



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The new Pharmacovigilance legislation: an EMA perspective

IPA Conference
Reinforcing patient safety in Europe,
14-15 June 2011, Zagreb, Croatia

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An agency of the European Union





In this talk

- Why?
- New PhV and Risk Assessment Committee PRAC
- Post Authorisation Studies (PASS and PAES)
- Risk management Plans
- Impact
- How we are preparing for the new legislation



Why?

To further strengthen pharmacovigilance



- 5% of all hospital admissions are for ADRs,
- 5% of all hospital patients suffer an ADR,
- ADRs are the 5th most common cause of hospital death,
- Estimated 197,000 deaths per year in EU from ADRs,
- EU Societal cost of ADRs Euro 79 Billion / year



Why?

High Level Objectives (1/2)



Promote and protect public health by reducing burden of ADRs and optimising the use of medicines:

- Clear roles and responsibilities
- Science based (embrace the evidence hierarchy)
- Risk based/proportionate
- Increased proactivity/planning
- Reduced duplication/redundancy
- Integrate benefit and risk



Why?

High Level Objectives (2/2)



Promote and protect public health by reducing burden of ADRs and optimising the use of medicines:

- Ensure robust and rapid EU decision-making
- Strengthen the EU Network
- Engage patients and healthcare professionals
- Increase transparency and accountability
- Provide better information on medicines



What: Key changes Committees

PRAC and Decision-making

New Pharmacovigilance Risk Assessment Committee - 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



Identified PRAC Activities (1/2)

Activity	Involvement
Risk Management Systems	Agreement on RMPs + monitoring their effectiveness
PSURs	List of harmonised submission frequencies and substances, assessment + recommendation
EV + PSUR repository	Functional specifications, any substantial changes
Products subject to additional monitoring	Addition to/removal from list, extension of timeframe, symbol
Signal Detection	Initial analysis + prioritisation assessment + recommendations



Identified PRAC Activities (2/2)

Activity

Involvement

Urgent Union Procedures

Assessment, public hearings, recommendations

Post Authorisation Safety Studies

Consultations on requests (pre and post MA), assessment of protocols (incl. amendments) + recommendations, assessment of results + recommendations

Literature ADR monitoring

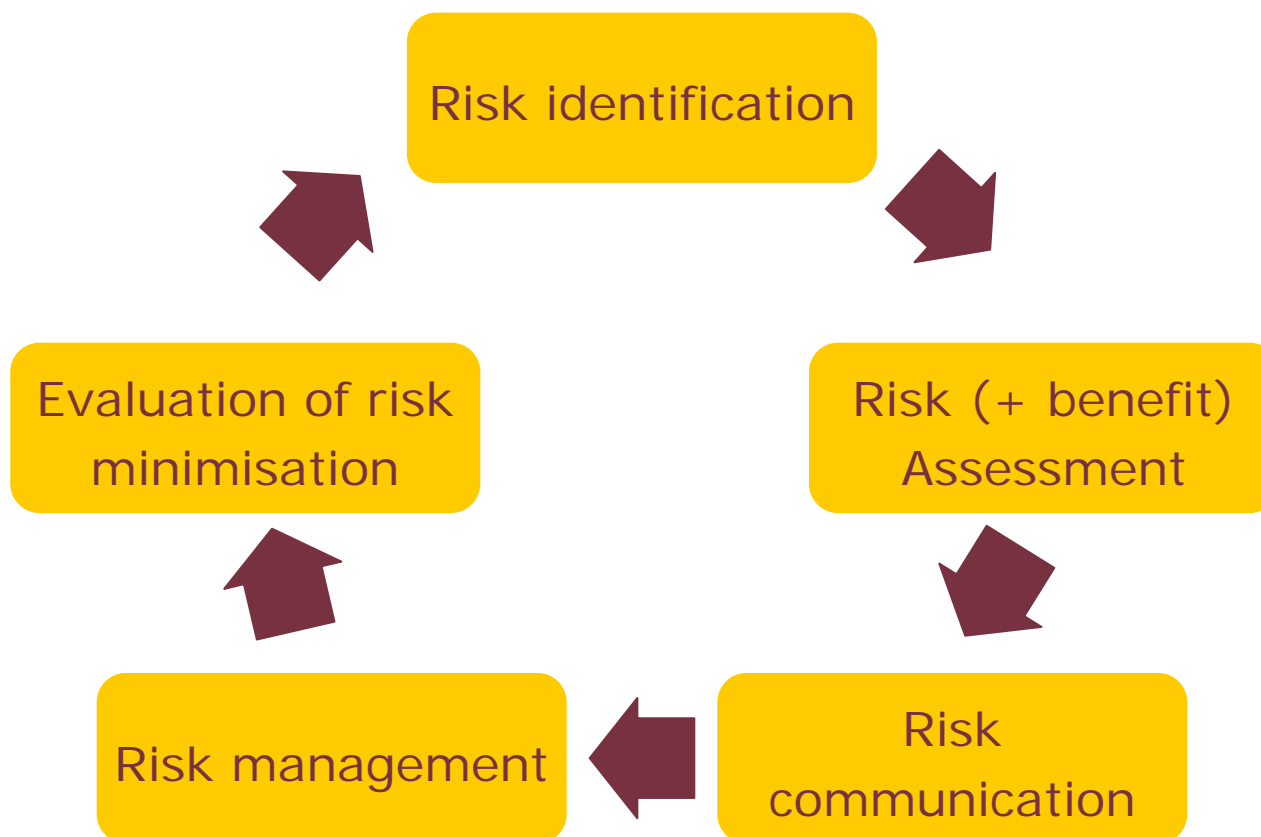
Consultation on list of active substances and medical literature subject to monitoring?

