EUROPEAN MEDICINES AGENCY DRUG SAFETY PRACTICES AND TOOLS

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European Medicines Agency, London
Contents

- Eudravigilance & Signal Detection
- EPITT
- THIN
- ENCePP
Background – Need To Further Strengthen Pharmacovigilance

• 5% of all hospital admissions are for Adverse Drug Reactions (ADRs)
• 5% of all hospital patients suffer an ADR
• ADRs are the 5th most common cause of hospital death
• Estimated 197,000 deaths per year in EU from ADRs
• EU societal cost of ADRs amounts to Euro 79 Billion per year

COMMISSION OF THE EUROPEAN COMMUNITIES Sept 2008
Post authorisation safety monitoring

- Pre-authorisation clinical trials are not of sufficient size to elucidate and characterise every adverse effect of a medicinal product
- Results cannot be assumed to be generalisable to patients who will use the product in a usual care setting
- Special populations such as the elderly are underrepresented in pre-authorisation clinical trials
- Spontaneous reporting systems are an important source for safety monitoring in post-authorisation “real-life” setting
EudraVigilance: A data processing network and management system for reporting and evaluating suspected ADRs in EEA

- National Competent Authorities (NCAs)
- Data-Processing Network: Secure e-reporting of Individual Case Safety Reports (ICSRs)
- Marketing Authorisation Holders (MAHs)
- Signal Detection and Data Analysis for EMA/Member States (MSs)
- ICSRs for all medicines authorised in the EEA
- ICSRs outside the EEA
EudraVigilance

- An average of ~72,000 ICSRs reported monthly from Jan-Jun 2011
- Total number of ICSRs approaching 5 million
- Approx. 8,000 users and >100,000 product presentations in EV Medicinal Product Dictionary
- Almost 24,000 queries performed in EV Data Analysis System (EVDAS) by National Competent Authorities (NCAs) (Jan-Jun 2011)
- EudraVigilance now ranks within the 3 largest databases on adverse drug reactions in the world
EudraVigilance Reports per month

Number of ICSRs (excluding backlog) received per month in EV (2004 - 2011)
Signal Management (SM) definition and steps

• SM – set of activities to determine whether there are new risks associated with a medicinal product or whether risks have changed based on various data sources*

• Steps:
  • signal detection
  • signal validation and confirmation
  • prioritisation, analysis and assessment
  • recommendation for action

* ICSRs (EudraVigilance, national databases, company specific), data from active surveillance systems or studies, literature and other available
Signal Detection at the EMA

• Signal detection and Data analysis section within the Pharmacovigilance and Risk Management Sector of the Patient Health Protection Unit

• Focused on EudraVigilance data

• In liaison with (Co)-Rapps and PhVWP

• Scope: ~ 600 Centrally Authorised Products (CAPs) plus new MAA under evaluation at EMA

• Periodic signal detection for centrally authorised products based on reaction monitoring reports
Signal Detection at the EMA

Main tool for signal detection is the electronic Reaction Monitoring Report (e-RMR):

• A periodical formatted Excel file which contains ICSRs historically submitted in EudraVigilance + new data submitted during the period of interest;

• Tool that facilitate screening and filtering of large dataset to support signal detection activities;

• Facilitates review of signals of disproportionality reporting (SDR)

• Allows selection of cases of interest to view CIOMS forms.
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<th>Anemia &amp; Blood Disorders</th>
<th>MDS/Marrow</th>
<th>DME/DM</th>
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<td>Aplastic Anaemia</td>
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<td>Cardiac Failure</td>
<td>Neutropenia</td>
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<td>Cardiac Failure</td>
<td>Cardiac Failure Congestive</td>
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<td>Myocardial disorders</td>
<td>Myocardial Disorders Nec</td>
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<td>Cardiac Failure</td>
<td>Cardiac Failure Congestive</td>
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</tbody>
</table>
# Structure of the e-RMR worksheet

