EudraVigilance to support EU Pharmacovigilance Activities

EU Regulatory Network
Challenges and Opportunities for Croatia

5th Anniversary of the ALMP
13 – 14 November 2008

Rijeka, Croatia

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EudraVigilance - Overview

- EudraVigilance is the system to support EU pharmacovigilance activities
- It contains adverse reaction reports (Individual Case Safety Reports - ICSRs) for medicines licensed in the EU
- Such reports are received from National Competent Authorities (NCAs), marketing authorisation holders (MAHs) and Sponsors of clinical trials

Important milestones:

- *EudraVigilance Post-authorisation Module (EVPM) entered into production December 2001*
- *EudraVigilance Clinical Trial Module (EVCTM) entered in production May 2004*
- *Mandatory electronic reporting of ICSRs in the EEA as of 20 November 2005*
- *Release of the EudraVigilance Data Warehouse and Data Analysis System (EVDAS) to the EU NCAs on 2 July 2007*
- *Current number of reports (status 31 Aug. 08): 2.2 mill ICSRs*

What is the purpose of EudraVigilance?

- **Support EU pharmacovigilance and risk management activities:** aim is the protection of public health
- **Collection of suspected adverse reactions** in the pre- and post-authorisation phases
- **Monitoring of reporting compliance** with expedited reporting requirements by NCAs and MAHs
- **Ad hoc evaluation of potential safety issues**
- **Monitoring of core risk profiles** as outlined in EU Risk Management Plan (EU-RMP)
- **Support decision making process** at the level of the Committee for Human Medicinal Products (CHMP) and related working parties

Data collected in EudraVigilance

Post Authorisation Module (EVPM)

- Suspected serious adverse reactions
  - Health care professionals' spontaneous reporting
  - Post-authorisation studies (non-interventional)
  - Worldwide scientific literature (spontaneous, non-interventional)
- Suspected transmission via a medicinal product of an infectious agent

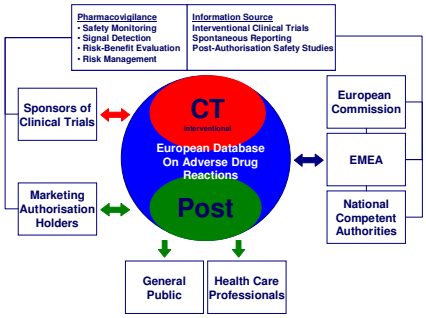
Applicable to all medicines authorised in the EEA independent of the authorisation procedure

Pre Authorisation Module (EVCTM)

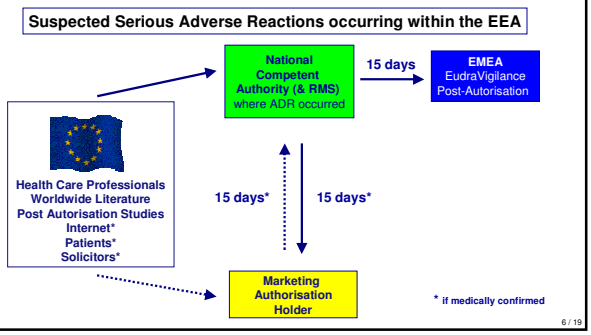
- Suspected Unexpected Serious Adverse Reactions (SUSARs) reported by sponsors of clinical trials
  - Interventional clinical trials

Applicable to all investigational medicinal products for clinical trials authorised in the EEA

Protection of Public Health

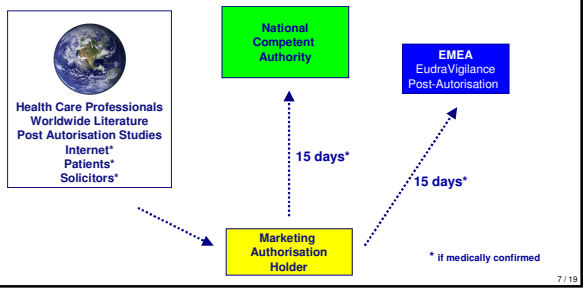


Reporting Requirements EEA



Reporting Requirements non-EEA

Suspected Serious (Unexpected) Adverse Reactions occurring outside the EEA



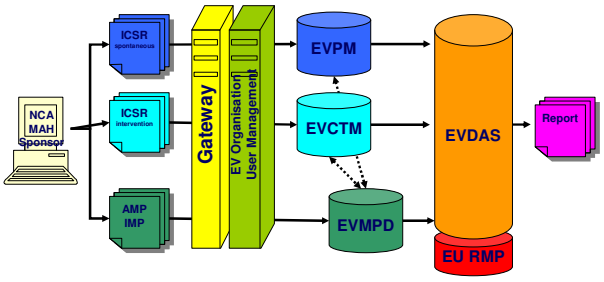
EU Risk Management Plans and EudraVigilance

