MedDRA in pharmacovigilance - industry perspective

SFDA-ICH MedDRA Workshop, Beijing, 13-14 May 2011

Christina Winter, MD, FFPM
Medical director
GlaxoSmithKline R&D / ICH MedDRA Management Board
Disclaimer:

- The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Safety (pharmacovigilance) database

- Expedited individual case safety reports (ICSRs)
  - Electronic transfer directly to regulatory databases; e.g. FDA, Europe.
  - From regulators, e.g. individual cases from MHRA
  - Electronic transfer between company’s global safety database and local Japanese safety database enabled by MedDRA translations

- Data stored
  - Clinical trial Serious Adverse Events (SAEs)
  - Post marketing
    - Published case reports
    - Spontaneous reports from consumers, health care professionals, regulators, other manufacturers, lawyers etc.
MedDRA in pharmacovigilance – industry perspective

Safety database – data entry

• Coding working practices based on ICH MedDRA Term Selection Points to consider document

• MedDRA required for specified ICH E2B fields

• Coding may be assisted by
  o Physician
  o Optional tools: autoencoder and synonym list

• Reports received in a variety of formats, unlike clinical trial SAEs.
  o Care in selecting event for case as that determines the SOC in line listings
## Data output – single case

### INTERNATIONAL EVENT REPORT

**DESK COPY**

### EVENT INFORMATION

1. **PATIENT INITIALS**
   - PRIVACY
2. **COUNTRY**
   - United States
3. **DATE OF BIRTH**
4. **AGE**
5. **SEX**
6. **EVENT ONSET**
   - Jan 2010
7. & 13. **DESCRIBE EVENT(S)**
   - Convulsion, Hypersensitivity, Drug interaction, Swelling face, Swollen tongue, Lip swelling, Dyspnoea, Tremor, Dyskinesia, Muscle twitching, Musculoskeletal stiffness,

This case was reported by a consumer, via , and described the occurrence of seizure-like activity in a -year-old patient who received unspecified tablet for post-traumatic stress disorder and premenstrual dysphoric disorder. A physician or other health care professional has not verified this report.

The patient’s past medical history included penicillin allergy. Concurrent medical conditions included depression, fibromyalgia, idiopathic hypersomnia, obstructive sleep apnea, post-traumatic stress disorder and premenstrual dysphoric disorder. Co-suspect medication included and

On an unknown date, the patient started (oral) at 1 tablet twice per day. On January 2010, the patient

### DRUG INFORMATION

14. **IDENTIFIED DRUG(S)**
   - 1) tablet unknown

15. **DAILY DOSE**
   - 2 tablet

16. **ROUTE OF ADMINISTRATION**
   - Oral

17. **INDICATION(S) FOR USE**
   - POST-TRAUMATIC STRESS DISORDER, PREMENSTRUAL DYSPHORIC DISORDER, DEPRESSION

18. **DID EVENT ABATE AFTER STOPPING DRUG?**
   - YES

19. **DID EVENT REAPPEAR AFTER REINTRODUCTION?**
Cumulative data output

- For Periodic safety update reports, license renewals
  - Formats include MedDRA line listings, summary tabulations, graphical displays etc
- For routine safety signal detection
- For answering regulatory and other queries
- For collaboration with another company
**PSUR: example of line listing**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Country</th>
<th>Report Source</th>
<th>Age/Sex</th>
<th>Form’n or Route</th>
<th>TDD</th>
<th>Treatment Dates†</th>
<th>Event Onset</th>
<th>TTO / TTOSLD</th>
<th>Events</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>#0087698A</td>
<td>Germany</td>
<td>MD</td>
<td>30-39 Years/F</td>
<td>TABX</td>
<td>U</td>
<td>U</td>
<td>Unknown/U</td>
<td>Leukocytosis</td>
<td>U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#5085793A</td>
<td>Spain</td>
<td>MD,RP</td>
<td>48 Years/F</td>
<td>TABX 150MG</td>
<td>01Feb2010- 26Oct2010</td>
<td>U</td>
<td>Acute myocardial infarction, Chest pain, Electrocardiogram ST segment elevation, Coronary artery occlusion, Vasospasm, Angina pectoris</td>
<td>R</td>
<td>Stopped smoking 15 years ago. Family history of ischaemic heart disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#0876895A</td>
<td>Canada</td>
<td>CM,MD</td>
<td>U/F</td>
<td>TABR 450MG</td>
<td>U</td>
<td>U/U</td>
<td>Arrhythmia</td>
<td>U</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PSUR: example of summary tabulation

