



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# The EudraVigilance System How Can it Facilitate Work Sharing?

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Strengthening of Work Sharing on Clinical Trials in Europe  
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# Overview

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- Legal Requirements
- EudraVigilance objectives
- EudraVigilance system components
- EudraVigilance statistics
- EudraVigilance enhancement
- EudraVigilance and work sharing in clinical trials
- Conclusions



# Legal Requirements Establishing European Database

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## Pre-Authorisation: Directive 2001/20/EC

- Article 17 (3) define the requirements for the reporting of Suspected Unexpected Adverse Drug Reactions (SUSARs) to the EudraVigilance Clinical Trial Module (EVCTM)
  - It lays down the obligations of each Member State who shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in EVCTM.
- Article 10, provides for the obligation of the Agency for the operation of EVCTM.
- No defined legal requirements for electronic adverse reaction reporting, addressed in Guidance documents.



## Legal Requirements Establishing European Database

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### Post-Authorisation: Regulation 726/2004 and Directive 2001/83/EC as amended

- Article 105 of Directive 2001/83/EC provides for the setting of a data processing network for the exchange of pharmacovigilance information.
- Article 26 of Regulation (EC) No 726/2004 refers to the pharmacovigilance database and data processing network for the rapid transmission of information to the Competent Community Authorities.
- To facilitate the population of the database, Article 24 of Regulation (EC) No 726/2004 and Article 104 of Directive 2001/83/EC as amended state that save in exceptional circumstances, suspected adverse drug reaction shall be transmitted electronically.



# EudraVigilance Objectives



- Common database accessible at a single point in EEA
- Suspected serious (unexpected) adverse reactions associated to all medicinal products
  - With a marketing authorisation in EEA (Dir. 2001/83/EC, Reg. (EC) 726/2004),
  - Subject to clinical trial authorised in EEA (Dir. 2001/20/EC).
- Since 2001 for safety reporting in post authorisation phase.
- Since 2004 for SUSARs reporting from clinical trials.
- Between 2007 and 2009, of 972 users of NCAs, MAHs and sponsors were trained on EudraVigilance.



