

The Use of MedDRA in the EEA and EudraVigilance

MedDRA Users Group Meeting

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Regulatory Background

- ★ Use of MedDRA is defined in Community legislation in the European Economic Area (EEA) for adverse reaction reporting related to
 - ★ ❖ **Authorised Medicinal Products**
 - ★ ✓ Regulation (EC) No. 726/2004
Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (*centrally authorised medicinal products*)
 - ★ ✓ Directive 2001/83/EC as amended
Community Code relating to Medicinal Products for Human Use (*mutually and other nationally authorised medicinal products*)
- ★
- ★

Regulatory Background

- ✓ Volume 9 Pharmacovigilance: Medicinal Products for Human use and Veterinary Medicinal Products
 - Use of the appropriate Low Level Terms
 - Use of the latest version of MedDRA

Applies to reporting of

- ❖ Suspected serious adverse reactions occurring within the EEA
- ❖ Suspected serious unexpected adverse reactions occurring outside the EEA

Regulatory Background

- ★ Use of MedDRA is defined in Community legislation in the European Economic Area (EEA) for adverse reaction reporting related to
 - ❖ **Investigational Medicinal Products**
 - ✓ Directive 2001/20/EC
- ★ Implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (*interventional clinical trials phase I-IV*)
- ★
- ★

Regulatory Background

- ✓ Implementing Texts (Guidance documents)
 - Use of the appropriate Low Level Terms
 - Use of the latest version of MedDRA
 - Where medically appropriate, signs and symptoms can be lumped into diagnoses

Applies to reporting of

- ❖ Suspected unexpected serious adverse reactions (SUSARs)
- ❖ Suspected serious adverse reactions (SARs)
- ❖ Occurring within and outside the EEA

ICH E2B(M) Guideline applied in the EEA

- Version 4.4.1 of 5 February 2001 and Use of MedDRA in the EEA
 - ❖ ICH ICSR Patient Characteristics (B.1)
 - ✓ Structured info relevant medical history (B.1.7.1)
 - ❖ Relevant past drug history indication (B.1.8)
 - ✓ Reported cause(s) of death (B.1.9.2)
 - ✓ Autopsy-determined cause(s) of death (B.1.9.4)
 - ✓ Relevant medical history parent (B.1.10.7)
 - ✓ Relevant past drug history/parent indication (B.1.10.8)

ICH E2B(M) Guideline applied in the EEA

❖ ICH ICSR Section Reaction(s) (B.2)

- ✓ Reaction in MedDRA terminology (B.2.i.1)
- ✓ ICH ICSR Section Drug(s) Information (B.4)
- ✓ Indication for use in the case (B.4.k.11)
- ✓ Which reaction(s) recurred? (B.4.k.17.2)

❖ ICH ICSR Section Narrative case summary (B.5)

- ✓ Sender's reclassification of reaction (B.5.3)

❖ ICH ICSR Section Tests and Procedures (B.3)

- ✓ Tests/investigation of the patient (B.3.1)

Mandatory Electronic Reporting

- Electronic reporting of adverse reactions
 - ❖ EVWEB for Small and Medium Size Enterprises and Non-Commercial Sponsors in the EEA
 - ✓ Facilitates the use of MedDRA for adverse reaction reporting
 - ✓ MedDRA Management Board approved special EudraVigilance MedDRA Licensing policy

EudraVigilance MedDRA Licensing Policy

- EudraVigilance Fee Waiver MedDRA subscription is available:
 - ❖ To organisations that are going to use EVWEB for adverse reaction reporting to NCAs in the EEA and the EMEA
 - ❖ To organisations that qualify as:
 - ✓ Small or Micro Enterprise
 - ✓ Sponsors of non-commercial clinical trials conducted in the EEA
- No limit of number of ICSRs as a criterion to qualify for a EudraVigilance Fee Waiver MedDRA subscription

SMEs MedDRA Licensing Policy



Enterprise category	Turnover	or	Balance sheet total
Medium-sized	$\leq \text{€ } 50 \text{ million}$		$\leq \text{€ } 43 \text{ million}$
Small	$\leq \text{€ } 10 \text{ million}$		$\leq \text{€ } 10 \text{ million}$
Micro	$\leq \text{€ } 2 \text{ million}$		$\leq \text{€ } 2 \text{ million}$

