EudraVigilance to support EU Pharmacovigilance Activities

EU Regulatory Network
Challenges and Opportunities for Croatia

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Dr. Thomas Goedecke
Scientific Administrator
Pharmacovigilance and Risk Management
EMEA

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 million 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

Suspected Serious Adverse Reactions occurring within the EEA

- National Competent Authority & EMA
  - 15 days EMA
  - 15 days* EMA (if medically confirmed)
- Health Care Professionals
  - Worldwide Literature
  - Post-Authorisation Studies
  - Internet*
  - Patients’/ Solicitors’

CT = Centralised System
EC = European Commission
EMA = European Medicines Agency
NC = National Competent Authority
C = Centralised Procedure
N = National Procedure
Reporting Requirements non-EEA

Suspected Serious (Unexpected) Adverse Reactions occurring outside the EEA

- Health Care Professionals
- Worldwide Literature
- Post Authorization Studies
- Internet*
- Patients*
- Solicitors*

15 days*

EMEA EudraVigilance Post-Authorisation

Marketing Authorisation Holder

National Competent Authority

* if medically confirmed

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

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

Interpretation of Signals of Disproportionate Reporting

- 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.)


Draft EudraVigilance Access Policy

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

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<th>Stakeholder</th>
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<td>European Commission, National Competent Authorities and the EMEA</td>
<td>Online access to all data in EVDAS</td>
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<td>Healthcare Professionals and General Public</td>
<td>Aggregated data to be published on the EudraVigilance website</td>
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<tr>
<td>Marketing Authorisation Holders and Sponsors of Clinical Trials</td>
<td>Restricted online access to data in EVDAS sender based</td>
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Example: Reactions per System Organ Class

Example: Number of reactions (PT level) per SOC

Example: Number of reactions per age group
### Acronyms

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