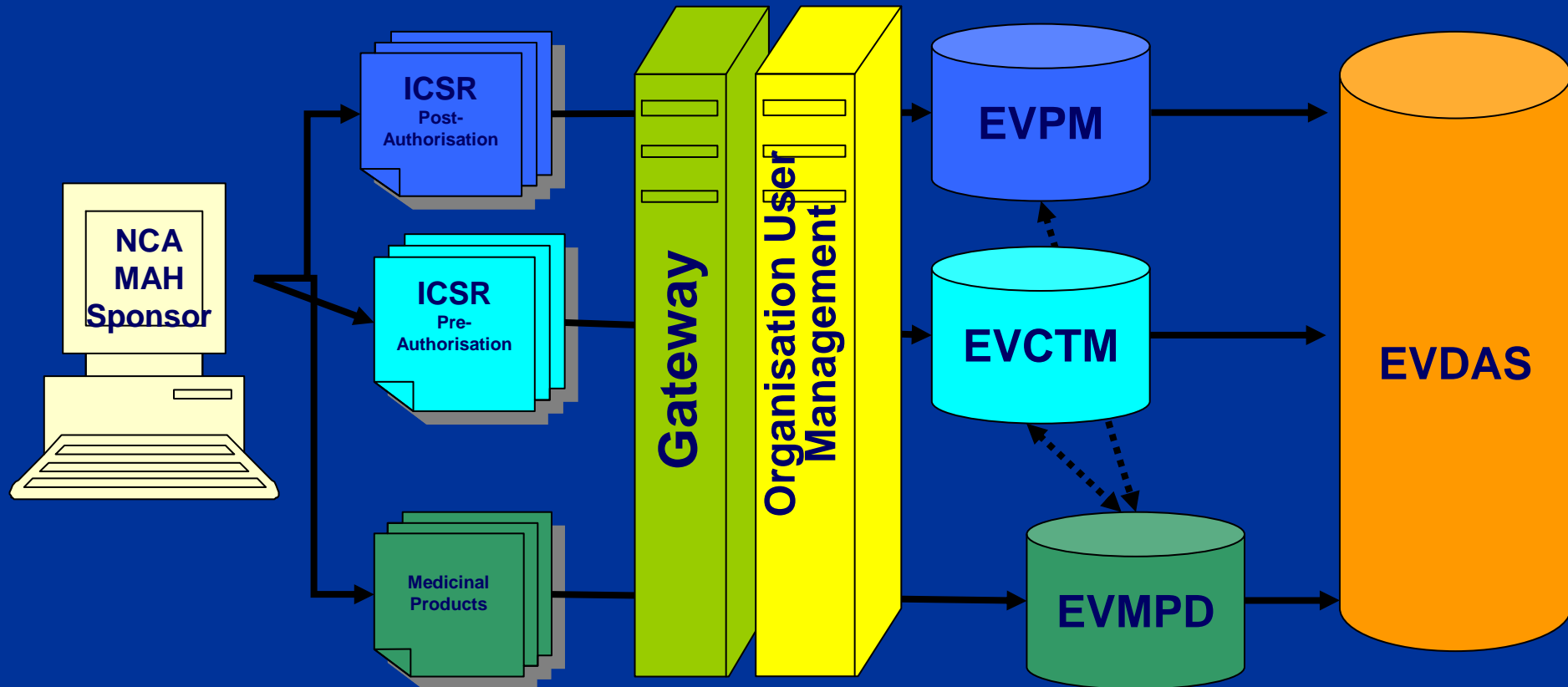
# EudraVigilance Objectives



- Support EU pharmacovigilance and risk management activities with the aim to protect public health.
  - Use by NCAs and EMA for signal detection activities.
  - Important contribution in monitoring of vaccines and antiviral medicinal products in H1N1 pandemic (pre and post phase).
- Facilitate the decision making process as regards the safety of medicinal products or classes of medicines
  - Committee for Human Medicinal Products (CHMP) and its scientific committees and working parties.
  - Average 43,000 expedited ICSRs processed per month, directly available for data analysis and signal detection to experts of NCAs and of EMA.



# EudraVigilance System



7 ICSR: Individual Case Safety Report  
EVPM: EudraVigilance Post Authorisation Module  
EVCTM: EudraVigilance Clinical Trial Module

EVDAS: EudraVigilance Data Analysis System  
EVMPD: EudraVigilance Medicinal Product Dictionary



# EudraVigilance System Components



## EudraVigilance Gateway

- Common electronic reporting network in the EEA for fully automated and secure data exchange between all stakeholders: Sponsors, MAHs, NCAs, EMA.

## Organisation and User Management system

- Automatic synchronisation of electronic data exchange between the various parties.
- Complies with all aspects of data privacy and data protection.
- Define users access and users rights in transactional database,
- Used in implementation of EudraVigilance Access Policy.



# EudraVigilance System Components



## EudraVigilance Database Management System (1)

Core repository of ICSRs, composed of two modules:

### 1. The EudraVigilance Clinical Trial Module (EVCTM):

- SUSARs originating in clinical trials as defined in Dir. 2001/20/EC,
  - Related to investigational medicinal products used in clinical trials authorised in the EEA.
  - Related to medicinal products authorised in EEA for clinical trials authorised outside EEA only.



# EudraVigilance System Components



## EudraVigilance Database Management System (2)

### 2. EudraVigilance Post-Authorisation Module (EVPM):

- Suspected serious adverse reactions<sup>#</sup> originating from:
  - Healthcare professionals (spontaneous reports),
  - Post-authorisation studies (non-interventional studies)
  - Named-patient / compassionate use programmes,
  - Worldwide scientific literature (spontaneous reporting, non-interventional studies);
- Suspected transmission of infectious agents via a medicinal product<sup>#</sup>.