Safety announcements

Advice



PRAC membership expertise – Core areas





PRAC membership expertise – Additional (specialised) Areas

- Drug safety in pregnancy and lactation
- Drug utilisation studies
- Medication errors leading to ADRs
- Pharmacogenetics and safety of medicines
- PhV in special populations (paediatrics, elderly)
- PhV of biological and biosimilar substances
- PhV and quality defects
- PhV of Vaccines



PRAC membership

**Appointed by each
Member State:**



- 1 member + alternate



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



- 1 patient organisations¹ rep + alternate
- 1 healthcare professionals¹ rep + alternate
- 6 members to ensure relevant expertise available (pharmacology, pharmacoepidemiology)

¹ *Criteria for involvement in EMA activities*



Post-authorisation Safety Studies (PASS) (1/4)

Strengthened legal basis

- Regulators can require PASS at first authorisation
- Regulators can require PASS post-authorisation
- PASS is a condition of the authorisation and is legally binding
- In the event that the same *safety concern applies to more than one medicinal product*, the EMA/national competent authority shall encourage the marketing authorisation holders concerned to *conduct a joint post-authorisation safety study*



Post-authorisation Safety Studies (PASS) (2/4)

Principles for and oversight of PASS

Definition:

'Any study relating to 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 of measuring the effectiveness of risk management measures'

Principles and oversight for non-interventional PASS which are:

initiated, managed or financed by the MAH voluntarily or pursuant to obligations imposed [by regulators] and which involve the collection of data on suspected adverse reactions from patients or healthcare professionals.

Still may have additional MS requirements on well being and rights of participants in non-interventional PASS



Post-authorisation Safety Studies (PASS) (3/4)

Principles for and oversight of *all* PASS (initiated, managed or financed by MAH)

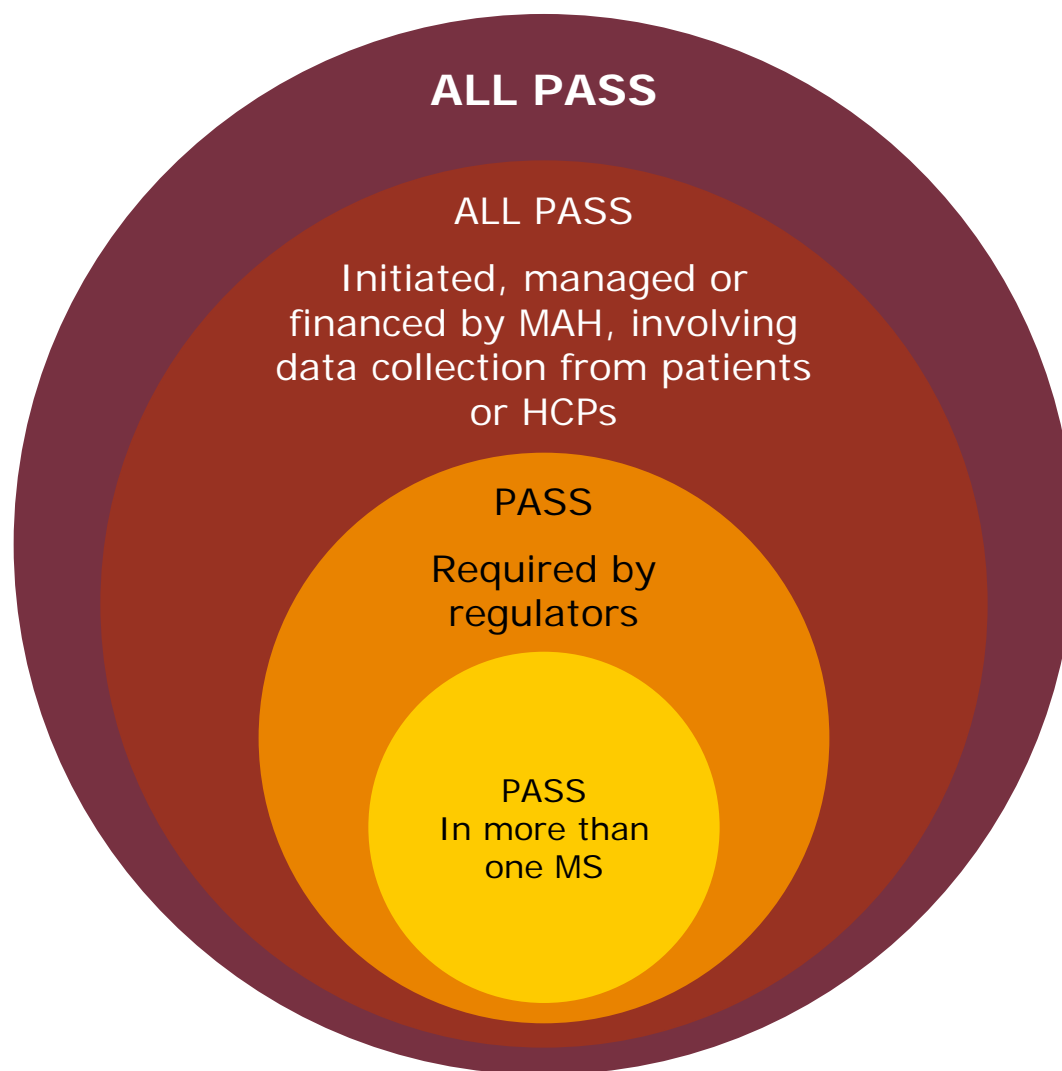
- The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.
- Payments to healthcare professionals for participating in non-interventional PASS shall be restricted to the compensation for time and expenses incurred.
- National competent authority may require the MAH to submit the protocol and the progress reports to the competent authorities of the MSs in which the study is conducted.
- MAH shall send the final report to the competent authorities of the MSs in which the study was conducted within 12 months of the end of data collection.
- Any new information which might influence the evaluation of the risk-benefit balance of the medicinal product shall be communicated [by company] to the competent authorities of the MS in which the product has been authorised.