![Image](image_url)

| J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | AA | AD | AE | AF | AG | AH | AI |
| 1 | 3 | 0 | 0 | 1 | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 3 | 2.040 | 2.040 | 0 | 0 | 0 | 0 | 0 |
| 23 | 1469 | 0 | 8 | 0 | 9 | 0 | 639 | 0 | 801 | 0 | 566 | 22 | 1385 | 22 | 1452 | 1.673 | 3.097 | 0 | 4 | 2 | 10 | 2 | 3 |
| 2 | 943 | 1 | 15 | 0 | 3 | 0 | 215 | 0 | 614 | 0 | 308 | 1 | 765 | 1 | 933 | 1.301 | 1.314 | 0 | 0 | 0 | 7 | 1 | 2 |
| 1 | 19 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 13 | 1 | 7 | 0 | 17 | 1 | 19 | 1.206 | 1.489 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | 738 | 0 | 12 | 0 | 0 | 0 | 311 | 0 | 474 | 16 | 282 | 0 | 637 | 16 | 724 | 3.116 | 3.280 | 0 | 2 | 0 | 11 | 0 | 1 |
| 2 | 2333 | 1 | 18 | 0 | 7 | 0 | 559 | 0 | 1740 | 0 | 722 | 0 | 2027 | 1 | 2330 | 4.081 | 10.203 | 0 | 1 | 0 | 1 | 1 | 1 |
| 1 | 7 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 7 | 0 | 3 | 0 | 7 | 1 | 7 | 1.170 | 3.442 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 878 | 1 | 22 | 0 | 7 | 0 | 432 | 0 | 563 | 0 | 354 | 0 | 691 | 1 | 864 | 1.957 | 2.681 | 0 | 6 | 0 | 4 | 3 | 4 |
| 3 | 42 | 0 | 0 | 0 | 3 | 0 | 18 | 0 | 22 | 1 | 16 | 0 | 29 | 1 | 35 | 1.649 | 1.773 | 0 | 2 | 0 | 3 | 2 | 2 |
| 1 | 15 | 0 | 0 | 0 | 0 | 0 | 7 | 1 | 9 | 0 | 6 | 0 | 14 | 1 | 15 | 2.077 | 2.415 | 0 | 0 | 0 | 0 | 0 | 0 |
| 19 | 336 | 0 | 0 | 0 | 0 | 0 | 117 | 19 | 245 | 0 | 114 | 0 | 287 | 19 | 326 | 2.230 | 3.485 | 0 | 0 | 0 | 3 | 0 | 0 |

**Legend:**
- **EV Cases:** EV卓事件
- **Fatal Cases:** 告別事件
- **Paediatric Cases:** 儿童事件
- **Geriatric Cases:** 高齢者事件
- **EEA Cases:** 地域事件
- **HCP Cases:** 医療機関事件
- **Serious Cases:** 重要事件
- **Total Cases:** 合計事件
- **PRR(-)/PRR:** PRR(-)/PRR
- **New Spontaneous:** 新規自発事件
- **New PRR(-)/PRR:** 新規PRR(-)/PRR
- **New Literature:** 新規文献
- **Total Literature:** 合計文献
- **New Observations:** 新規観察
- **Total Observations:** 合計観察
- **New CT:** 新規CT
### 3/3 - Structure of the e-RMR worksheet