*<sup>#</sup>Related to any medicinal product authorised in the EEA, independent of the authorisation procedure*



# EudraVigilance System Components



## EudraVigilance Medicinal Product Dictionary (EVMPD)

- Standards for core information on authorised and development medicinal products
  - For coding of medicinal product information in ICSRs.
- Data are provided by MAHs and sponsors of clinical trials.
- Integrates all terminologies applicable to identification of a medicinal product:
  - E.g., medicinal product, active substances, excipients, pharmaceutical forms, routes of administration and strength units
  - Names, synonyms, translations



# EudraVigilance System Components



## EudraVigilance Data Warehouse & Analysis System (EVDAS)

- Core component supporting pharmacovigilance (PV) analysis.
  - Data from all EudraVigilance system components,
  - MedDRA dictionary.
- Assists users in
  - Signal detection and monitoring of safety of medicinal products (traditional and quantitative methods of signal detection).
  - Analysis and evaluation of individual cases,
  - Monitoring of compliance of expedited reporting timelines and of quality of ICSRs data.
- Currently accessible to all NCAs in EEA.
  - 184 experts in NCAs (clinical trial, PV) trained by EMA on EVDAS
- Future access to MAHs, sponsors, research organisations, Healthcare professionals and patients
  - Draft Access Policy under review after public consultation in 2009.



# EudraVigilance: Use by Sponsors

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## 3 Steps to submit SUSARs

### 1. Simple registration process

- At level of principal sponsor and subordinates if any.
- Each individual users must register.
- Through Responsible Person for EudraVigilance or EU-QPPV for commercial sponsors.

### 2. Training

- 3 days course in London, UK or locally in Member States.
- 1 trained user can train other users affiliated to the same sponsor.
- Reduced fees (50%) for Small and Medium-sized Enterprises (SMEs) and non-commercial/academic sponsors.

### 3. Transmission of SUSARs via Gateway or EV-Web tool

- 17 mandatory fields through 8 screens per case.
- MedDRA included in EV-WEB.



# EudraVigilance Statistics (31 Dec.2009)

## Cumulative Statistics on Processing of ICSRs

Core Repository	Number of ICSRs #	Number of Cases #	Origin of Cases EEA/Non-EEA (%)	Source of Cases MAH-Sponsors/NCAs (%)
EVPM	2,847,218	1,992,818	39 / 61	70 / 30
EVCTM	339,442	140,148	51 / 49	81 / 19

# Including backlog

## Organisations Reporting on Monthly Basis in 2009

Core Repository	MAHs/Commercial Sponsors	Non-Commercial/Academic Sponsors	NCAs
EVPM	173	NA	29
EVCTM	138	14	9



# EudraVigilance Enhancement - Data Quality

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## Revision of Business Rules – Effective 1 Jun. 2010

- New validation rules improve the quality of the data received in EudraVigilance by mandating provision of
  - Active substance name for reports submitted to EVCTM when the drug is considered suspect or interacting,
  - Presentation of a valid EudraCT number in the field Study Name for all ICSRs transmitted to EVCTM and originating within the EEA,
  - Country of the primary source,
  - Primary source qualification (healthcare professional, non-healthcare professional),
  - Seriousness of the ICSR and the seriousness criteria,
  - Outcome of the reactions/events at the time of the last observation,
  - Characterisation of the drug role (suspect, interacting, concomitant).



# EudraVigilance Enhancement - Data Quality

## Proposal of New Business Rules for EVCTM (1)

- Events unrelated to the investigational medicinal product often reported together with adverse reactions within ICSRs submitted by sponsors to EVCTM.
- For each reported event/reaction a causality assessment must be provided from the investigator and/or sponsor against any of the medicinal products classified as suspect or interacting.
- Any initial ICSR must contain at least one reaction with a causality assessment '**Reasonable possibility**' to at least one of the reported medicinal products classified as suspect or interacting. This rule is not applied to follow-up ICSR.
- If these requirements are not followed, the ICSR is classified as an error report and requires correction and resubmission if applicable.