Post-authorisation Safety Studies (PASS) (4/4)

Principles for and oversight of PASS for studies required by regulators

- Protocols actively approved prior to study (single country = MS, multiple country = PRAC)
- Protocol amendments actively approved
- Final report and abstract submitted
- Automatic, formal assessment and decision-making based on results
- Company updates product information





European Network of Centres for Pharmacoepidemiology and Pharmacovigilance



Objective:

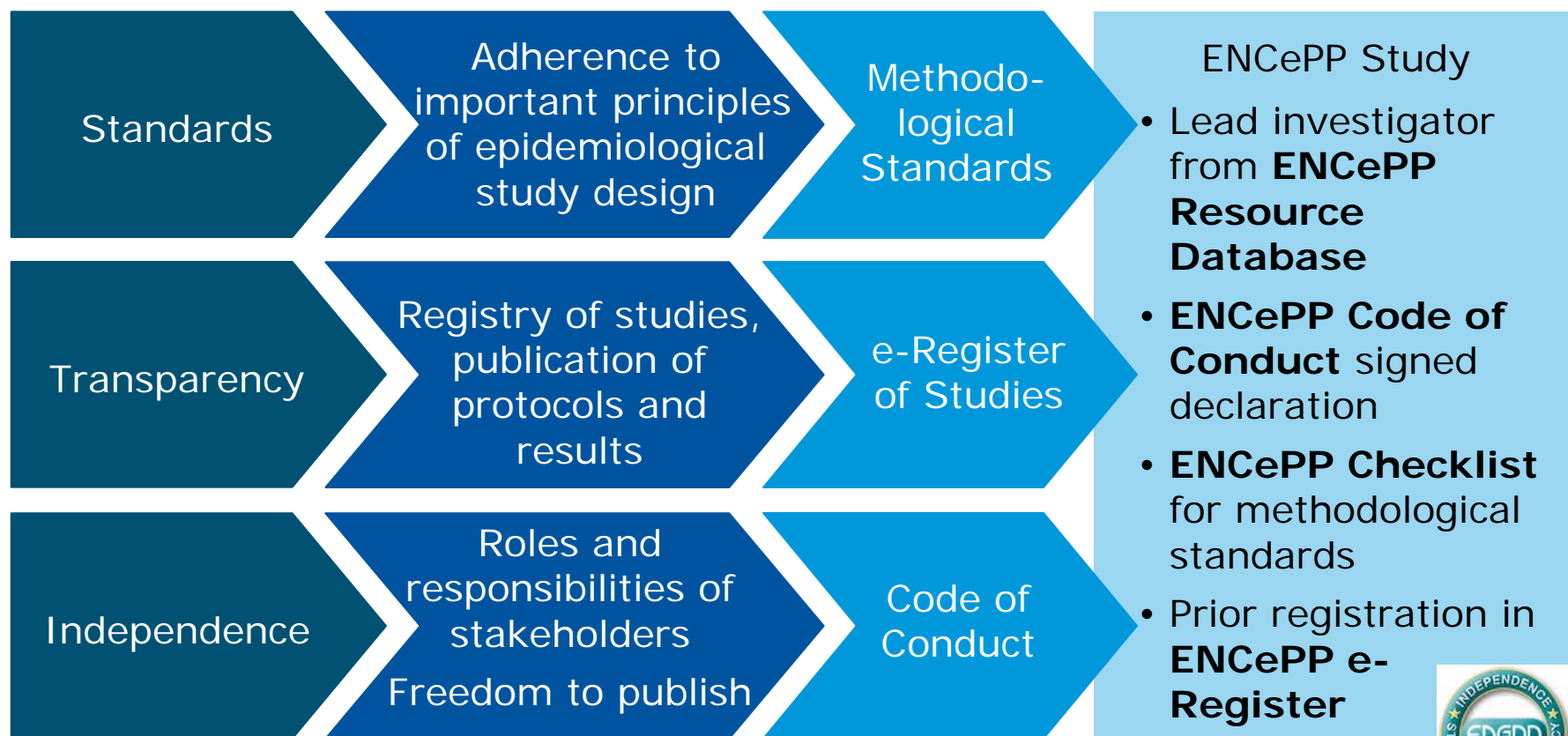
Strengthen further the post-authorisation monitoring of medicinal products in Europe, **facilitate post-authorisation studies: high quality; independent; multi-centre.**