EudraVigilance and MedDRA

- ★ EMEA follows the MedDRA® MSSO's
 - Recommendations for Single Case Reporting using Semi-annual Version Control
 - ❖ All reporting should be done using the most recently released version of MedDRA
 - ❖ The version number of the MedDRA release used to code the report should be included in all reports
 - ❖ A new version of MedDRA should become the reporting version on the first Monday of the second month after it is released i.e. midnight GMT, Sunday to Monday, for the switchover
- ★
- ★
- ★
- ★

EudraVigilance and MedDRA

EMEA supports the MedDRA® MSSO's

- Recommendations for MedDRA Implementation and Versioning for Clinical Trials (Option 5 and 6)
- Option 5 - Freeze version at the beginning of each trial within a project and optionally re-code data with the latest version at the conclusion of the trial

Always output the data utilizing the most recent version of MedDRA

- Option 6 – Re-code the trial data for all trials in a project on an ongoing basis with the most recent version of MedDRA

EudraVigilance and MedDRA

- ★ EMEA supports since January 2005 the MedDRA® MSSO's
 - ★ ■ Recommendations for the Implementation of MedDRA Supplemental Terms
 - ★ ❖ Supplemental Terms are accepted

Harmonised Versioning Policy required
for Supplemental Terms

EudraVigilance and MedDRA

- ★ The main emphasis on the use of MedDRA in line with E2B(M) is put on data analysis
- ★ ❖ Currently most of the scientific queries are based on MedDRA
- ★ ❖ MedDRA SMQs have been tested and will be implemented in EudraVigilance
- ★ Example: Proportional Reporting Ratio (PRR) and signal detection in EudraVigilance
- ★

Main Factors

- PRR – Proportional Reporting Ratio
 - 95% Confidence interval for PRR
 - χ^2 – Chi Square
 - Number of Cases/Reactions
- (can be applied at different levels of MedDRA hierarchy)

Contingency Table



	Reaction R	All Other Reactions
Drug D	a	b
All Other Drugs	c	d

Proportional Reporting Ratio

The PRR for the reaction R with the drug D is calculated as following:

$$PRR(R, D) = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Confidence Interval for PRR

The 95% CI for the PRR is calculated as following:

$$\exp(\ln\{ PRR\} \pm 1.96 \times S)$$

where

$$S = \sqrt{(1/a + 1/c - 1/(a+b) - 1/(c+d))}$$

CHI Square Test

Using the hypothesis that the value for a,b,c,d are independent the Chi² test is calculated:

$$\chi^2 = \sum_{i \in \{a,b,c,d\}} \frac{(O_i - E_i)^2}{E_i}$$

Number of Cases

The number of cases for which a certain reaction occurred for a specific drug is also used