<table>
<thead>
<tr>
<th>PT Code</th>
<th>IME</th>
<th>DME</th>
<th>Changes</th>
<th>SDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10010370</td>
<td>Ime</td>
<td></td>
<td>Increased</td>
<td>SDR (9)</td>
</tr>
<tr>
<td>10016256</td>
<td></td>
<td></td>
<td>Increased</td>
<td>SDR (14)</td>
</tr>
<tr>
<td>10025482</td>
<td></td>
<td></td>
<td>Increased (fatal)</td>
<td>SDR (14)</td>
</tr>
<tr>
<td>10061458</td>
<td></td>
<td></td>
<td>Increased</td>
<td>SDR (14)</td>
</tr>
<tr>
<td>10030095</td>
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<td></td>
<td>Increased (fatal)</td>
<td>SDR (14)</td>
</tr>
<tr>
<td>10061128</td>
<td>Ime</td>
<td>Dme</td>
<td>Increased</td>
<td>SDR (4)</td>
</tr>
<tr>
<td>10016173</td>
<td></td>
<td></td>
<td>Increased (fatal)</td>
<td>SDR (14)</td>
</tr>
</tbody>
</table>
Key activities in screening the e-RMR

• Selection of a reference period
• Prioritisation of ADRs for review based on several criteria
• Grouping/selection of paediatric/geriatric ADRs
• Filtering by new literature reports received in EV
• Filtering/selection of ADRs from studies/RCTs
• Comparison of various ‘Totals’
• Search at the level of the SOC/HLGT/HLT
• Filtering by multi-axial SMQs
Factors in signal detection

• Clinical judgment
• Clinical relevance and potential impact on public health (e.g. hepatic failure, agranulocytosis, serious allergic reactions, fatal medication errors)
• Number of reports ≥3, statistical threshold applied to screen for signals
• Check for expectedness against the latest approved or submitted product information
• Evaluation of the signal by the Rapporteur
• Evaluation of the signal by a scientific committee (e.g. CHMP, PhVWP)
• Ongoing regulatory procedure relevant to the signal
Validation of activities

• Statistical methods can lead to earlier detection of safety signals – approx. 54% signals were detected earlier (mean time saved 2.45 years)

• 20% signals detected earlier by traditional methods

• 26% not detected by statistical methods - established pharmacovigilance and PRR analysis are complementary

• Validation of Statistical Signal detection for CAPs in EudraVigilance
  • Drug Saf 2010; 33:(6):475-487
New PV legislation

• ADRs are big burden to patients and society
• Signal Detection using spontaneous reporting systems is an important source for safety monitoring in post authorisation “real-life” setting.
• The main objective of the new pharmacovigilance legislation is to promote and protect public health by reducing the burden of ADRs and optimising the use of medicines
• There are opportunities for improved data collection and enhanced signal detection that should be considered carefully in order to further strengthen pharmacovigilance
EPITT
(European Pharmacovigilance Issues Tracking Tool)

• Database facilitating the tracking and sharing of safety information related to the medicinal products / substances for human use, between the NCAs and the Agency (about 350 users within the European Economic Area)

• 4 “main modules”: Safety Issues, Safety Signals, PSURs (Periodic Safety Update Reports), RMPs (Risk Management Plans)
EPITT

• Objectives:
  • Tracking of Safety Issues and Signals independently of the marketing authorisation type (incl. PhVWP discussions, Rapid Alerts, PhVWP recommendations and SmPC wordings updates...),
  • Tracking and monitoring of the PSUR cycles, timetable for the assessments and related documents (scope: Centrally Authorised Products + Work Sharing project),
  • Tracking of the EU-RMP Annexes 1 submitted by the Marketing Authorisation Holders, together with the implementation of the regulatory actions they require,
  • Support to the European Incident Management Plan procedure.
Welcome to EPITT
European Pharmacovigilance Issues Tracking Tool (Ver 2.3)

Welcome
Issues  Signals  Drugs  PSURs  Stats  Links  Guides  RMPs

1/ Latest RAs and NUIs (click on name to view)
NUI from UK (04/04/2012): Usage data requested of high dose statin therapy for each statin and... (10599)
NUI from EM (02/04/2012): NCAs requirements for PSURs submission during the Transitional Period (13199)
NUI from UK (20/03/2012): NUI on levodopa and dopamine agonists and Impulse Control Disorders (371)
NUI from EM (27/03/2012): Management and reporting of non-EEA serious suspected adverse reactions and EEA... (13141)
NUI from EM (23/03/2012): Compilation of responses on the eRMR for NCA (Pilot) (15273)

