EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmacovigilance. Building capacity and improving methods

DIA European Regulatory Affairs Forum

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EMA

In this talk

- EMA is the hub of the European Network
- Eudravigilance
- EPiTT
- ENCePP
- Other initiatives
- IMI Protect
- International work
- Integrating benefits and risks
- Looking forward

EMA is the hub of the European Network

"coordination of the supervision, under practical conditions of use, of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation"

EudraVigilance

- EudraVigilance: operational since December 2001
- Provides a data-processing network, which interlinks the EMA with all Member States, the EC and marketing authorisation holders
- Operates between ‘trusted’ (registered) users only
- Supports fully automated, rapid, secure (encrypted), electronic exchange of case reports between registered users
- Provides a common EU pharmacovigilance database accessible to all Member States (all member states can report to the system and all Member States can analyse the data to conduct safety reviews)

EudraVigilance

- New business rules to improve utility (especially important for SUSARs)
- EudraVigilance Access policy – policy finalised 2010
- Data quality tender – to start 2010
- International standardisation – see later

EudraVigilance

- Contains 1.5 million case reports* of suspected serious adverse reactions for medicinal products authorised in the EU
  - Average new case reports per month: 39.700*
- Supports the EU pharmacovigilance and risk management activities
  - All Member States can analyse world-wide data – repeated training offered and 'Eudravigilance support program' for rapporteurs
- Facilitates the EU decision making process related to the benefit risk evaluation of medicinal products
- Key tool to protect public health of EU citizens:
  - Allows new or changing risks to be detected early
  - Allows rare adverse effects to be detected
  - Allows assessment for risk factors and thus possibilities for minimising risk
  - Allows comparisons between products
- MSs and EMA share safety 'signals' based on EV data
- RMS and rapporteurs analyze the EV data to support their monitoring role

EudraVigilance

- Eudravigilance validation study
  - Direct evidence that more than 54% of serious safety issues can be detected earlier if Eudravigilance is used in addition to other pharmacovigilance resources

  - Why – Analysis of pooled data:
    - Detection of rare ADRs
    - ADRs detected earlier as absolute numbers are greater

Reference:*Drug Safety*, 33(6), pp. 475-487

EPITT (European Pharmacovigilance Issues Tracking Tool)

- Database facilitating the sharing of safety information of the medicinal products for human use between the National Competent Authorities (NCAs) and the Agency
- 4 “main modules”: Safety Issues, Safety Signals, PSURs, RMPs
- Objectives:
  - Tracking of the Safety Issues and Signals “life cycles” (independently of the authorisation type)
  - Tracking of the PhVWP recommendations and SPC wordings within the EU
  - Tracking and monitoring of the PSURs cycles and Risk Management Plans together with the implementation of the regulatory actions they require
  - Support to the European Incident Management Plan Procedure
  - Easy retrieval of the documents related to the safety of a medicinal product
- EPITT is:
  - 280 Users within the EU (Agency and NCAs)

EU-RMP Annex 1 Update

- The EU-RMP Annex 1 is:
  - The structured electronic representation of the EU Risk Management Plan (EU-RMP)
  - The interface between EU-RMPs and EudraVigilance

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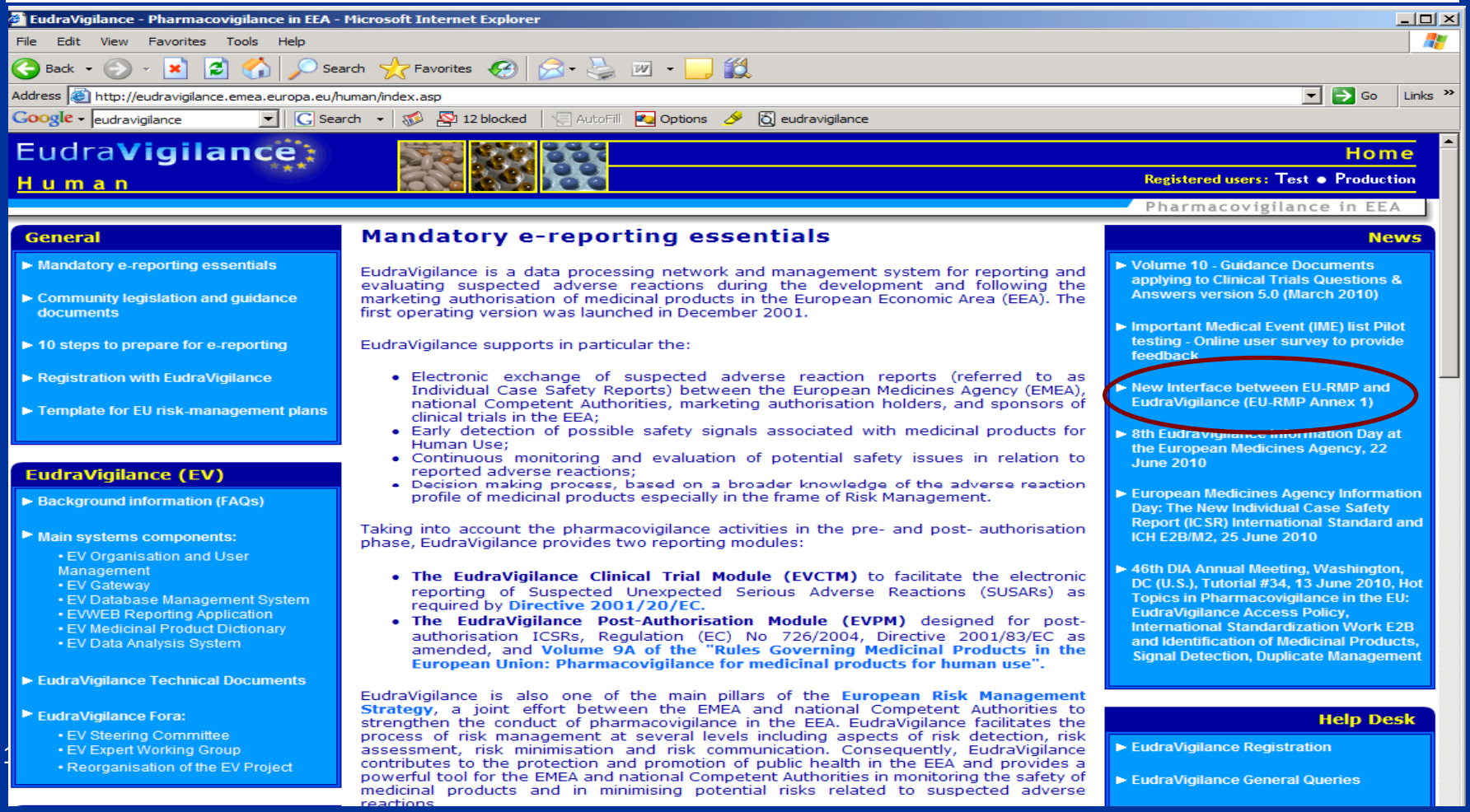
EU-RMP Annex 1 in the EudraVigilance webpage