# EudraVigilance Enhancement - Data Quality

## Proposal of New Business Rules for EVCTM (2)

- ICH E2B(R2) allows the possibility to provide several results of causality assessment by using one or more methods of assessment.
- At least one method of assessment corresponding to the binary decision method<sup>[1]</sup> ('Reasonable possibility' or 'No reasonable possibility'), should be used to report the causal association between a medicinal product and a reported event/reaction. Use of other methods is optional.
- When using other methods of causality assessment, the sponsor should decide which categories of causality assessment result correspond to 'Reasonable possibility' and which ones refer to 'No reasonable possibility'.

<sup>[1]</sup> CIOMS Working Group VI, Management of Safety Information from Clinical Trials CIOMS Working Group VI (CIOMS, Geneva 2005).



# EudraVigilance Enhancement - Data Quality

## Data Quality Management Project

- Agreement at HMA (2008) to outsource EudraVigilance Data Quality Management activities on behalf of whole Network.
- Tender published on 6 October 2009 (ITT 77) includes:
  - Detection and management of duplicate cases,
  - Validation and 'cleaning' of medicinal products information in EVMPD,
  - Coding of medicinal products and active substances reported in ICSRs against the EVMPD data,
  - Notifications on expedited reporting compliance,
  - Implementation of recently enhanced business rules.
- 6.5 millions Euro for 4-year period applicable to prospective and retrospective data.
- Attribution of tender expected at 4<sup>th</sup> quarter 2010.



# EudraVigilance Enhancement - Data Quality

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## International Standardisation

- EMA is providing major input to international standardisation work
  - Identification of Medicinal Products (IDMP),
  - Revision of the electronic format for ICSRs.
- Both standards are recognised as joint initiative projects at the level of international standardisation organisations (ICH, ISO, HL7).
- Major steps forward in improving ADRs reporting in clinical trials and post-authorisation settings,
  - New fields available in ICSRs (e.g. EudraCT number),
  - Standards for reporting medicinal product information in ICSRs.
- Final standards are expected by 2011 for the ICSRs and 2012 for the IDMP.



# EudraVigilance Enhancement - CTFG collaboration

## EudraVigilance Expert Working Group (EV-EWG)

- Define policies on all aspects related to the practical implementation, operation of and access to EudraVigilance.

## EV-EWG Clinical Trial Subgroup

- Provide support to EV-EWG in clinical trial domain:
  - Specific requirements to further improve EVCTM and EVDAS functionalities based on input from CTFG and to develop standards reports in EVDAS for NCAs,
  - Revision of Detailed Guidance documents related to safety monitoring in clinical trials and electronic reporting to EudraVigilance (ENTR/CT 3 & ENTR/CT 4),
  - Initiative of the EC in the Assessment of the functioning of the Clinical Trial Directive,
  - Develop EudraVigilance training applicable to sponsors,
  - Q&As on safety reporting in clinical trials in relation to Vol. 10.



# EudraVigilance Enhancement - Clinical Trials

## Strengthening Regulatory Aspects

- Simplification of reporting rules for SUSARs in EEA:
  - Ambiguous on who should report (NCA or sponsor) to EVCTM and what should be reported.
    - Due to lack of clear harmonised requirements within the current Clinical Trial Directive, each individual Member State being responsible to implement reporting of SUSARs to EVCTM (Art. 17-3a).
      - Lead to duplication of reporting or no reporting at all.
- Need for mandated, structured data collection of Investigational Medicinal Products (IMPs) in EVMPD to allow for unique identification of IMPs in SUSARs
  - List of all active substances in EVMPD to be made available in public domain for use in completing relevant fields in EudraCT.



## EudraVigilance - Work Sharing in Clinical Trials

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- EudraVigilance is an important and comprehensive adverse reactions/events reporting and analysis systems in EU
  - Data from pre-authorisation and post-authorisation phase.
- Work sharing with EudraVigilance can be implemented for
  - Approval of CTA by assessing safety of active substance(s) of IMP if used in previous CTs or already authorised in EEA (or same type of active substance with same properties),
  - Regular monitoring of safety of ongoing clinical trials through standard reactions monitoring/alert reports containing pre and post data,
  - Evaluation of ASR/DSUR through aggregated reports with all SARs related to IMP by mandating periodic provision of SEARs electronically to EVCTM.
    - Full set of SARs available for evaluation of marketing authorisation application by NCAs.



