III - Pharmacovigilance Plan
  - Part IV - Plans for studies on effectiveness and longterm efficacy
  - Part V – Risk Minimization Measures
  - Part VI – Summary of the RMP
    - Shall be published
    - Shall include key elements of the RMP addressing important potential and identified risks and missing information + a summary of risk minimization measures
  - Part VII - Annexes

PASS and PAES

- PASS - Any study with an authorised medicinal product conducted with the aim of
  - identifying, characterising or quantifying a safety hazard
  - confirming the safety profile of the medicinal product or
  - measuring the effectiveness of risk management measures
- Strengthened legal basis for request, clear rules for supervision
- PAES – Delegated act specifying criteria for PAES awaited from EC
- Efficacy concern?
  - if there are indications that previous efficacy evaluations could be significantly changed

EU network opportunities

- Knowledgesharing
  - Decisions of high scientific quality
  - Harmonization – best practice
- Worksharing
  - Appropriate use of ressources
- Coordination
  - Same recommendation simultaneously across EU countries

New legislation – Major achievements

- Clarification of roles and responsibilities of various stakeholders
- New paradigm – decision-making based on cumulative international data
- Strengthening of the risk-adjusted approach
- Improvement of transparency and communication
- Reduction of duplication of work
- Strengthening and clarification of procedures in relation to the use of PASS and of RMP
- Involvement of patients

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Thank you for your attention!

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