- **Electronic interface between EU-RMP and EudraVigilance**
  - Monitor identified and potential risks and important missing information as outlined in the EU-RMP Safety Specification
- **Integration of core risk profile** in **Reaction Monitoring Reports** generated in EudraVigilance to support pharmacovigilance activities for centrally authorised products
  - Risk monitoring (identification and characterisation)
  - Evaluation of the effectiveness of risk minimisation measures
- The interface between EU-RMP and EudraVigilance is a **living document** due at
  - Submission of final version of EU-RMP at time of CHMP Opinion
  - Each time the EU-RMP is updated in the future

EudraVigilance System - Functions

- **Data processing network** interlinking all National Competent Authorities in the EEA, the European Commission and the EMEA to exchange information in pharmacovigilance
- **Electronic data exchange** of adverse drug reaction reports in line with **ICH standards** (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
- **Unique repository** of **EU and non-EU adverse drug reactions** for development and authorised medicinal products
- Incorporates the international medical terminology **Medical Dictionary for Regulatory Activities** (MedDRA)

EudraVigilance Data Processing



ICSR = Individual Case Safety Report
AMP = Authorised Medicinal Product
IMP = Investigational Medicinal Product

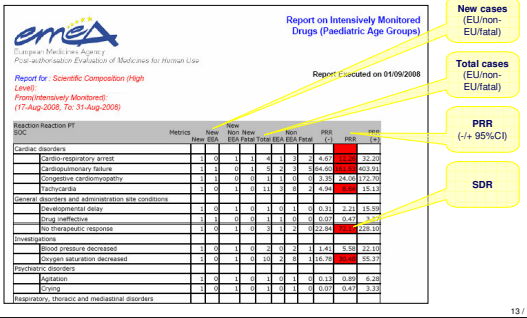
General Aspects of Signal Detection

- **Signal Detection** describes a **routine review of all ICSRs** reported to EudraVigilance:
  - For each product under monitoring all reactions reported within defined timeframes are listed for each System Organ Class
  - Reviewed by scientific staff at the EMEA in collaboration with Rapporteur/Co-Rapporteur
- **'Signals'** are based on **statistical algorithms** (e.g. Proportional Reporting Ratio: an event is relatively more often reported for a medicinal product compared to the number of reports of this event for all other medicinal products in the database)
- Each signal requires **careful medical evaluation** to be confirmed as causally related with the product

EudraVigilance Reaction Monitoring Report

- **Reaction Monitoring Report** is generated based on:
  - All spontaneously reported ICSRs over the last 15 or 30 days to EVPM
  - Generated at active substance level
  - All reports flagged as "suspect" and "interacting" by sender
- **List of reactions (MedDRA Preferred Terms)** for each product at substance level, **ranked by System Organ Class (SOC)** indicating
  - New cases/fatal cases associated with reaction
  - Total number of cases
  - Origin (EU/non-EU) of cases
  - Proportional Reporting Ratio (PRR) and 95% Confidence Interval
- **Signals of Disproportionate Reporting (SDR)** are highlighted in red if
  - N ≥ 3 and
  - Lower bound of 95% Confidence Interval of PRR ≥ 1

EudraVigilance Reaction Monitoring Report



Reaction Reaction PT SOC	Metrics	New New	New Non EEA	New New Fatal	Non Total	Non EEA	Non Fatal	PRR (-)	PRR	PRR (+)
Cardiac disorders										
	Cardio-respiratory arrest	1	0	1	1	4	1	3	2	4.67	18.26	32.20
	Cardiopulmonary failure	1	1	0	1	5	2	3	5	64.60	185.38	403.91
	Congestive cardiomyopathy	1	1	0	0	1	1	0	0	3.35	24.06	172.70
	Tachycardia	1	0	1	0	11	3	8	2	4.94	6.66	15.13
General disorders and administration site conditions												
	Developmental delay	1	0	1	0	1	0	1	0	0.31	1.21	15.59
	Drug ineffective	1	1	0	0	1	1	0	0	0.02	0.47	2.23
	No therapeutic response	1	0	1	0	2	1	1	0	22.94	50.47	228.10
Investigations												
	Blood pressure decreased	1	0	1	0	2	0	2	1	1.41	5.58	22.10
	Oxygen saturation decreased	1	0	1	0	10	2	8	1	16.75	55.17	55.17
Psychiatric disorders												
	Agitation	1	0	1	0	1	0	1	0	0.13	0.89	6.28
	Crying	1	0	1	0	1	0	1	0	0.07	0.47	3.33
Respiratory, thoracic and mediastinal disorders												

Interpretation of Signals of Disproportionate Reporting

Statistical Signal ≠ Drug Safety Issue

- **No implication of causal relationship** → each drug-event pair requires **medical evaluation** based on case report details
- **Artificial thresholds** for Signals of Disproportionate Reporting
- **Nature and quality of data** in database on which PRR is calculated needs to be considered → influence on PRR
- **Various sources of bias** (e.g. underlying disease, statistical artefacts, etc.)
- **Criteria for prioritisation** (e.g. labelledness/listedness, impact on public health, change of frequency or seriousness, subgroup analysis etc.)