What is ENCePP? www.encepp.europa.eu

European Network of Centres for Pharmacoepidemiology (PhEpi) & Pharmacovigilance (PhV) is an Agency-led project to bring together the available expertise and research experience in the fields of PhEpi and PhV scattered across Europe in a **Network of Excellence**, [research centres, healthcare databases, electronic registries and existing networks].

The **aim** is to **further strengthen the post-authorisation monitoring of medicinal products** in Europe by facilitating the conduct of high quality, multi-centre, independent post-authorisation studies focusing on safety and on benefit: risk.

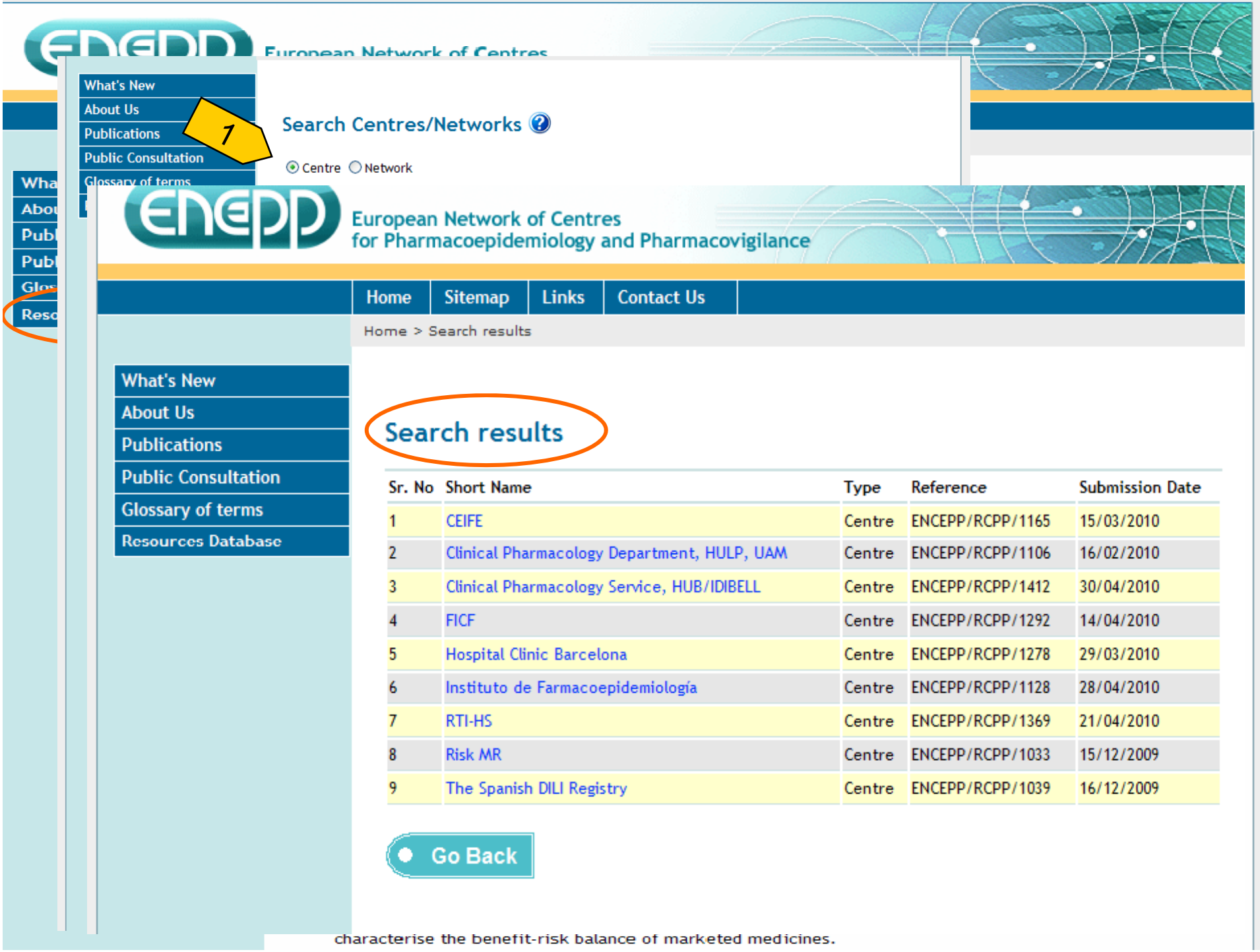
ENCePP Resource Database

ENCePP aims to **increase the capacity** to conduct quality Post-Authorisation studies in Europe.

