MedDRA in pharmacovigilance - industry perspective

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

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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.

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**
  - Physician
  - Optional tools: autoencoder and synonym list
- **Reports received in a variety of formats, unlike clinical trial SAEs.**
  - Care in selecting event for case as that determines the SOC in line listings

Data output –single case

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 3)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
PRIVACY	United States				Jan2010

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

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- ☐ PATIENT DIED AS OUTCOME OF EVENT
- ☒ RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- ☐ OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) 1) tablet unknown

15. DAILY/[illegible] DOSE: 2 tablet

16. ROUTE OF ADMINISTRATION: Oral

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

20. DID EVENT ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ N/A

21. 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

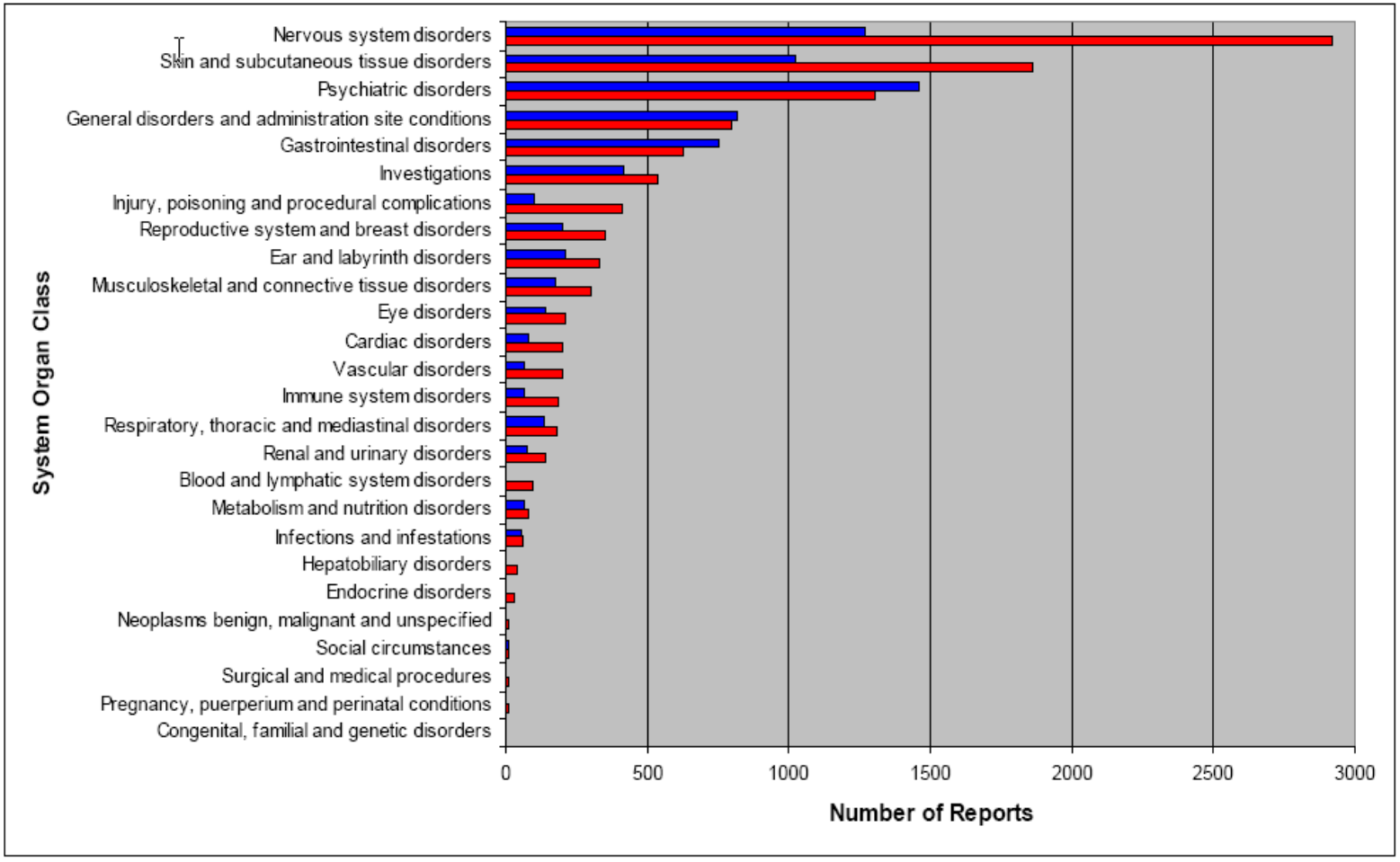
Case No.	Country	Report Source	Age/Sex	Form'n or Route	TDD	Treatment Dates†	Event Onset	TTO / TTOSLD	Events	Outcome	Comments
Blood and lymphatic system disorders											
#D0067668A	Germany	MD	30-39 Years/F	TABX	U	U		Unknown/U	Leukocytosis	U	
Cardiac disorders											
#B0685798A	Spain	MD,RP	48 Years/F	TABX	150MG	01Feb2010- U	26Oct2010	Unknown/U	Acute myocardial infarction, Chest pain, Electrocardiogram ST segment elevation, Coronary artery occlusion, Vasospasm, Angina pectoris	R	Stopped smoking 15years ago. Family history of ischaemic heart disease.
A0876895A	Canada	OM,MD	U/F	TABR	450MG	U		U/U	Arrhythmia	U	

