EudraVigilance and Risk Management
Session on Pharmacovigilance

Presented by: Dr. Thomas Goedecke, European Medicines Agency (EMA)
Outline

EudraVigilance

• Role in Pharmacovigilance
• System Components and Functions
• Signal Detection – Signal Evaluation

EU Risk Management

• Why needed?
• Legal basis and requirements
• EU-RMP template
Protection of Public Health

Pharmacovigilance
- Safety Monitoring
- Signal Detection
- Risk Management
- Benefit-Risk Evaluation

Information Sources
- Interventional Clinical Trials
- Spontaneous Reporting
- Post-Authorisation Safety Studies

CT interventional
European Database On Adverse Drug Reactions

Sponsors of Clinical Trials
Marketing Authorisation Holders

European Commission
EMA
National Competent Authorities

General Public
Health Care Professionals
Data collected in EudraVigilance

Post Authorisation Module (EVPM)
- Suspected serious adverse reactions (ICSRs)
  - Health care professionals’ spontaneous reporting
  - Post-authorisation studies (non-interventional)
  - Worldwide scientific literature (spontaneous, non-interventional)
- Suspected transmission of infectious agents

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
Reports handled in EudraVigilance

Post-Authorisation reports:

- EEA ICSRs: 968,295
- Non-EEA ICSRs: 1,283,730
- **Total: 2,252,025**

Clinical Trial reports:

- EEA ICSRs: 211,228
- Non-EEA ICSRs: 190,970
- **Total: 402,198**

All figures are between January 2002 and September 2010 (excluding backlog reports)
Reports (ICSRs) over time (total)

All figures are between January 2002 and September 2010 (excluding backlog reports)
EudraVigilance System - Functions

- **Data processing network** interlinking all National Competent Authorities in the EEA, the European Commission and the EMA to exchange information in pharmacovigilance

- **Electronic data exchange** of adverse drug reaction reports (ICSRs) 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)**

- Monitoring of core risk profiles (identified/potential risks, missing information) defined in **EU Risk Management Plans (EU-RMP)**
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 CAPs under monitoring all reactions reported within defined timeframes are listed by System Organ Class
  - Reviewed by EMA Signal Detection Team in collaboration with Rapporteur/Co-Rapporteur team

- **Signals** are based on statistical algorithms measuring disproportionality: Proportional Reporting Ratio (PRR)
  - an event \((R)\) is relatively more often reported for a medicinal product \((P)\) compared to the number of reports of this event for all other medicinal products in the database

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<tr>
<th></th>
<th>Event R</th>
<th>All other events</th>
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<td>b</td>
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<tr>
<td>a + c</td>
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<td>b + d</td>
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</table>

\[
PRR = \frac{a/(a+b)}{c/(c+d)}
\]
EudraVigilance Reaction Monitoring Report

• Reaction Monitoring Report used for Signal Detection

• Report criteria:
  • All spontaneously reported ICSRs to EV Post Module
  • Generated at active substance level
  • CAPs authorised ≤ 2 years: intensive monitoring (2-weekly), all others: routine monitoring (monthly)

• List of reactions (MedDRA Preferred Terms) grouped by System Organ Class (SOC) indicating
  • New cases/fatal cases associated with reaction
  • Total number of cases/fatal cases
  • Origin (EU/non-EU) of cases
  • Proportional Reporting Ratio (PRR) and 95% Confidence Interval

• Signals of Disproportionate Reporting are highlighted if
  • Number of ICSRs ≥ 3 and
  • Lower bound of 95% Confidence Interval of PRR ≥ 1
## Example: Reaction Monitoring Report

### Reaction Monitoring Report - Intensive

**SOC=METABOLISM AND NUTRITION DISORDERS Active Substance(s)**

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<th>New EEA</th>
<th>Total EEA</th>
<th>New Non EEA</th>
<th>Total Non EEA</th>
<th>New Total</th>
<th>PRR(-)</th>
<th>PRR</th>
<th>PRR (+)</th>
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**Reference period: 01SEP2010 - 14SEP2010**
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**Case Report in CIOMS format**

- Gastric ulcer haemorrhagic
- Appetite lost, Reduced general condition, Stool tarry, Ulcer bleeding gastric, Vertigo, Vomiting
- Bleeding gastric ulcer, Hematemesis, Melena, Syncope
Interpretation of SDRs

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, impact on public health, change of frequency or seriousness, subgroup analysis etc.)