→ **Database** describing resources in ENCePP and facilitating searches.

- 60 research centres
- 8 specialised networks (e.g. cutaneous ADRS, psoriasis, paediatric population…)
- Data sources (Eurocat, GPRD, Memo, etc)

http://www.encepp.eu/encepp/resourcesDatabase.jsp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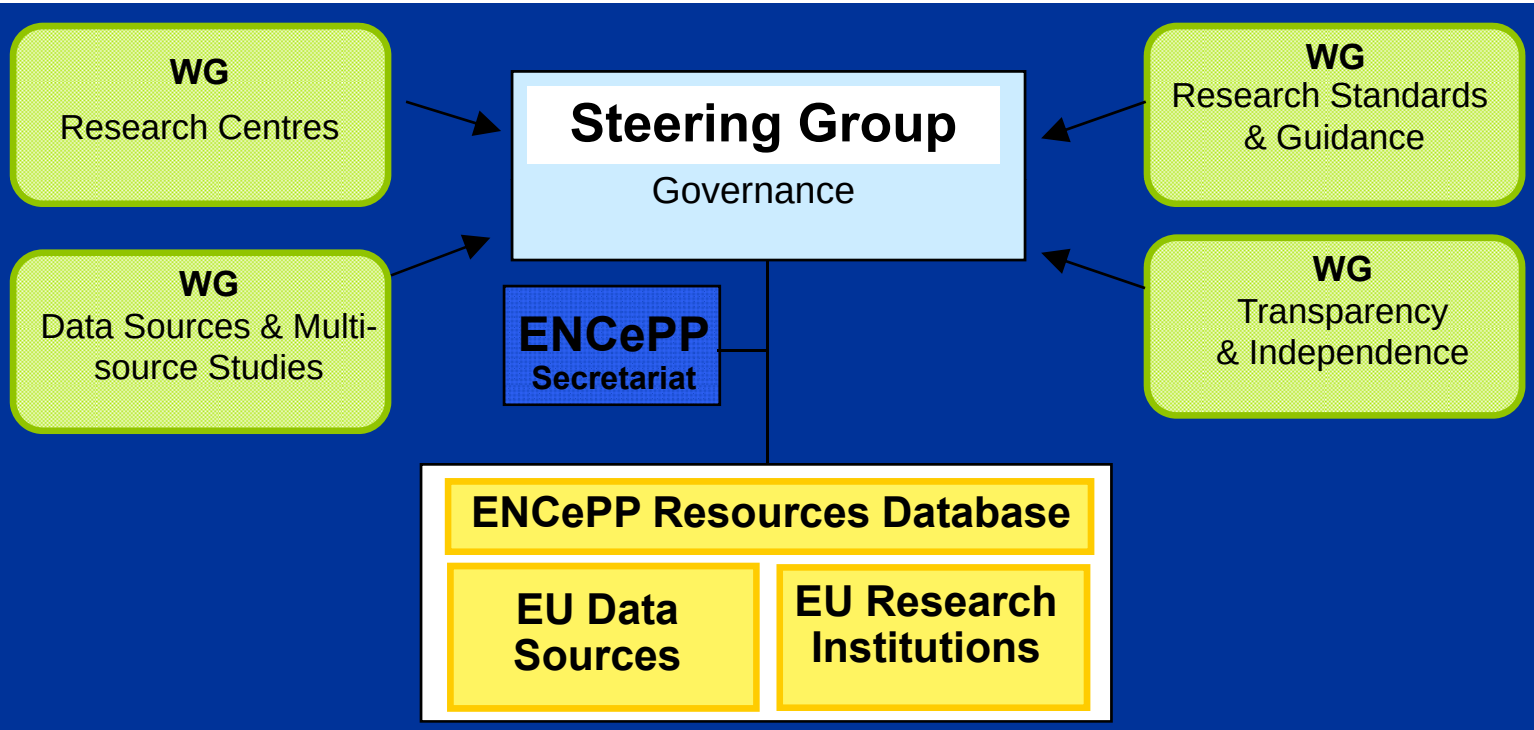
Go Back
characterise the benefit-risk balance of marketed medicines.

ENCePP–Structure and main components



ENCePP Code of Conduct for Studies

Govern the responsibilities of and interaction between stakeholders (funder-investigator) in the conduct of studies to ensure **transparency** and promote **scientific independence.**

Essentially a charter of rights and obligations covering the development of the study protocol, study conduct, data ownership, access to data, publication of results, communication, etc.

ENCePP Register of Post-authorisation studies

Purpose: i) Reduce publication bias, ii) increase transparency, iii) promote information exchange and iv) facilitate collaborations within the scientific community.

Scope: mandatory only for “ENCePP studies” (largely non-interventional); voluntary for all others.

other registers of Post-authorisation studies exist (Spain, Italy, USA)…

"ENCePP study" - CoRe Principles

Any PhV/PhEpi study whose main investigator works at a centre included in the ENCePP database of resources and for which the following (CoRe) criteria are met:

- **ENCePP Code of Conduct**: signed declaration and checklist
- **Methodological standards for protocols**: signed checklist

The completed and signed declaration and checklists and study protocol must be sent to the ENCePP Secretariat before the start of the study. The declaration and the checklists will be made public.