Network of excellence:

- public, fully searchable database of centres, networks and data sources
- Public searchable **e-Register** of studies
- **Code of conduct** to define relationship between funder and researcher and to ensure transparency
- Methodological **checklist**



European Network of Centres
for Pharmacoepidemiology and Pharmacovigilance





Post-authorisation Efficacy Studies (PAES)

Strengthened legal basis

At authorisation:

‘where concerns relating to some aspects of the efficacy of the product are identified and can be resolved only after the product has been marketed’.

Post authorisation:

‘when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be modified significantly’.

EC may adopt implementing measures

EMA shall adopt scientific guidelines



Risk Management Planning

Definition:

‘a set of pharmacovigilance activities and interventions, such as studies and reports, designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions’

- Requirement for all new products but risk proportionate
- Legal basis to require a risk management system / plan for an authorised product (‘if there are concerns about the risks affecting the risk-benefit balance’)
- Safety and **Efficacy studies** included (towards integrated BR)
- **Systematic role for the new Committee (PRAC)**



Effectiveness of Risk Minimisation

New legal requirement that EMA/MSs shall:

'monitor the outcome of risk minimisation measures contained in risk management plans and of conditions....'



EU Medicinal Product Dictionary (Art 57 of Reg)



'the Agency shall establish a list of all medicinal products authorised in the Community. To this effect the following measures shall be taken:

- a) the Agency shall, by 2 July 2011, make public a format for the electronic submission of medicinal product information;
- b) MAHs shall, by 2 July 2011, electronically submit to the Agency information for all medicinal products authorised or registered in the Community, using the format referred to in point (a);
- c) from the date set out in point (b), MAHs shall inform the Agency of any new or varied authorisations (...).



Transparency and Communication

- EU and National Medicines web-portals
- Dramatic increase in transparency e.g. 'protocols and public abstracts of results as regards post authorisation safety studies'
- EMA to coordinate MS safety announcements
- Public hearings





Impact

- Very far reaching changes to the EU regulatory framework
- Biggest changes for human medicines since the establishment of the EMA in 1995
- Redistribution of industry costs from centralisation of functions at EU level (e.g. ADR reporting, PSURs)
- Major impact on existing regulatory processes
- Need for numerous new regulatory processes
- New work will require human resources and financial resources (for IT, for staff, for payment of rapporteurs, for access to healthcare data and for independent studies)