## Conclusions

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- EudraVigilance is a fully functional, robust system that makes an important contribution to public health.
- EMA endeavors to progress on the enhancement of EudraVigilance with view to enhance work sharing between NCAs and to simplify expedited reporting in the EEA
  - Revision of EudraVigilance Business Rules,
  - Data Quality Management Project,
  - Major input on ongoing international standardisation work,
  - Development of new standard reports for NCAs applicable to clinical trials.
- Room for improvement in clinical trials domain is multi-factorial:
  - Quality of data submitted to EudraVigilance
  - Need of strengthening current legislation on reporting of SUSARs.



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Thank You

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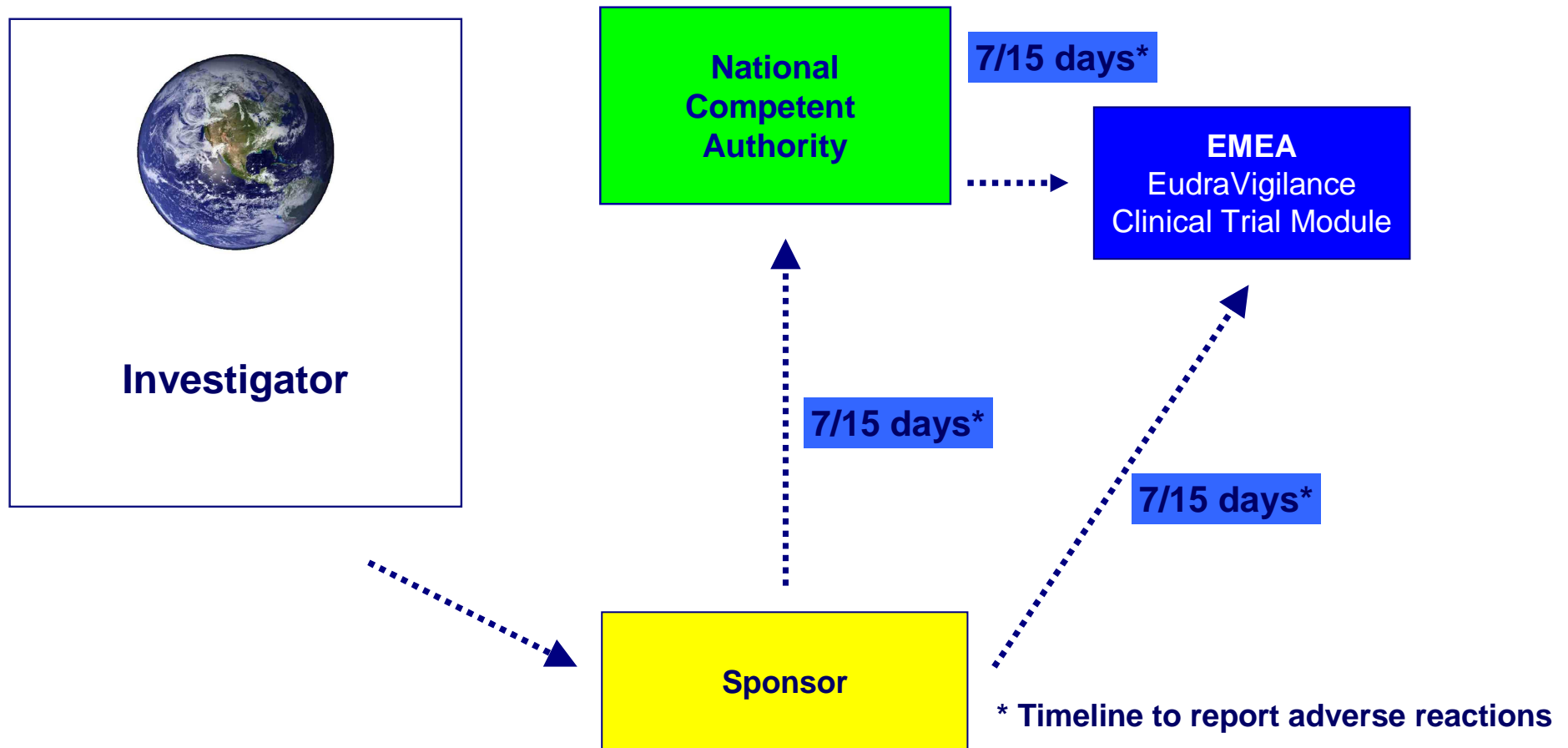
# Back-up Slides