- **e-Register of post-authorisation studies**: Registration in the Register before study start

Basically, the main investigator agrees to conduct the study according to ENCePP rules and methodological research standards.

Benefits of ENCePP

ENCePP will contribute to:

- Identify, characterise and promote access to PhV/ PhEpi resources in the EU.
- Improve research standards
- Increase independency and transparency in research
- Stimulate collaboration/ exchange of information and experience

ods

Collaboration European Commission [FP-7]

List of priorities in drug safety research (off-patent or class effects)

Multinational research projects, including academic centres, hospitals, SMEs, patient groups, industry, etc

Duration is ~ 5 years; Public funding ~ € 3 million

- 2nd Call (2007) – CV and GI Safety of NSAIDs

  http://www.sos-nsaids-project.org/

- 3rd Call (2008) – Arrythmogenic potential of several classes of medicines.

  http://www.aritmo-project.org/

Collaboration European Commission [FP-7]

- 4th Call (2009)

  EMA prepared summary of each priority and published on web
  - Long-term effects of methylphenidate in children treated for ADHD *
  - Long-term adverse effects of immunomodulators *
  - Long-term adverse skeletal effects of biphosphonates
  - Medicine use in pregnancy (design of effective pregnancy prevention programmes, recommendation for safe use in pregnancy, etc) *
  - Suicidal behaviour in relation to certain drug use (antidepressants, antipsychotics, varenicline, montelukast) *
  - Safety aspects of antipsychotics in demented patient

- 5th Call (July 2010 ?)

PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics by an European ConsorTium

PROTECT is receiving funding from the European Community's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu).

PROTECT Goal

To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

These methods will be tested in real-life situations.

Rationale: what are the needs ?

- **Data collection**
  - efficient and simple methods for early data collection directly from patients
  - non-prescribed medicines
  - linkage to health event databases
- **Signal detection**
  - spontaneous reports: in-depth analysis of methods and good practice recommendations
  - better use of electronic health records and clinical trials
- **Signal evaluation**
  - understanding of variability in results of studies of same safety issue in same or different data sources
  - detailed guidance and standards regarding design of pharmacoepidemiological studies
- **Benefit-risk assessment**
  - widely accepted method for integrating data on benefits and risks from clinical trials, observational studies and drug reaction reports
  - display of benefit-risk assessment for use by patients, prescribers, regulators...

Partners

Public

Regulators:
EMA (Co-ordinator)
DKMA (DK)
AEMPS (ES)
MHRA (UK)

Academic Institutions:
University of Munich
FICF (Barcelona)
INSERM (Paris)
Mario Negri Institute (Milan)
University of Groningen
University of Utrecht
Imperial College (London)
University of Newcastle Upon Tyne

SMEs:
Outcome Europe
PGRx

Others:
WHO UMC
GPRD
IAPO
CEIFE

Private

GSK (Deputy Co-ordinator)
Sanofi- Aventis
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer Schering
Astra Zeneca
Lundbeck
NovoNordisk

Work Packages

WP2: Framework for Pharmacoepidemiological Studies
To develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies, applicable to different safety issues using different data

WP3: Methods for Signal Detection
To develop new methods, and assess existing ones, for signal detection from spontaneous reports, electronic health records and clinical trials

WP4: New tools for data collection from consumers
To develop modern methods of data collection directly from consumers in their natural language in several EU countries, including using web-based data collection, and computerised telephone interviews.

Work Packages

WP5: Benefit-Risk Integration and Representation
To develop methods for use in benefit-risk assessment including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods.

WP6: Validation studies involving an Extended Audience
To validate methods developed in WP2 to 5 in various data sources owned or managed by Consortium Partners or members of the Extended Audience.

WP7: Training and Communication
To identify training opportunities and support training programmes in the fields addressed by PROTECT.

The PROTECT community

International work

European Economic Area – 30 member states

EMA/Commission bilaterals:

- FDA
- Japan
- Health Canada

Multilateral / global

- CIOMS
- ICH
- ISOP
- ISPE
- WHO
- ISO / CEN / HL7 / CDISC

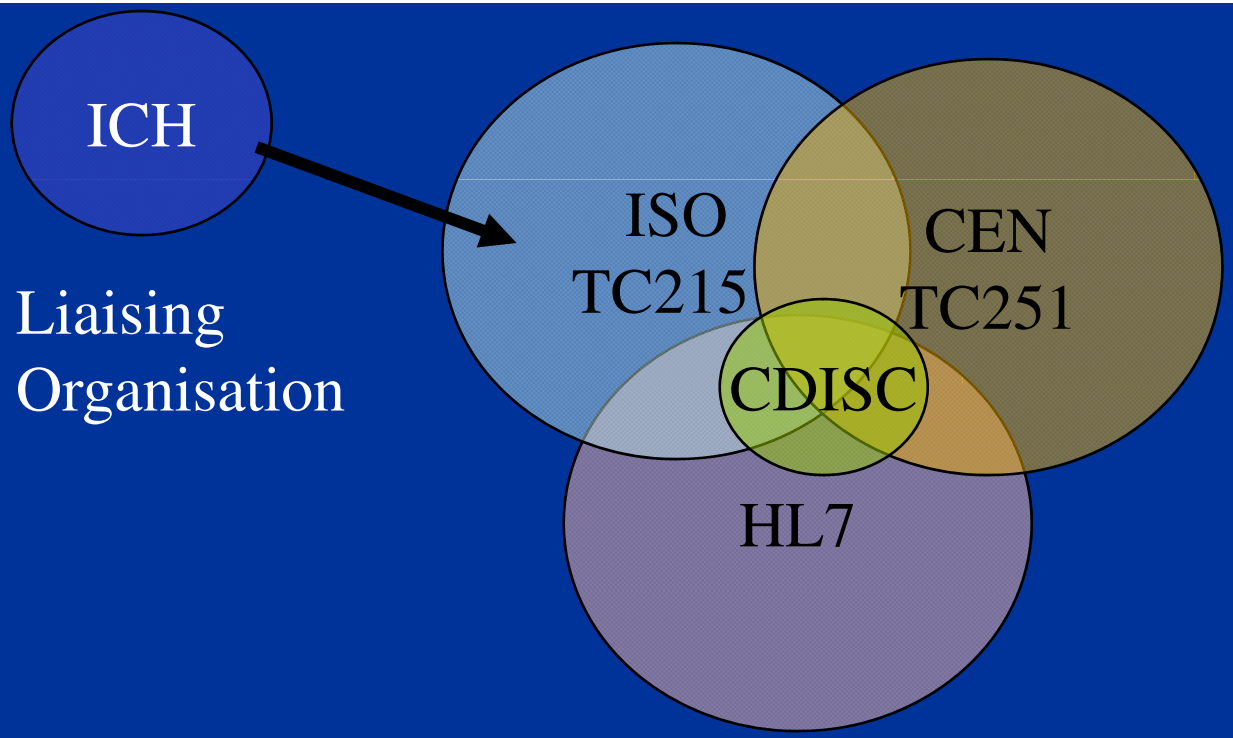
Advantages of International collaboration

- Pooling / sharing of expertise
- Peer review of each others work
- Benchmarking
- Sharing standards
- Bigger population from which to collect data
- Bigger databases – greater power to detect (e.g. EudraVigilance)
- Different healthcare systems – allows comparisons of use and impact of risk minimisation measures

Standardisation

- Identification of Medicinal Products (IDMP)
- Individual Case Safety Report (ICSR)
- Electronic Health Records
- Clinical Trial Registration and Reporting