EMA Signal Detection Process

1. EudraVigilance
2. Reaction Monitoring Report
3. Check number of cases, PRR, labelling, previous reviews
4. List of potential new signals
5. Identify true cases
6. Check data quality (HCP-Consumer)
7. Clinical assessment
8. Report with proposed action
9. Signal Validation Meeting
10. Decision on Signal
11. Tracking
12. EPITT
13. Monitoring
14. Closed
15. Monitored
16. Rapp Com.
Outline

EudraVigilance

• Role in Pharmacovigilance
• System Components and Functions
• Signal Detection – Interpretation of SDRs

EU Risk Management

• Why needed?
• Legal basis and requirements
• EU-RMP template
Authorising medicines: What we know...

At the time of authorisation:

- Dossier of evidence submitted by the companies on quality, safety and efficacy
- Full assessment by the regulators
- Benefits must outweigh risks based on evidence from clinical trial program

What we know:

- Usually good evidence from clinical trials demonstrating efficacy in the specific indication and populations studied
- Good evidence from clinical trials on the most common adverse reactions
...and what we don’t know

- Effectiveness of the product in **normal clinical practice**: compliance, resistance, populations not included in trials
- Full safety profile including **adverse drug reactions** which are:
  - Rare
  - Delayed
  - From chronic exposure
  - From interactions
  - Medication errors
  - Off-label use
  - Associated with abuse/misuse
  - Associated with populations not studied in trials (children, very elderly, pregnancy, lactation, co-morbidity)

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<td>8.2</td>
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<tr>
<td>30000</td>
<td>5.0</td>
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</tbody>
</table>

Table 1 — Chance that a very rare side-effect (0.01%) will not be observed

Amery K Pharmacoepidemiology and Drug Safety, 8: 61±64 (1999)
Why the Concept of Risk Management?

- In the past high profile safety issues warranted urgent regulatory actions (suspension, withdrawal)
- Pro-active monitoring of drug safety to evaluate changes in benefits and risks
- Changing environment of drug safety
  - More information with better access
  - Increased expectations from health authorities, public and media

ICH E2E guideline on pharmacovigilance planning

- To support pharmaceutical industry and regulators in planning of pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug

- Basis for documenting risks: **Safety Specification**

- Structure for a **Pharmacovigilance Plan** (pre- or post-authorisation)
EU Legislation on Risk Management


- Article 9(4)(c) of Regulation (EC) No 726/2004 → lays down Conditions & Restrictions for supply and safe and effective use


- EU Risk Management Template (EU-RMP) (EMEA/192632/2006)
Risk Management Definition

• CHMP Guidance on Risk Management Systems
  «... a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions»

• Obligations can be fulfilled by submitting a Risk Management Plan (RMP), in the format of the EU-RMP Template

• EU-RMP is a binding contract between EU regulators and MAH
The Risk Management Cycle

1. Clinical Trials Phase I-III/IV
2. Spontaneous Reporting
3. Scientific Literature
4. Epidemiological Studies - Registries

- Risk Identification
- Effectiveness Measurement
- Risk Management
- Risk Characterisation
- Risk Assessment
- Risk Minimisation & Communication
The Risk Management Cycle

Clinical Trials
Phase I-III/IV

Spontaneous
Reporting

Scientific
Literature

Epidemiological
Studies - Registries

Safety
Specification

Risk
Characterisation

Risk
Management

Effectiveness
Measurement

Risk
Minimisation

Pharmacovigilance
Planning

Risk
Minimisation & Communication
When is an EU-RMP required? (1)

a) New marketing authorisation

- New active substance
- A similar biological medicinal product
- Generic/hybrid* where safety concern requiring additional risk minimisation has been identified with reference product

b) Significant Changes to Marketing Authorisation

- New pharmaceutical form
- New route of administration
- Significant change to indication/patient population

Unless agreed not needed
When is an EU-RMP required? (2)

c) On request from the Competent Authority
d) On company initiative e.g., safety issue with a marketed medicine
e) Update to previous EU-RMP

Situations where an EU-RMP might be required:

- “Known active substances”
- Hybrid medicinal product where the changes compared with reference product suggest different risks
- Bibliographical applications
- “Fixed combination” applications
To be valid the EU-RMP must contain:
1. Safety Specification
2. Pharmacovigilance Plan
3. Evaluation
Safety Specification

Aim & purpose:

- Summary of what is known/not known at authorisation
  - Identified risks
  - Potential risks
  - Important missing information

- To identify need for specific data collection in post-authorisation phase and to construct the pharmacovigilance plan

- To evaluate the need of additional risk minimisation activities and to construct the risk minimisation plan

- To evaluate the need of efficacy follow-up and to construct the efficacy follow-up plan (for ATMPs only)

*Probably the most important bit!*
Pharmacovigilance Plan

Aim & purpose:

- To identify and characterise known and unknown risks
- To set up an action plan for each safety concern
- For products with no special concerns **routine pharmacovigilance** may be sufficient (i.e. ADR reporting, signal detection, PSURs,...)
- For products with safety concerns **additional pharmacovigilance activities** should be considered
Why Pharmacovigilance Planning?