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>HLGT</th>
<th>Event (PT)</th>
<th>Listed</th>
<th>Serious</th>
<th>Non-serious</th>
<th>Total Cases for current period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>White blood cell disorders</td>
<td>Leukocytosis</td>
<td>No</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac arrhythmias</td>
<td>Tachycardia</td>
<td>Yes</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Cardiac disorder signs and symptoms</td>
<td>Palpitations</td>
<td>Yes</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disorders</td>
<td>Acute myocardial infarction</td>
<td>No</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Inner ear and VIIIth cranial nerve disorders</td>
<td>Tinnitus</td>
<td>Yes</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
MedDRA in pharmacovigilance – industry perspective

Graphical displays
Blue: consumer reporting/ Red: Health care professional

- Nervous system disorders
- Skin and subcutaneous tissue disorders
- Psychiatric disorders
- General disorders and administration site conditions
- Gastrointestinal disorders
- Investigations
- Injury, poisoning and procedural complications
- Reproductive system and breast disorders
- Ear and labyrinth disorders
- Musculoskeletal and connective tissue disorders
- Eye disorders
- Cardiac disorders
- Vascular disorders
- Immune system disorders
- Respiratory, thoracic and mediastinal disorders
- Renal and urinary disorders
- Blood and lymphatic system disorders
- Metabolism and nutrition disorders
- Infections and infestations
- Hepatobiliary disorders
- Endocrine disorders
- Neoplasms benign, malignant and unspecified
- Social circumstances
- Surgical and medical procedures
- Pregnancy, puerperium and perinatal conditions
- Congenital, familial and genetic disorders

Number of Reports
Signal detection

• Variety of signal detection techniques: AEs may be sorted by
  o Any level of MedDRA hierarchy
  o Primary SOC, Secondary SOC
  o Standardised MedDRA Queries (SMQs)
  o Ad hoc queries (within company)
  o Safety signal score

• Optional tool like that used for clinical trial signals
  o Compares signal score in company database vs score on FDA Adverse Event Reporting (AERSs) database
    - Others may use WHO Uppsala database
Signal detection principles

- Usually compare reporting rates of MedDRA PTs for drug of interest against all other drugs in database
- Can also compare
  - any selected MedDRA hierarchial level
  - Any SMQ
- Variety of statistical methods employed
- Variety of tools available commercially
  - FDA, MHRA and GSK use the same signal detection tool
Search strategies

• Signal detection may lead to search of database and full review
  o False signals may occasionally result from MedDRA version changes

• SMQs applied as first search strategy
  o Preferred by ICH regulators
    - Standardised so regulator knows what the search criteria are

• Scan cumulative summary of all PTs for product
  o To ensure complete search

• Record search strategy applied
Search output

• Search output is medically reviewed

• If issue appears to be drug related, consider updating product label or other risk management strategy.

• If label update requires addition of undesirable effect, consider which MedDRA term is most appropriate: usually PT but may be LLT or higher hierarchical level

• Update risk management plans as appropriate
Post marketing product labels

Examples:

- European summary of product characteristics (SmPC)
- US prescribing information (PI)
EU Summary of Product Characteristics

• MedDRA required
  - Use any hierarchical level (often PT), arranged by SOC and by frequency
  - Use internationally agreed SOC order (translates across languages)

• Frequencies
  - One company has lists of PTs used to aggregate events to determine frequency
    - e.g. “rash” includes PTs Rash, Rash erythematous, Rash maculo-papular, Rash pruritic but does not include Systemic lupus erythematosus rash
<table>
<thead>
<tr>
<th>Immune system disorders*</th>
<th>Common</th>
<th>Hypersensitivity reactions such as urticaria.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very Rare</td>
<td>More severe hypersensitivity reactions including angioedema, dyspnoea, bronchospasm and anaphylactic shock.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Anorexia.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Blood glucose disturbances</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very common</td>
<td>Insomnia (see section 4.2)</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Agitation, anxiety</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Depression (see section 4.4), confusion</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams including nightmares, depersonalisation, delusions, paranoid ideation</td>
</tr>
</tbody>
</table>
US Prescribing information (PI)

• No requirement for MedDRA:
  - use natural language

• If clinical studies used MedDRA,
  - the incidence of ADRs is derived with MedDRA PTs
  - Arranged by MedDRA SOC
  - PTs by descending frequency for drug
### MedDRA in pharmacovigilance – industry perspective

<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Placebo&lt;sup&gt;a&lt;/sup&gt; (N = 245)</th>
<th>Drug 600 mg/day&lt;sup&gt;b&lt;/sup&gt; (N = 163)</th>
<th>Drug 1,200 mg/day&lt;sup&gt;c&lt;/sup&gt; (N = 269)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence/sedation</td>
<td>6</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Flatulence</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Iritability</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Feeling abnormal</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1</td>
<td>&lt;1</td>
<td>3</td>
</tr>
</tbody>
</table>