From local to global: standardisation - Joint Initiative



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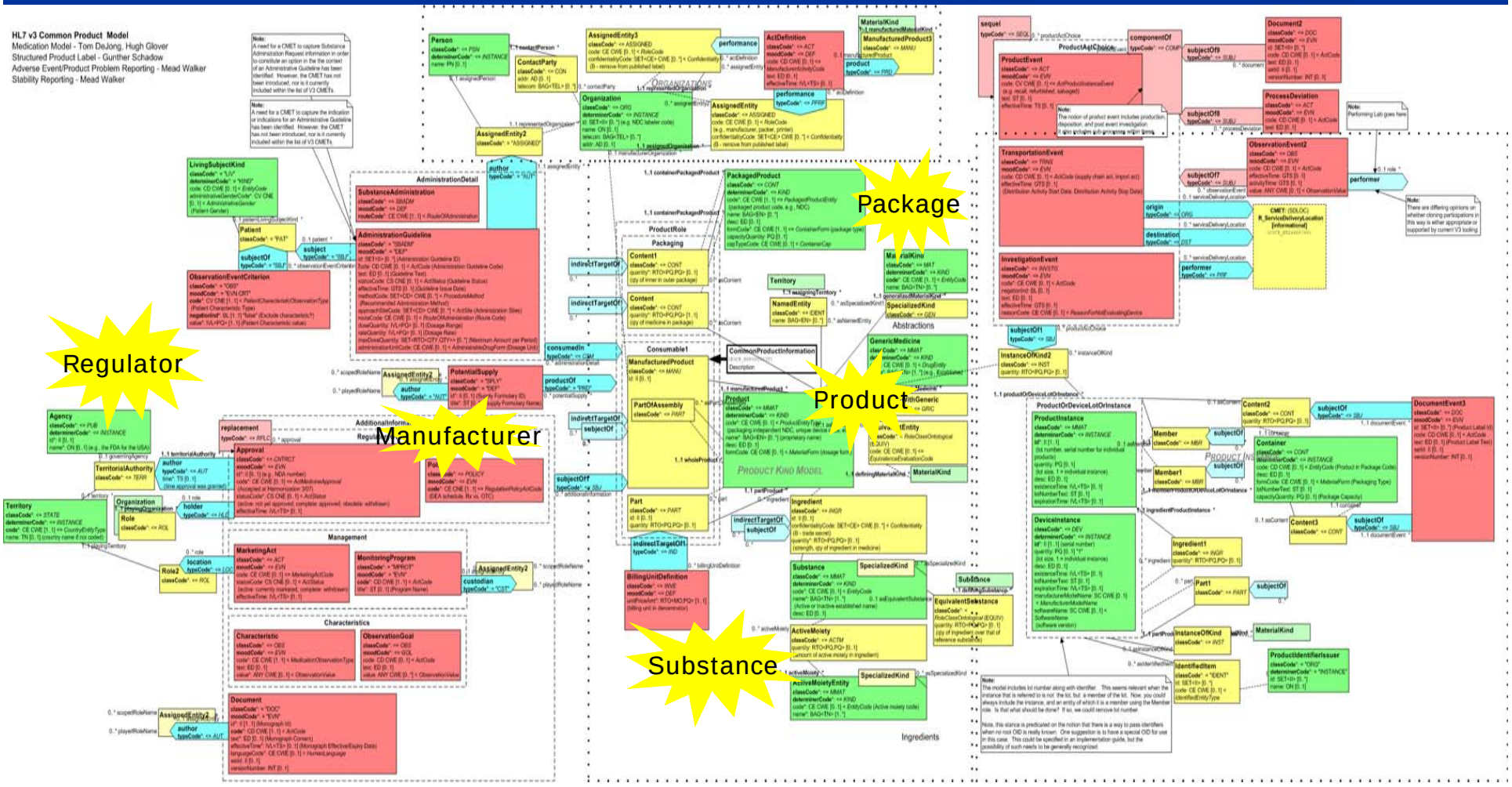
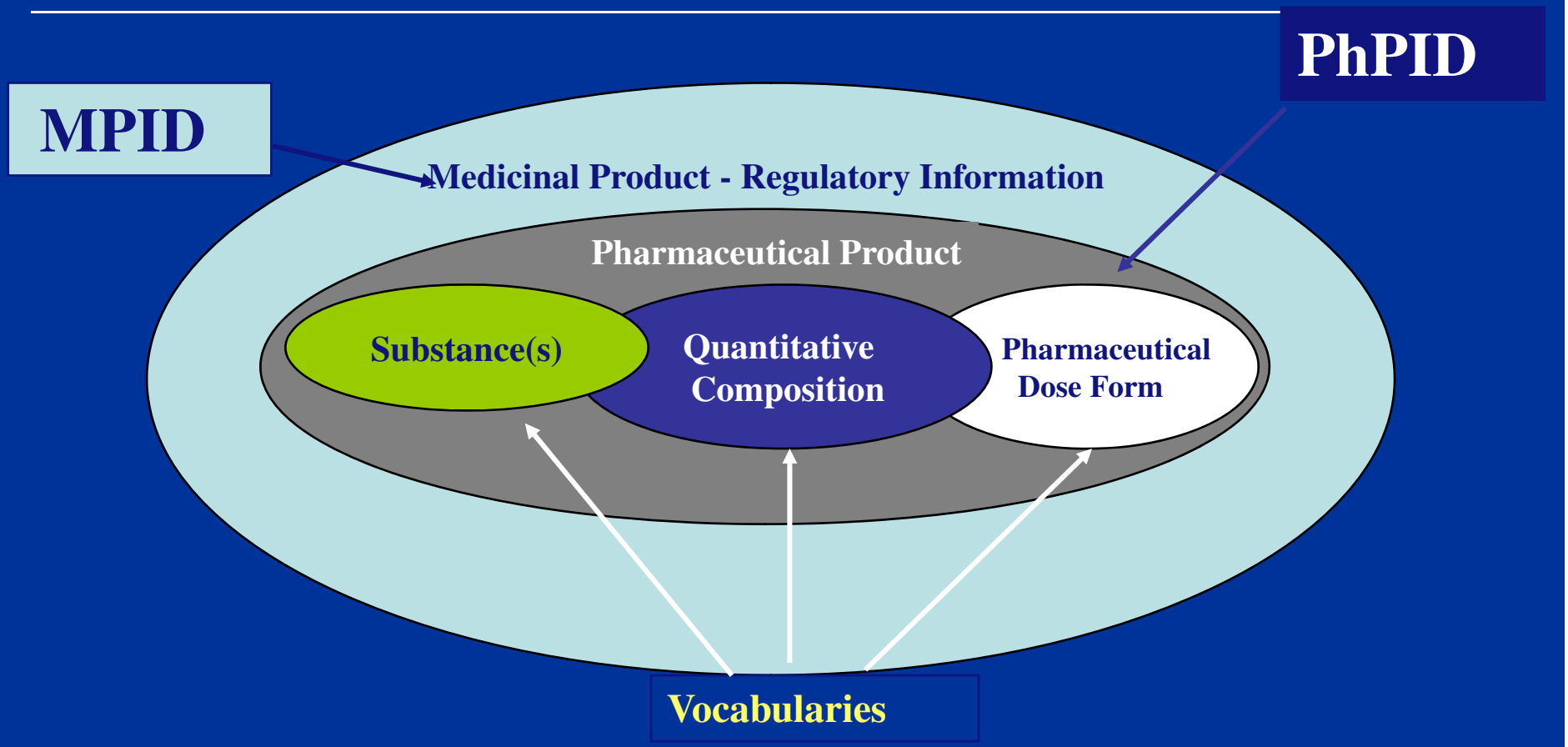
Identification of Medicinal Products