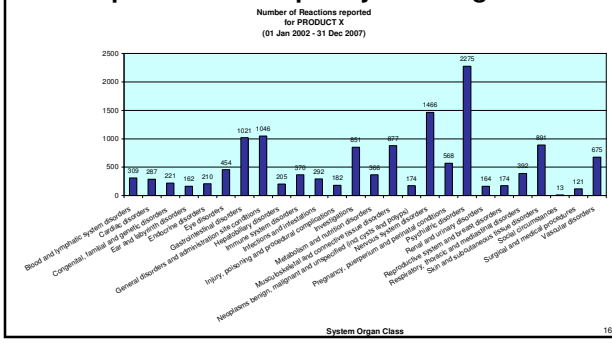
Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System, Doc. Ref. EMEA/106464/2006 rev. 1

Draft EudraVigilance Access Policy

According to Article 26, paragraph (3) and Article 57, paragraph (1)(d) of Regulation (EC) 726/2004

Stakeholder	Data access proposal
European Commission, National Competent Authorities and the EMEA	**Online access to all data** in EVDAS
Healthcare Professionals and General Public	**Aggregated data** to be published on the EudraVigilance website
Marketing Authorisation Holders and Sponsors of Clinical Trials	**Restricted online access** to data in EVDAS sender based

Example: Reactions per System Organ Class

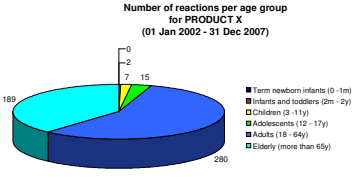


Example: Number of reactions (PT level) per SOC

Number of reactions reported at Preferred Term level per System Organ Class (SOC) for PRODUCT X (01 Jan 2002 - 31 Dec 2007)

SOC	Reaction Preferred Term	Total	EEA	Non EEA
Blood and lymphatic system disorders				
	Aplastic anaemia	6	2	3
	Autoimmune thrombocytopenia	3	2	1
	Bone marrow failure	9	6	3
	Coagulopathy	90	20	70
	Coombs negative haemolytic anaemia	1	0	1
	Disseminated intravascular coagulation	52	12	40
	Eosinophilia	28	14	14
	Factor V inhibition	1	0	1
	Factor VIII inhibition	1	1	0
	Febrile neutropenia	4	1	3
Cardiac disorders				
	Acute myocardial infarction	6	0	6
	Angina pectoris	1	0	1
	Arrhythmia	19	5	14
	Arteriosclerosis coronary artery	3	0	3
	Atrial fibrillation	22	2	20
	Atrioventricular block	5	2	3
	Cardiac failure	14	11	3
	Cardiotoxicity	10	0	10
	Hypertensive heart disease	2	0	2
	Myocardial fibrosis	1	0	1
	Myocardial infarction	36	11	25
	Myocardial ischaemia	2	1	1
	Nodal arrhythmia	1	0	1
Congenital, familial and genetic disorders				
	Cleft lip and palate	1	1	0
	Congenital anomaly	2	1	1
	Congenital aortic stenosis	1	0	1
	Congenital eyelid malformation	1	1	0
	Dysmorphism	3	2	1
	Epidermolysis	1	1	0
	Intestinal malrotation	1	0	1
	Limb reduction defect	1	1	0

Example: Number of reactions per age group



Acronyms

AMP	Authorised Medicinal Product
CHMP	Committee for Human Medicinal Products
EEA	European Economic Area
EMEA	European Medicines Agency
EU-RMP	EU Risk Management Plan
EVCTM	EudraVigilance Clinical Trial Module
EVDAS	EudraVigilance Data Warehouse and Analysis System
EVMPD	EudraVigilance Medicinal Product Dictionary
EVPM	EudraVigilance Post-Authorisation Module
ICH	International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities1
NCA	National Competent Authority
PT	Preferred Term
RMS	Reference Member State
SDR	Signal of Disproportionate Reporting
SOC	System Organ Class
SPC	Summary of Product Characteristic
SUSAR	Suspected unexpected serious adverse reaction