Impact – risk

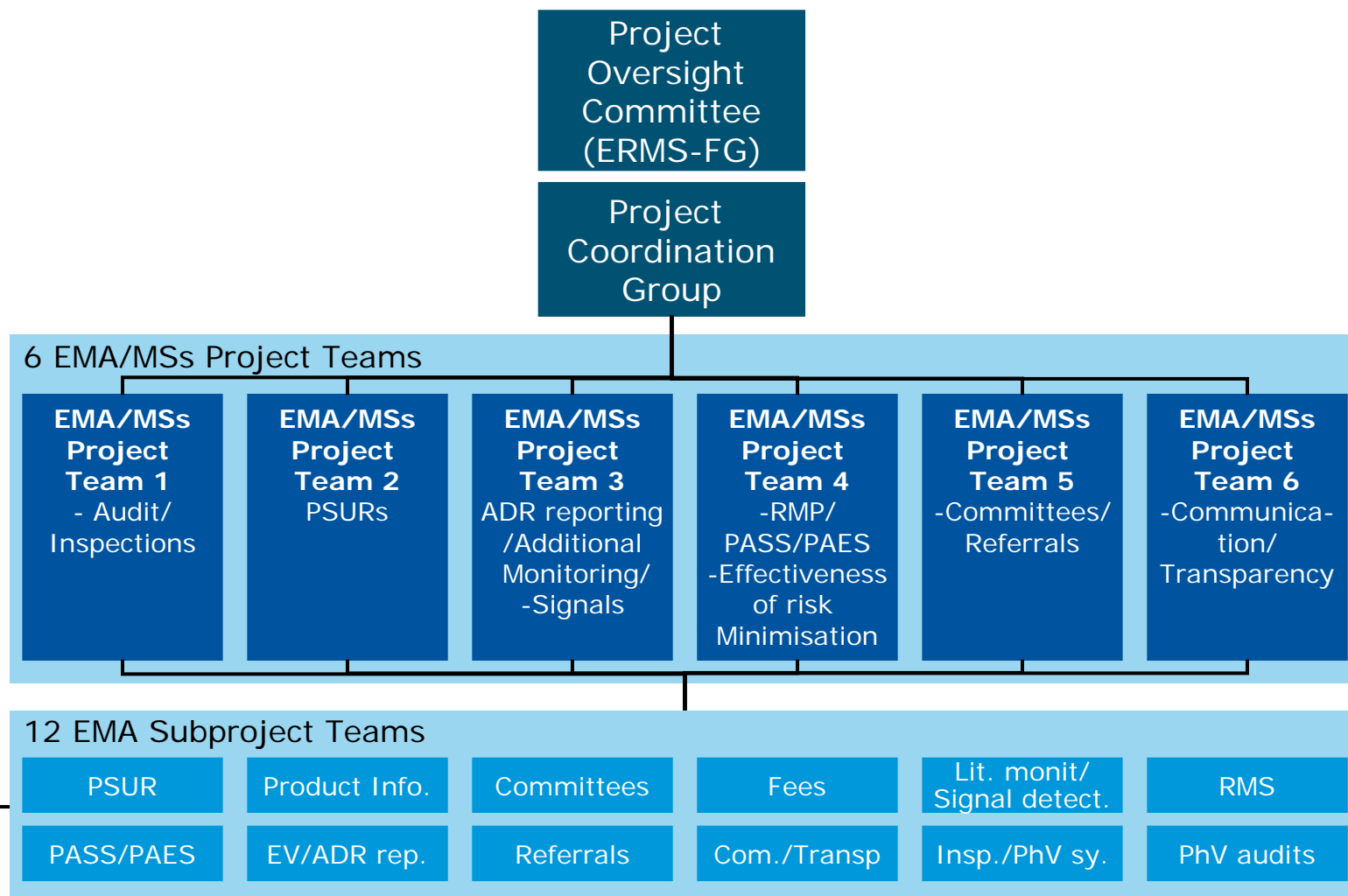


Lack of resource is the biggest risk to the implementation and operation of the new legislation:

- Currently, no additional resources for 2011
- Resources for 2012 not yet secured
- Longer term – if there is appropriate change to the fees regulation this will allow adequate funding of the new legislation



Governance – EU Network





Stakeholders liaison and consultation

Stakeholders meetings involving EMA, Member States, EC, Industry, Patients and Healthcare Professionals representatives:

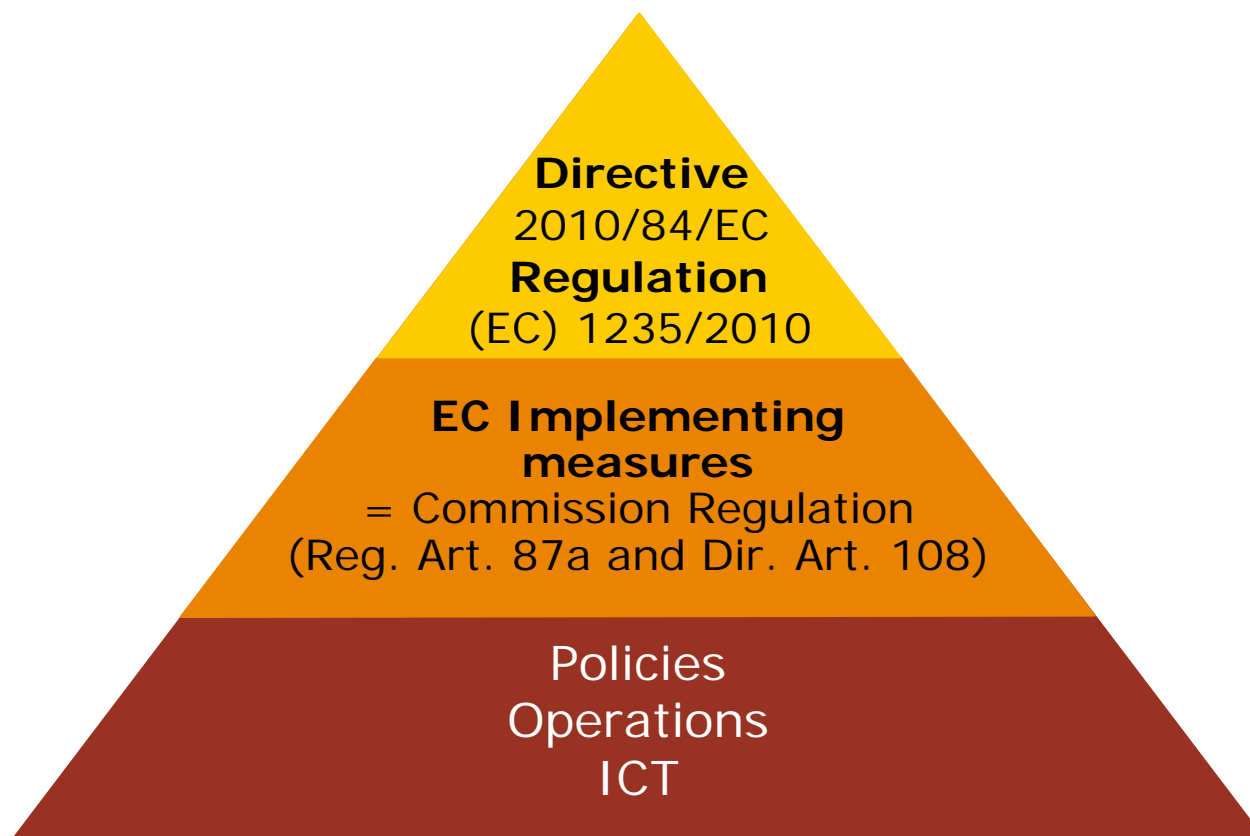


Formal public consultations by EC and EMA



What will be delivered?