IDMP: Conceptual Overview



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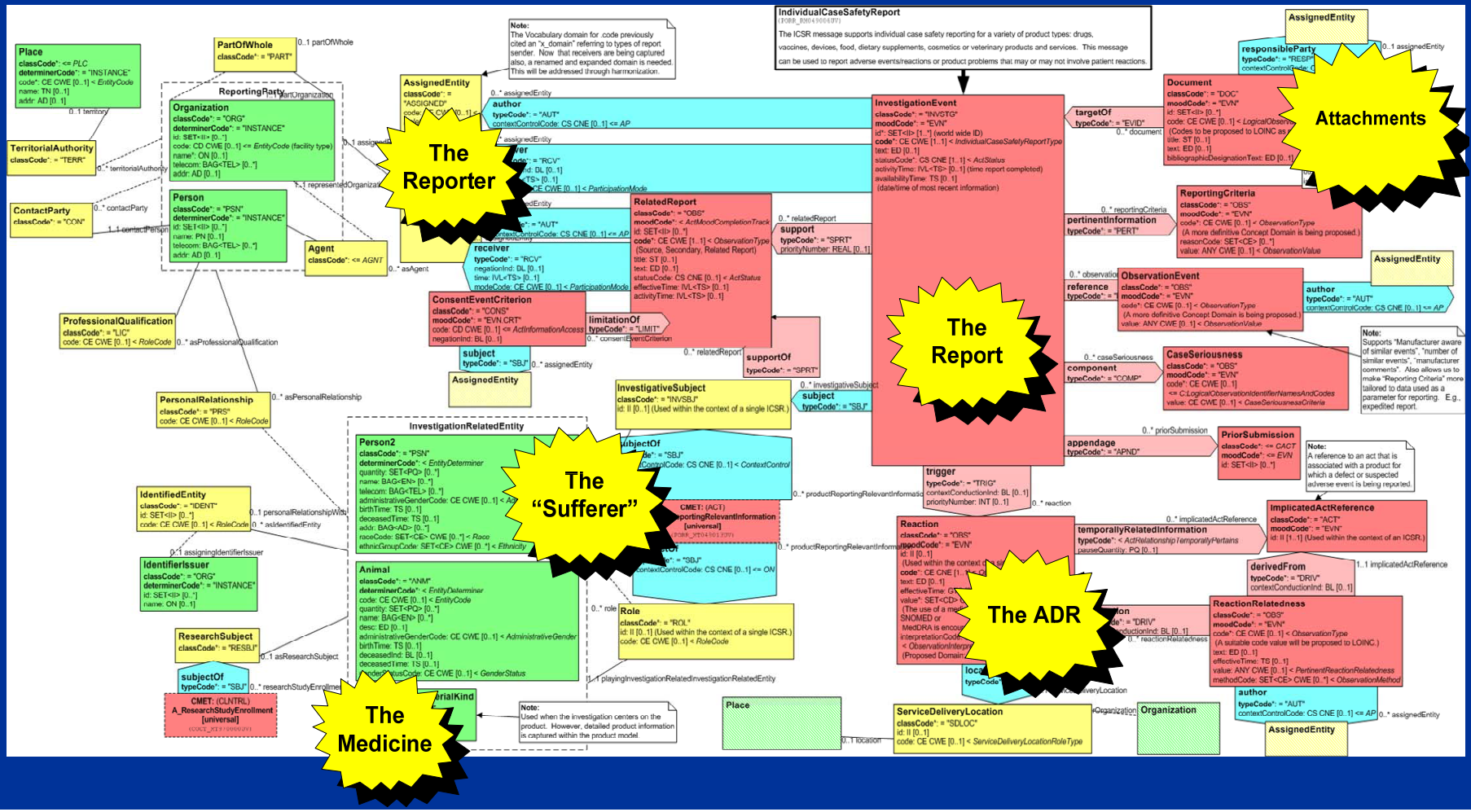
ICSR Standard



Standardisation

ICSR – 2011 (mid)

IDMP – 2011 (late)

From risk to benefit risk

- EU Paediatric Regulation: planning pharmacovigilance and effectiveness
- EU Advanced Therapies Regulation: planning pharmacovigilance and effectiveness
- Revised EU Risk management guideline 2010
- Pandemic monitoring

The European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring

The European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring

- April 2009 novel H1N1 influenza outbreak starts in Mexico
- June 2009 WHO declares pandemic
- September 2009 Commission authorizes pandemic vaccines
- September 2009 Post-authorisation benefit-risk monitoring strategy in place
- How did they do that?

Preparation and collaboration!

European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 25 June 2009
Doc. Ref: EMEA/359381/2009

CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine

Adopted by CHMP in November 2006

Revision 1.0 adopted by CHMP on 25 June 2009

- Recommendations developed by a Working group composed of members of the Pharmacovigilance Working Party, the EMA and vaccine manufacturers
- This document describes additional pharmacovigilance activities and additional risk minimisation activities that should be presented, if applicable, by vaccine manufacturers in the Risk Management Plan to be submitted at the same time as an authorisation application.
- Recommendations made legally mandatory in the European Commission Decision.