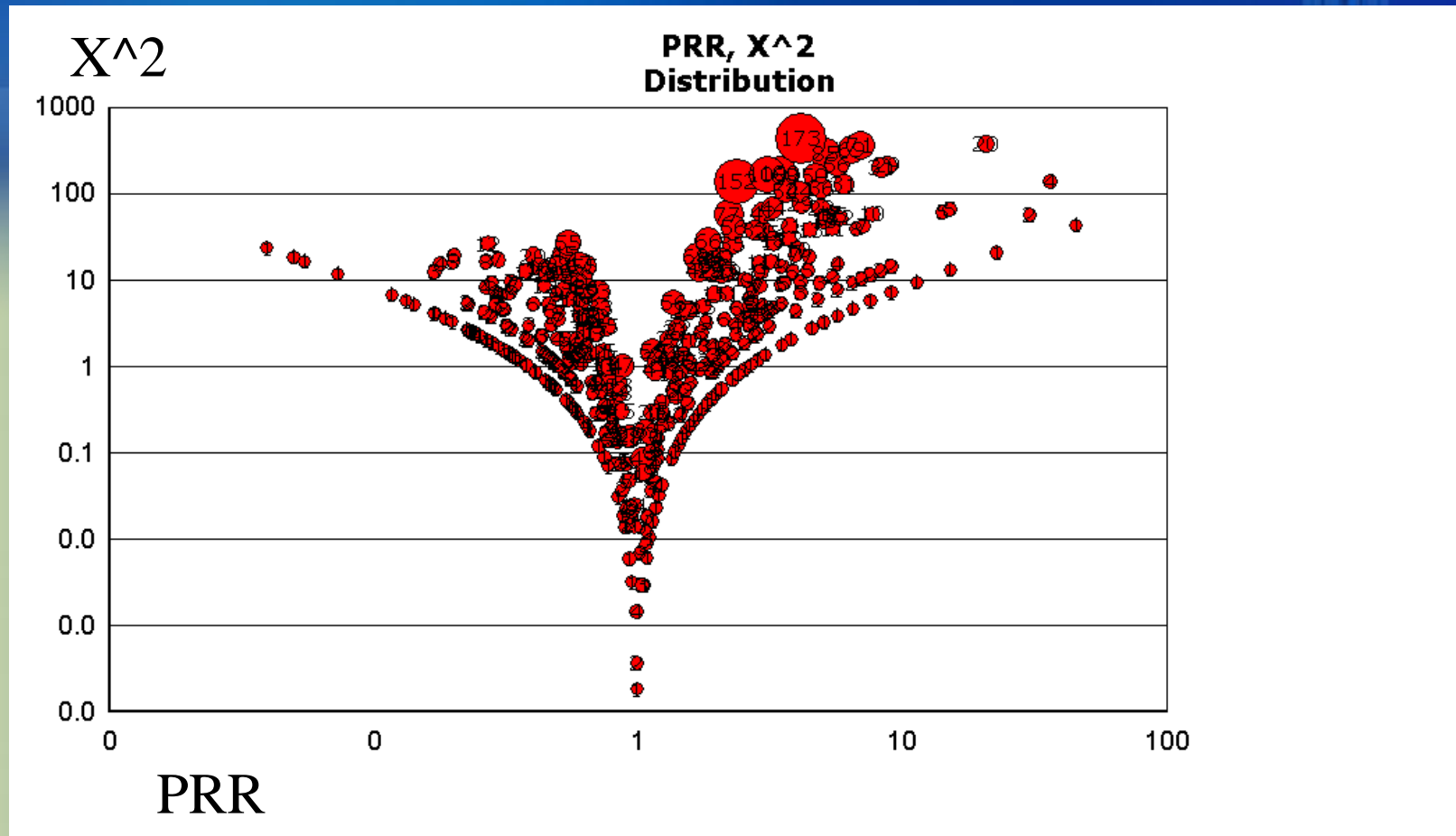
Conditions for a Potential Signal

There are no universally accepted rules to define a signal but many suggestions

For example:

- Lower 95% bound on $PRR > 1$ and $\#Cases \geq 3$
or
- $PRR > 2$, $Chisquare > 4$ and $\#Cases \geq 3$

Signal Detection Methodologies



Static PRR at PT level

Routine Listings for High Level Case Review

Drug Substance Name: Active X

Print Run: 03/05/2005 - 14/05/2005

Product Names: Product XX



PT Name:

Non-EU:

EU:

PRR:

New Old Fatal | New Old Fatal



Anaemia

1 8 2 | 0 5 0 0.44 (0.26-0.74)

Aplastic anaemia

0 0 0 | 1 1 0 1.66 (0.42-6.7)

Eosinophilia

0 0 0 | 1 0 0 0.49 (0.07-3.51)

Lymphadenitis

0 0 0 | 1 0 0 3.27 (0.46-23.48)



Lymphadenopathy

0 2 0 | 1 4 0 2.76 (1.31-5.81)

Splenomegaly

0 0 0 | 1 1 0 1.87 (0.47-7.54)

Thrombocytopenia

0 1 1 | 2 5 0 0.35 (0.18-0.71)



Acute myocardial infarction

1 4 5 | 0 0 0 2.03 (0.84-4.9)

Atrial fibrillation

1 6 4 | 1 6 3 1.83 (1.09-3.1)

Summary Prints

- Prints are split to reflect EU and Non-EU data
- Prints normally are produced for active ingredient but some are produced for specific products
- Proportional reporting ratio (PRR)
- Lower and Upper 95% confidence intervals
- New cases received between defined period
- Previous cases received for the same reaction
- Terms are reflected as MedDRA PTs and grouped by primary MedDRA SOC