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# Adverse Reaction Reporting Principles (Back up)

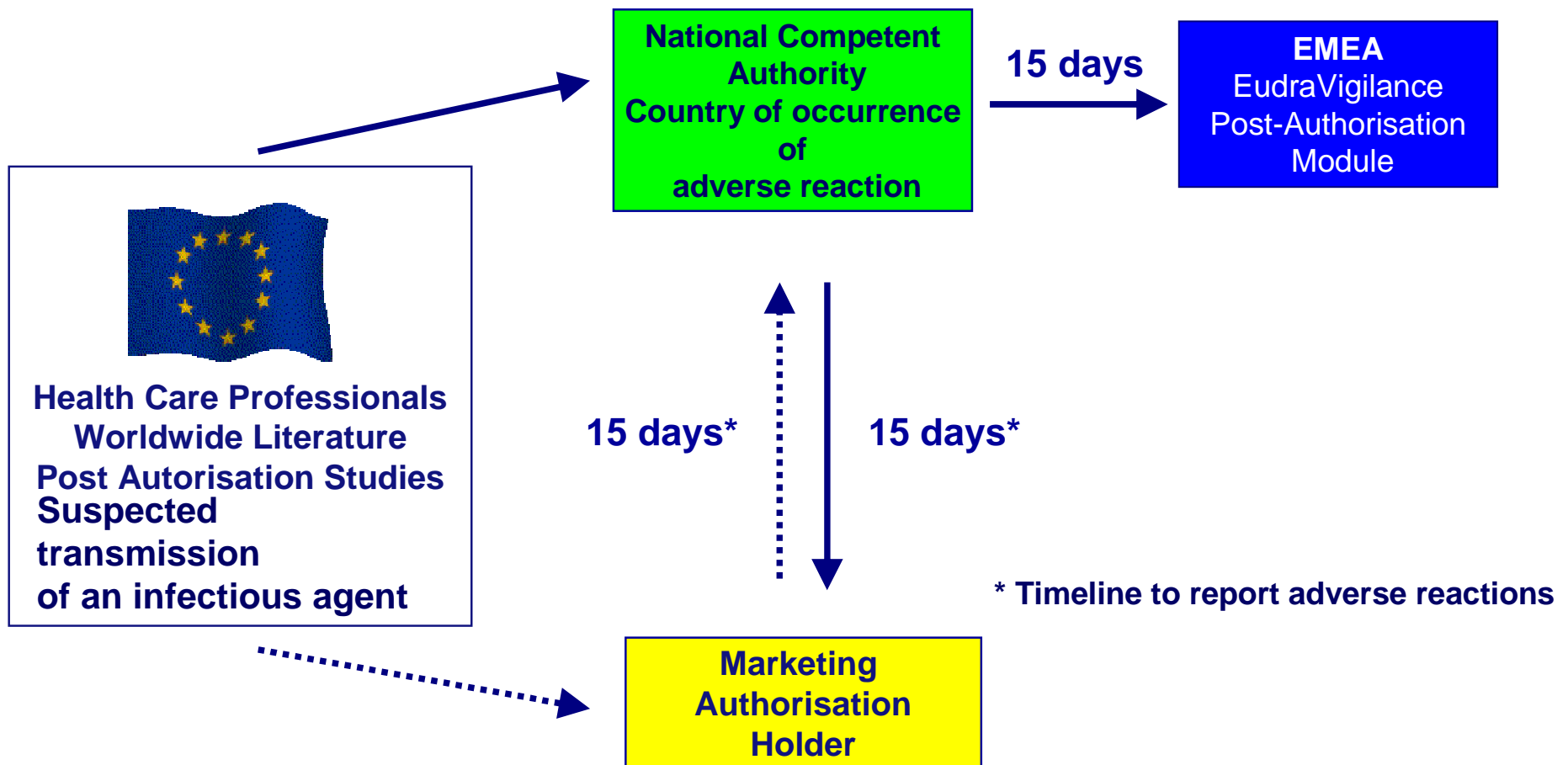
**Suspected Serious (Unexpected) Adverse Reactions associated to IMPs used in Interventional clinical trials authorised in EEA**