© 2011 ICH
Company specific applications

- Case awareness tool
- Automated listedness
- Automated seriousness
Case awareness tool – Clinical trial SAEs and Spontaneous (post marketing) cases

• Bespoke safety database permits selection of PTs of interest
  o Designated medical events (DMEs, common for all products)
  o Selected PTs for each compound/protocol

• Automatically retrieves cases with selected terms
  o Clinical SAEs and spontaneous reports

• Assigned safety reviewer checks retrieved cases regularly

• Case alert may trigger full search and review
### Case awareness tool

#### MedDRA in pharmacovigilance – industry perspective

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Case Type</th>
<th>Protocol ID</th>
<th>Project ID</th>
<th>Country (Admin Loc)</th>
<th>Age (Gender)</th>
<th>Case Outcome</th>
<th>Primary Suspect Drug</th>
<th>Other Suspect Drugs</th>
<th>Events</th>
<th>Receipt Dates for Company Safety Dept (Tracking Memo)</th>
<th>Case Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>80821795A</td>
<td>S</td>
<td></td>
<td></td>
<td>GB (M)</td>
<td>21 Y (M)</td>
<td>Resolved</td>
<td>Atropine mesilate</td>
<td>Morphine</td>
<td>Anaphylactic reaction</td>
<td>18Feb2010, 16Jan2010</td>
<td></td>
</tr>
<tr>
<td>30527796A</td>
<td>S</td>
<td></td>
<td></td>
<td>US (M)</td>
<td>23 Y (F)</td>
<td>Fatal</td>
<td>Methadone</td>
<td>Morphine, Cocaine</td>
<td>Death, Cardiorespiration</td>
<td>18Jan2010, 18Jan2010</td>
<td></td>
</tr>
<tr>
<td>30527799A</td>
<td>S</td>
<td></td>
<td></td>
<td>US (M)</td>
<td>45 Y (M)</td>
<td>Fatal</td>
<td>Methadone</td>
<td>Morphine</td>
<td>Drug</td>
<td>18Jan2010, 18Jan2010</td>
<td></td>
</tr>
<tr>
<td>30527795A</td>
<td>S</td>
<td></td>
<td></td>
<td>US (M)</td>
<td>37 Y (F)</td>
<td>Fatal</td>
<td>Methadone</td>
<td>Morphine, Cocaine</td>
<td>Drug</td>
<td>18Jan2010, 18Jan2010</td>
<td></td>
</tr>
</tbody>
</table>
Automated listedness

- Listedness* may be assessed inconsistently in a large organisation
  - Example: if headache is labelled, is migraine listed?

- For consistency, some companies maintain a set of MedDRA terms that are considered listed for each undesirable effect in the core safety information

* Expectedness of undesirable effect that is in the core safety information
Serious list of terms (PTs or LLTs)

• EU, FDA and ICH SAE definitions include medically important events
  o those requiring medical intervention to prevent a regulatory serious outcome
  o such cases require expedited reporting to regulators

• For consistency, company may maintain list of MedDRA terms that are always serious
  o Manual check against list in some companies
  o Automated check in one company’s safety database
    - for spontaneous, post-marketing and literature cases
Serious list of terms (2)

- European Medicines Agency (EMA) has equivalent list (Important medical events) for prioritising safety signal detection
  - Formerly MHRA list but refined by Eudravigilance working party
  - Was in pilot, receiving comments from interested parties
  - List of MedDRA PTs, maintained for MedDRA versions

Industry – regulator interface in EU

• Eudravigilance database
• EVWEB – Eudravigilance web application
Eudravigilance - Regulator/industry interface

- Central data-processing network and management system in the European Union (EU) to promote the protection of public health
  - Links European Medicines Agency (EMA) and National competent authorities (NCAs) in EU and European Economic Area (EEA)
  - Implemented 2001 with access to all NCAs
    - Final aim is to include healthcare professionals, public and industry
  - Over 45,000 ICSRs/month
  - Provides electronic reporting facilities to companies and sponsors of clinical trials
Eudravigilance network

NATIONAL COMPETENT AUTHORITIES (NCAs)

EUDRAVIGILANCE

Central EU PhV System ICH E2B and MedDRA Standards

e-reporting MARKETING AUTHORISATION HOLDERS (MAHs)

SPONSORS
EVWEB - Eudravigilance web application

• EVWEB is for Small and Medium Size Enterprises (SMEs) and non commercial sponsors
  o which do not have a fully ICH E2B (R2) complaint pharmacovigilance system and /or ESTRI gateway in place

• A tool for SMEs to report electronically
  o Registration and training is required
Thank You!