- Are there unanswered pre-clinical or clinical questions?
- Are there safety concerns specific to a particular part of the target population?
- Is the medicine intended for long-term use?
- Is there a potential of medication error and/or off-label use?
- Are there safety concerns specific to special populations (e.g. paediatric, elderly)?

→ Conduct of Post-Authorisation Safety Studies to answer these questions!
Evaluation of the need for a Risk Minimisation Plan

EU-RMP Part II

For each safety concern evaluate if:

- Additional risk minimisation actions are needed?
- Is the product literature (SPC/PIL) sufficient for this purpose?
- If not, then a Risk Minimisation Plan is needed
- Potential for medical error?

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<td>Light beige</td>
<td>Beige</td>
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</table>
Risk Minimisation Plan

- Only needed if **additional** risk minimisation activities are required for at least one safety concern
- Should include **both routine and additional** activities for all safety concerns with risk minimisation
- Criteria to **assess the effectiveness of each (additional) activity** to reduce risk(s)
  - Health outcome measures that indicate the success or failure of the process implemented based on agreed standards
- Similar structure to Pharmacovigilance Plan
  - Objective and rationale
  - Proposed actions
  - Proposed review period
Summary of the EU-RMP

- Table of routine and additional pharmacovigilance and risk minimisation activities for each safety concern
- Key information, e.g. SPC labelling, study type and objective, type of education and key message

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed Pharmacovigilance Activities</th>
<th>Proposed Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identified Risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased intraocular pressure (IOP), glaucoma and ocular hypertension</td>
<td>Routine pharmacovigilance</td>
<td>Included in section 4.4 of the SPC:</td>
</tr>
<tr>
<td></td>
<td>Additional pharmacovigilance</td>
<td>• As expected with intravitreal injections, increases in intraocular pressure (IOP) may be seen.</td>
</tr>
<tr>
<td></td>
<td>• Added to the Sentinel Event List</td>
<td>Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately</td>
</tr>
<tr>
<td></td>
<td>• Phase III two-year clinical studies 12345-67 and 12345-89 to assess safety and efficacy of X</td>
<td>post injection as needed.</td>
</tr>
<tr>
<td></td>
<td>• Conduct of an observational study to gain experience with repeat administration (2nd or subsequent</td>
<td>• Increased IOP is included as “very common” adverse reaction in Section 4.8 (Undesirable effects).</td>
</tr>
<tr>
<td></td>
<td>implant) to collect long term safety data.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Educational material to instruct prescribers on the recommended injection technique and important</td>
</tr>
<tr>
<td></td>
<td></td>
<td>risks associated with X, including increased intraocular pressure and ocular hypertension.</td>
</tr>
</tbody>
</table>
Maintenance of the EU-RMP

- Updated throughout the product lifecycle
  - With each PSUR
  - With type II variations (extension of indication) and line extensions
  - When a milestone is reached

- Safety specification changes as new information gets available:
  - Results from ongoing/finalised clinical trials
  - Results from studies in the Pharmacovigilance Plan
  - Spontaneous reports and literature
  - Results from effectiveness measurements (health outcomes)

- Continuous update of Pharmacovigilance and Risk Minimisation Plans

→ EU-RMP is a planning tool to build up knowledge
→ PSUR is a periodic benefit/risk assessment tool
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AR</td>
<td>Annual (Study) Report</td>
</tr>
<tr>
<td>CAP</td>
<td>Centrally authorised product</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Human Medicinal Products</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organisations of Medical Sciences</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EU-RMP</td>
<td>EU Risk Management Plan</td>
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<tr>
<td>EVCTM</td>
<td>EudraVigilance Clinical Trial Module</td>
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<tr>
<td>EVDAS</td>
<td>EudraVigilance Data Warehouse and Analysis System</td>
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<tr>
<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>FUM</td>
<td>Follow-up measure</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MedDRA</td>
<td>Medicinal Dictionary for Regulatory Activities</td>
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<tr>
<td>NCA</td>
<td>National Competent Authority</td>
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<tr>
<td>PAC</td>
<td>Post-authorisation commitment</td>
</tr>
<tr>
<td>PIL</td>
<td>Patient Information Leaflet</td>
</tr>
<tr>
<td>PRR</td>
<td>Proportional Reporting Ratio</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<tr>
<td>SDR</td>
<td>Signal of Disproportionate Reporting</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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</tbody>
</table>
Hvala!
Thank you!

Dr. Thomas Goedecke
thomas.goedecke@ema.europa.eu