# Adverse Reaction Reporting Principles (Back up)

**Suspected Serious Adverse Reactions occurring within the EEA**





# Adverse Reaction Reporting Principles (Back up)

**Suspected Serious (Unexpected) Adverse Reactions occurring outside the EEA**



Health Care Professionals  
Worldwide Literature  
Post Authorisation Studies  
Suspected transmission  
of an infectious agent

**National  
Competent  
Authority**

**EMA  
EudraVigilance  
Post-Authorisation  
Module**

**Marketing  
Authorisation  
Holder**

15 days\*

15 days\*

\* Timeline to report adverse reactions



## EudraVigilance Statistics (31 Dec.2009)

### Number of Reports of SUSARs in EVCTM (Back up)

Year	Commercial Sponsors	Non-Commercial/ Academic Sponsors	NCA's	Total
2004	7,992	0	0	7,992
2005	28,080	27	6,747	34,854
2006	43,454	246	10,247	53,947
2007	51,774	329	12,166	64,269
2008	67,480	801	15,499	83,780
2009	70,726	739	23,135	94,600
Total	269,506	2,142	67,794	339,442



# EudraVigilance Enhancement - Data Quality

## Q&As Volume 10 Chapter II (Back up)

- Drafted by EV-EWG and CTFG and approved by the Ad Hoc Group on the Implementation of the Clinical Trials Directive
  - Minimum criteria as regards electronic reporting of SUSARs,
  - Definition of relevant follow-up information for expedited reporting,
  - Definition of clock start for expedited reporting of initial and follow-up reports,
  - Definition of timelines for expedited reporting for initial and follow-up (non-)fatal/life threatening reports,
  - ICH E2B(R2) format to use when data privacy rules apply,
  - The electronic reporting format of the EudraCT number in accordance with ICH E2B(R2) requirements and the new EudraVigilance Business Rules (01/Jun/2010),



# EudraVigilance Enhancement - Data Quality

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## Q&As Volume 10 Chapter II (continued) (Back up)

- Recommendations on the reporting of placebo that may be involved in SUSARs,
- Recommendations on the reporting of blinded SUSARs,
- Recommendations on the reporting of SUSARs described in the scientific literature,
- Reporting requirements for MAH, when informed by a sponsor of a SUSAR related to an authorised medicinal product which is an IMP in a clinical trial performed in the EEA,
- Recommendations on the reporting of SUSARs originating from a clinical trial authorised in the EEA, when the reaction is suspected to be related only to another authorised medicinal product taken concomitantly, which is not part of the clinical trial protocol.



# Acronyms

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- AE Adverse Event
- CT Clinical Trial
- CTA Clinical Trial Application
- CTFG Clinical Trials Facilitation Group
- EEA European Economic Area
- EV EudraVigilance
- EVCTM EudraVigilance Clinical Trial Module
- EVDAS EudraVigilance Data Analysis
- EV-EWG EudraVigilance Expert Working Group
- EVMPD EudraVigilance Medicinal Product Dictionary
- EVPM EudraVigilance Post Authorisation Module
- IDMP Identification of Medicinal Products
- ICSR Individual Case Safety Report
- IMP Investigational Medicinal Product
- MAH Marketing Authorisation Holder
- MS Member State
- NCA National Competent Authority
- SAE Serious Adverse Event
- SAR Serious Adverse Reaction
- SEAR Serious Expected Adverse Reaction
- SMEs Small and Medium-sized Enterprises
- SUSAR Suspected Unexpected Serious Adverse Reaction