ICH E2B(R) and MedDRA

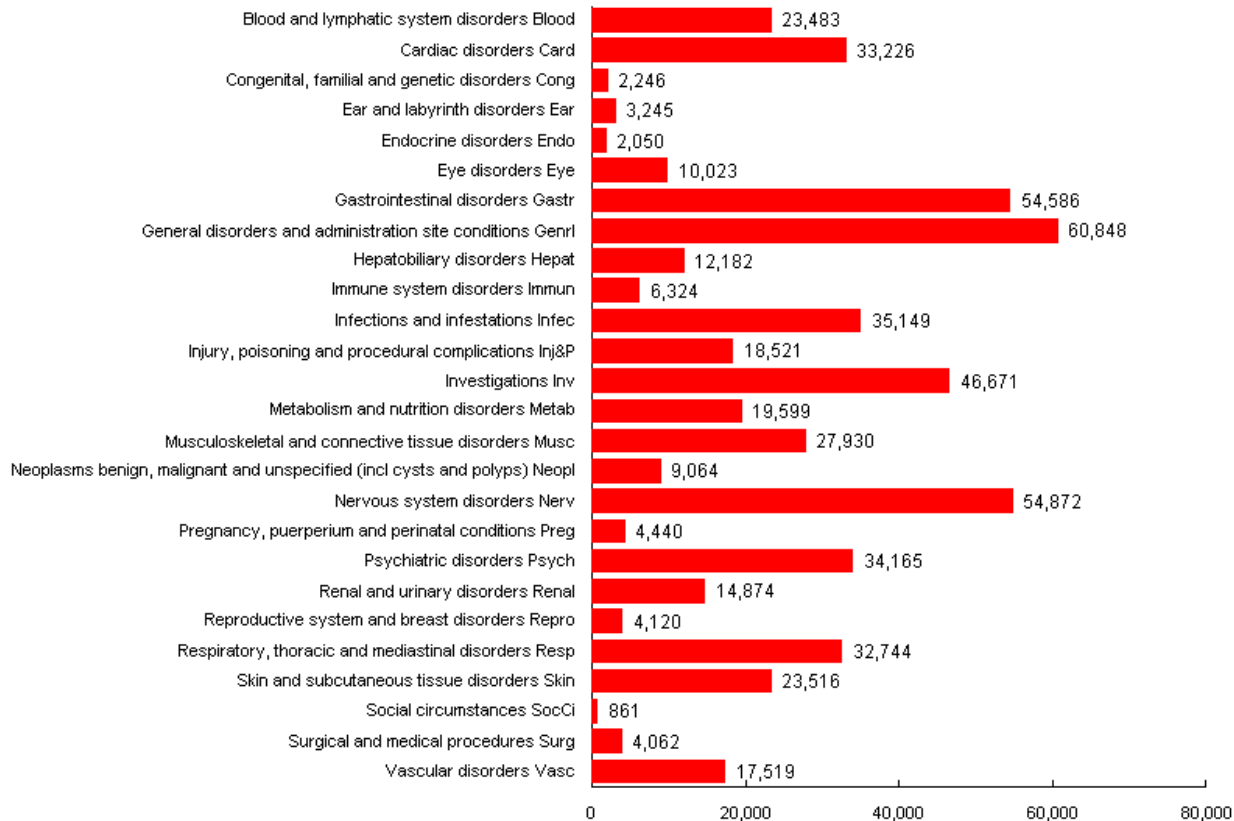
- ★ ■ Step 2 reached in Brussels in May 2005
- In the EU end of consultation period in September 2005
 - ★ ❖ All MedDRA fields capture the term at LLT level
 - ★ ❖ Single MedDRA version at case level (ICSR)
 - ★ ❖ MedDRA for Test Names
 - ★ ❖ Updated user guidance in E2B(R) on the use of MedDRA
 - ★ ❖ PT element (code and version) from event block deleted

EMA and MedDRA MSSO Collaboration

- ★ ■ Collaboration in the following areas:
 - ★ ❖ Recoding of test names
 - ★ ❖ Data quality and the use of MedDRA (comparison of MedDRA LLT coding with terms as reported by primary source; data privacy and confidentiality taken into account)
 - ★ ❖ Feedback on frequency of MedDRA terms used in ICSRs
 - ★

Frequency of MedDRA Terms by SOC

d. Number of Adverse Reactions Reported by SOC



Further Information

- Web Sites:
 - ❖ <http://pharmacos.eudra.org>
 - ❖ <http://eudravigilance.emea.eu.int>
- E-mail: eudravigilance@emea.eu.int
sabine.brosch@emea.eu.int
- EudraVigilance Helpline:
+44 (0) 207 523 7077

Acronyms

- EEA: European Economic Area
- EVWEB: EudraVigilance Web Application
- ICSRs: Individual Case Safety Reports
- NCAs: National Competent Authorities
- PRR: Proportional Reporting Ration
- SMEs: Small and Medium Size Enterprises

Questions