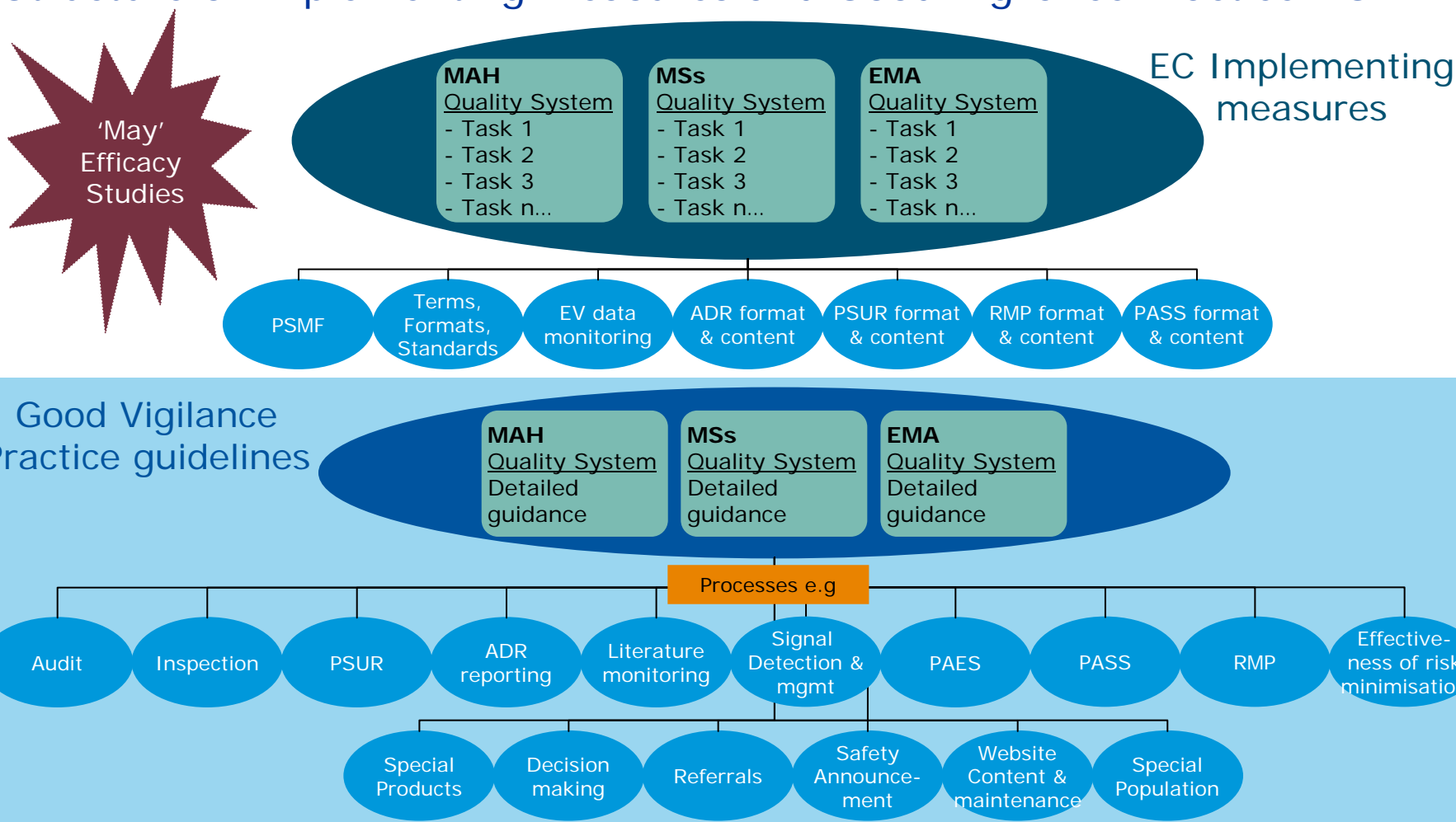
Hierarchy of rules





What will be delivered?

Structure of implementing measures and Good Vigilance Practice: 'GVP'





Implementation plan: key activities



- Overall implementation plan **on target**
- Concept Papers under development
- Technical contribution to EC implementing measures advanced
- Business Process Mapping exercise
 - well under way (to deliver efficient processes)
- IT requirements
 - Intensive gathering of business requirements
 - Weekly meetings between IT and business managers
- Implementation to 2013 and beyond....



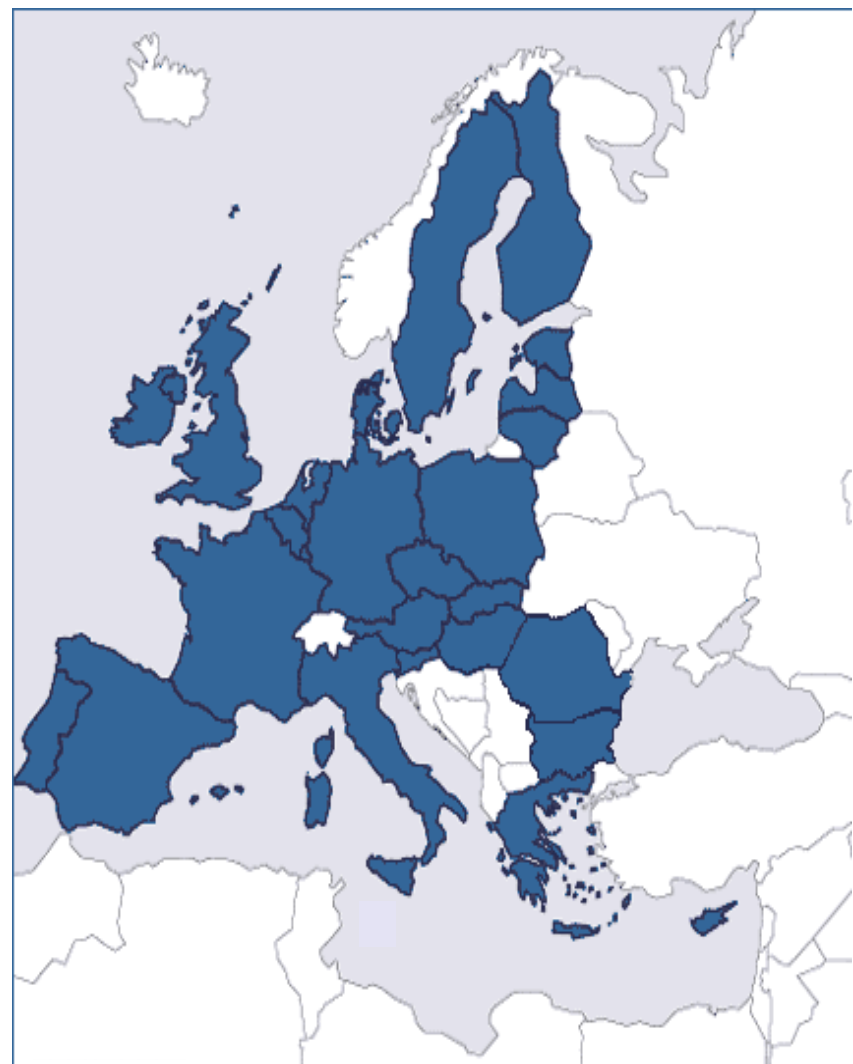
Conclusions – for excellent protection and promotion of public health

New vision:

- Draws on all relevant data sources
- Health data and epidemiology support lifecycle
- Embrace evidence hierarchy
- Ensure protection effective in real life

New legislation:

- Once in a generation opportunity to strengthen and rationalise public health
- Major work to ensure full and effective implementation
- Resources are needed and collaboration will be key





Hvala vam!

Questions?