The European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring: Rationale

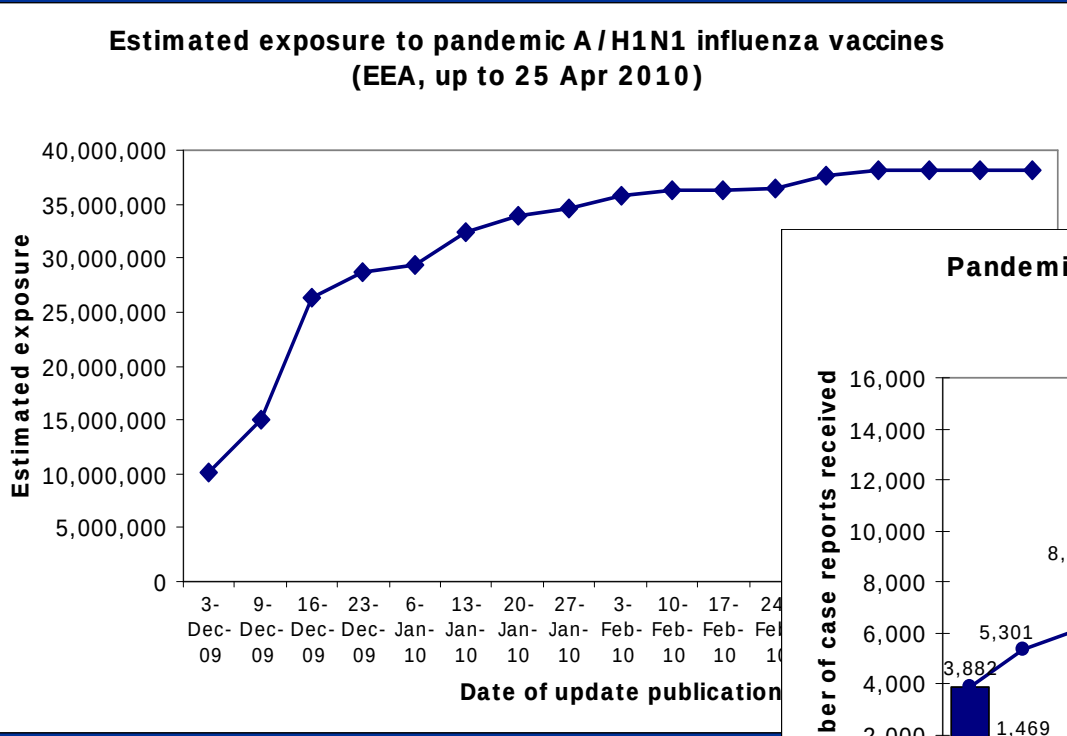
- CHMP Recommendations for the RMP provide obligations to VM
- Other research needs may not be covered
- 'Research groups' may generate useful data for the B/R of the vaccines or data with high media interest
- These data need to be rapidly evaluated by regulators in order to take quick decisions or respond quickly to public concerns
- Principles of exchange of information to be defined in advance
- Proposals for roles and responsibilities

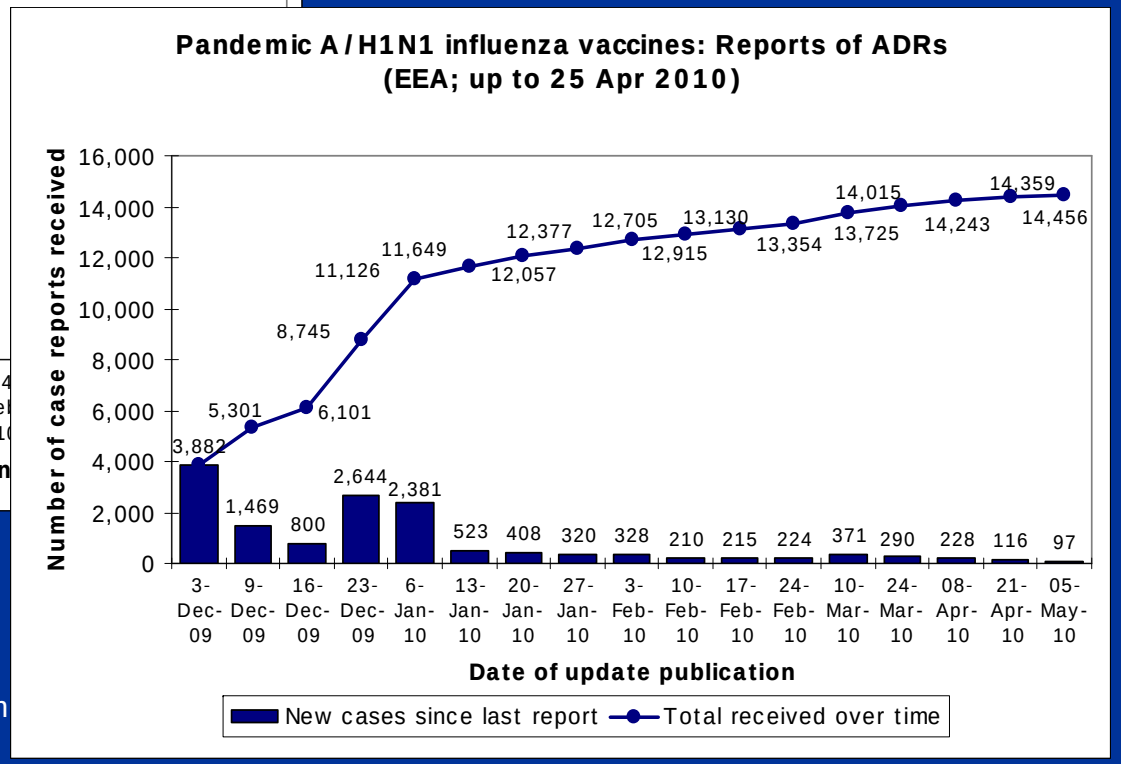
The European Strategy for Influenza /H1N1 Vaccine Benefit-Risk Monitoring:

- Operational formally since October 09
- Publicly announced November 09
- **First EMA pandemic pharmacovigilance report: published 3 December 2009**

A few results

Spontaneous reports: main data source for vaccine safety monitoring





	Exposure	ADR reports
Pandemrix:	30.6 million	10,912
Focetria:	6.5 million	3,018
Celvapan:	0.6 million	551

Be informed

- Be informed about key strategic developments:
  - EMA working to ensure stakeholders have the information needed for excellence pharmacovigilance and risk management:
    - The European Network for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is now operational. Opportunity to engage: ENCePP Info-Day 26 Nov 2010
    - EudraVigilance is the EU system for managing safety reports and detecting safety signals. EudraVigilance Info-Days: 22 June and 19 October 2010
    - Important work on international standardisation on pharmacovigilance. New individual case safety report Info-Day 25 June 2010

EMA is the hub of the European Network

Working with the Member States, industry, sponsors, health professionals and patients to build capacity and improve methods.