2/ Latest SIGNALs (click on name to view)
Signal from NL (11/04/2012): Everolimus - Votubia, Afinitor, Certican = Serious gastrointestinal disorders (15617)
Signal from NL (06/04/2012): Aripiprazole and hypothyroidism (15594)
Signal from NL (05/04/2012): Escitalopram and headache (15573)
Signal from NL (05/04/2012): Dronedarone - Multaq = Hyperthyroidism and decreased thyroid stimulating hormone (15554)
Signal from EM (03/04/2012): Signal UPDATE Sunitinib - SUTENT (Protein kinase inhibitor) = Erythema Multiforme, Stevens-Johnson

The next EPITT training sessions using Vitero are scheduled on:
- Basic training (Issues, Signals): To be defined
- Advanced training (PSURs, RMPs): To be defined

Please contact the EPITT team if you wish to participate: epitt@ema.europa.eu
The THIN database

- The Health Improvement Network Database at EMA
- Collects all data from subset of General Practice computer systems.
- Population based data - 5% UK population
- Practices geographically representative of England and Wales
- Anonymised at source
- Simple flat file structure
- Regularly updated
Clinical Databases

• Designed for patient management

BUT

• Allow opportunities to do rapid analyses on wide range of pre-existing clinical data. Hence very useful research tool.
Examples from EMA

• Investigation of dosages of Somatropin given to children in UK
  • Challenging because dose adjusted for body weight

• Rosiglitazone – Is it given even in presence of cardiac contraindications?
  • Complete GP data gives simple and powerful approach to this sort of question.
The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

The aim of ENCePP:

• Bring together expertise in the fields of pharmacovigilance & pharmacoepidemiology scattered across Europe.

• Further strengthen the post-authorisation monitoring of medicinal products in Europe.

• Focus on academia and not-for-profit organisations.

• Facilitate post authorisation studies:
  ✓ high quality
  ✓ independent
  ✓ multi-centre
How does ENCePP work?

ENCePP Steering Group

- 16 members in total:
  - 6 elected: from network
  - 6 appointed:
    - Heads of Medicines Agencies (HMA),
    - Committee for Medicinal Products for Human Use (CHMP),
    - Committee for Orphan Medicinal Products (COMP)
    - CHMP’s Pharmacovigilance Working Party (PWP),
    - CHMP’s Patient and Consumers Working Party (PCWP),
    - International Society of Pharmacoepidemiology (ISPE),
    - International Society of Pharmacovigilance (ISoP)
- 3 members from EMA
- 2 observers:
  - European Federation of the Pharmaceutical Industries & Associations (EFPIA)
  - Int’l Regulatory Agency (to be appointed)
Who are the ENCePP partners?

• Universities, hospitals;
• Owners of healthcare databases and/or electronic registries;
• Other public/non-profit research centres specialised in PhV;
• Existing European networks covering certain rare diseases, therapeutic fields and adverse drug events of interest.
• For-profit organisations
  • provided that they perform studies commissioned by third parties and their main focus is pharmacoepidemiology and pharmacovigilance research
Who are the ENCePP partners?

- 103 centres
- 14 networks
- 24 data sources

from 17 different European countries

(data as of 12 April 2012)
ENCePP guiding principles

- **Independence**
  - Clear roles and responsibilities of researcher & funder
  - Freedom to publish

- **Standards**
  - Stimulate consideration of important study principles in design of studies

- **Transparency**
  - Registration of studies
  - Publication of protocols and results

**Code of Conduct**

**Methodological Standards Checklist & Guide**

**E-Register of Studies (Code of Conduct)**
To reinforce the confidence of the public, other researchers as well as regulators that research done under the ENCePP “seal” is as far as possible free from biases and commercial, financial and personal influences.
For further information:

www.encepp.eu