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N.B. Directive Article 23 + Regulation Article 16

- MAH shall **inform of any prohibitions or restrictions** or any new information which may influence the evaluation of benefits and risks....'include both **positive and negative results of clinical trials** or other studies in **all indications and populations, whether or not included in the marketing authorisation**, as well as data on use of the medicinal product where such use is outside the terms of the marketing authorisation'.
- **MAH shall keep their product information up to date** with current scientific knowledge, including the conclusions of the assessments and recommendations on the **EU medicines web-portals**
- Regulators may at any time **ask the MAH to forward data** demonstrating that the BR balance remains favourable. MAH shall answer fully and promptly any such request.



What will be delivered? (1/2)

EMA/Member States technical contribution to EC implementing measures

Reg. (EC) 1235/2010 Art. 87a and Dir. 2010/84/EC Art. 108

- a) The content and maintenance of the pharmacovigilance system master file kept by the MAH;
- b) The minimum requirements for the quality system for the performance of pharmacovigilance activities by the Agency **(the NCAs and MAH)**;
- c) The use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;



What will be delivered? (2/2)

EMA/Member States technical contribution to EC implementing measures

Reg. (EC) 1235/2010 Art. 87a and Dir. 2010/84/EC Art. 108

- d) The minimum requirements for the monitoring of data included in the EV database to determine whether there are new risks or whether risks have changed;
- e) The format and content of electronic transmission of suspected adverse reactions by MSs and MAHs;
- f) The format and content of electronic PSURs and RMPs;
- g) The format of protocols, abstracts and final study reports of the PASS;



What: Scope: key measures in one slide! of changes

- Authorisation requirements change (PSMF, key risk management measures in MA)
- Risk Management Plan, risk proportionate, efficacy studies, and for all new products (+justified old)
- Legal basis for PASS + legal basis for efficacy studies
- Effectiveness of risk minimisation
- Product information change – ‘additional monitoring’ + encourages ADR reporting
- ADR reporting simplified + patient reporting + medication errors + role of EV + literature monitoring + reporting to WHO
- Signal detection has clear roles and responsibilities
- PSUR submission simplified (electronic) and single assessment + benefit: risk
- Committees (PRAC/CMD/CHMP) and decision-making
- Transparency and communication (webportals, EV access, coordinate MSs, hearings)
- Enhanced coordination of inspections
- Regular EMA and MS + MAH audit
- Fees for pharmacovigilance
- Access in small markets – labelling exemption etc.



PSUR decision-making (Art. 107g)

Single AR prepared by the Member State
appointed by the CMD

**"No CAP
concerned"**

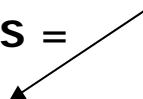


PRAC to adopt the AR



If any regulatory action results from the AR, CMD
to reach a position: maintenance, variation,
suspension or revocation + according timetable
for implementation

MS =



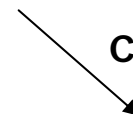
Decision sent the MAHs and MSs
concerned

MS ≠



Position of the majority of MSs to be
sent to the Commission which will
adopt a decision

CMD ≠ PRAC



Detailed explanations to be annexed.
CMD has the legal power



PSUR decision-making (Art. 107g)

Single AR prepared by the Rapporteur
appointed by the PRAC



**"At least 1 CAP
concerned"**

PRAC to adopt the AR



If any regulatory action results from the AR,
CHMP to adopt an opinion: maintenance,
variation, suspension or revocation + according
timetable for implementation



Commission **to adopt a decision**
concerning the regulatory action(s)



PSURs

- No line listings – ADR data already in Eudravigilance
- Company integrated assessment of benefit risk + exposure
- Submitted electronically to EMA (thereby Member States access)
- Likely inclusion of structured data using controlled terminologies
- For established substances, single EU assessment for all products
- Assessment leads to automatic regulatory action: variations, suspension, revocation
- Periodicity will be established by EMA (binding list on website)
- Likely to replace many referrals
- Increased transparency



RMPs vs. PSUR – tools to be used differently

at stages in the product lifecycle

RMP: main focus is *planning*:

Risk minimisation

Data collection

Ensuring effectiveness of measures

PSUR: main focus is benefit risk *evaluation*:

Ensure benefit risk balance remains favorable

Signal detection and evaluation

Ensure product information up to date

Establish and publish the known risks of a substance / combination 'core safety profiles'



Better ADR Reporting

New ADR definition: 'A response to a medicinal product which is noxious and unintended'

Medication errors that result in an ADR are reported

Patient reporting – the debate on 'if' is over! Now debate 'how'!

- After transitional period:

- All ADRs from companies and from Member States are sent to Eudravigilance only
- Member States are 'auto-forwarded' their national data
- Companies access reports in Eudravigilance



Signal detection

- For 1st time the concept is recognised in law
- Clear roles and responsibilities for EMA and Member States

‘monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk benefit balance’

- PRAC performs initial analysis and prioritisation of signals of new risks or risks that are changing or changes to the risk-benefit balance.