PSUR: example of summary tabulation

MedDRA SOC	HLGT	Event (PT)	Listed	Serious	Non-serious	Total Cases for current period
Blood and lymphatic system disorders	White blood cell disorders	Leukocytosis	No	1	0	1
Cardiac disorders	Cardiac arrhythmias	Tachycardia	Yes	0	3	3
	Cardiac disorder signs and symptoms	Palpitations	Yes	0	1	1
	Coronary artery disorders	Acute myocardial infarction	No	1	0	1
		Myocardial infarction	No	1	0	1
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	Tinnitus	Yes	0	2	2

Graphical displays

***Blue: consumer reporting/* Red: Health care professional**



Signal detection

- **Variety of signal detection techniques: AEs may be sorted by**
  - Any level of MedDRA hierarchy
  - Primary SOC, Secondary SOC
  - Standardised MedDRA Queries (SMQs)
  - Ad hoc queries (within company)
  - Safety signal score
- **Optional tool like that used for clinical trial signals**
  - 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**
  - False signals may occasionally result from MedDRA version changes
- **SMQs applied as first search strategy**
  - Preferred by ICH regulators
    - Standardised so regulator knows what the search criteria are
- **Scan cumulative summary of all PTs for product**
  - 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*

EU SMPC

Immune system disorders*	Common	Hypersensitivity reactions such as urticaria.
	Very Rare	More severe hypersensitivity reactions including angioedema, dyspnoea/bronchospasm and anaphylactic shock. 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.
Metabolism and nutrition disorders	Common	Anorexia.
	Uncommon	Weight loss
	Very Rare	Blood glucose disturbances
Psychiatric disorders	Very common	Insomnia (see section 4.2)
	Common	Agitation, anxiety
	Uncommon	Depression (see section 4.4), confusion
	Very rare	Aggression, hostility, irritability, restlessness, hallucinations, abnormal dreams including nightmares, depersonalisation, delusions, paranoid ideation

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

US PI

Body System/Adverse Reaction	Placebo[a] (N = 245) %	Drug 600 mg/day[b] (N = 163) %	Drug 1,200 mg/day[c] (N = 269) %
Nervous system disorders			
Somnolence/sedation	6	20	27
Dizziness	4	13	22
Headache	11	12	15
Gastrointestinal disorders			
Nausea	5	6	7
Dry mouth	2	3	4
Flatulence	<1	3	2
General disorders and administration site conditions			
Fatigue	4	6	7
Irritability	1	4	4
Feeling drunk	0	1	3
Feeling abnormal	<1	<1	3
Peripheral edema	1	<1	3

Company specific applications

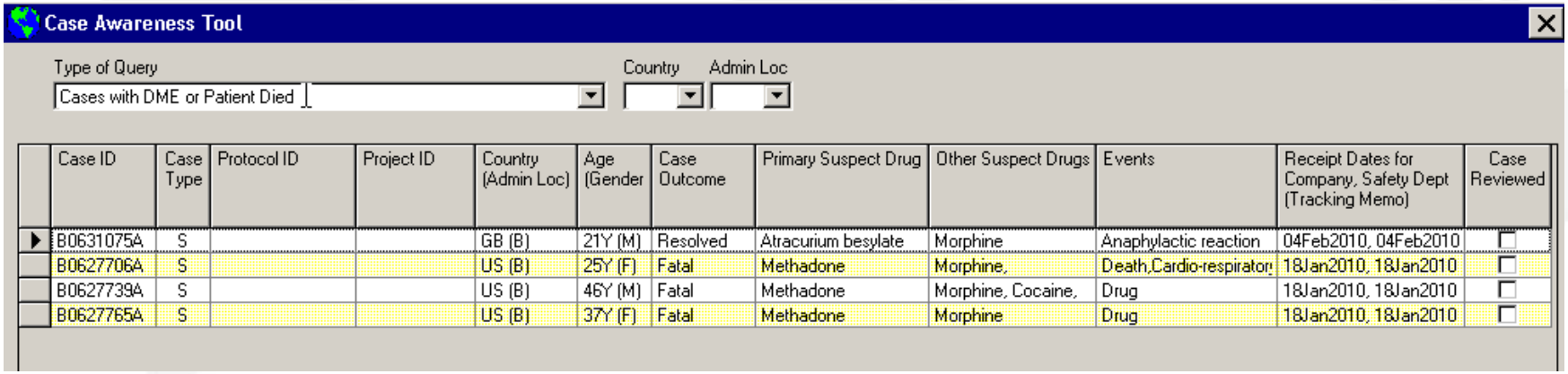
- Case awareness tool
- Automated listedness
- Automated seriousness

Case awareness tool –

Clinical trial SAEs and Spontaneous (post marketing) cases

- **Bespoke safety database permits selection of PTs of interest**
  - Designated medical events (DMEs, common for all products)
  - Selected PTs for each compound/protocol
- **Automatically retrieves cases with selected terms**
  - Clinical SAEs and spontaneous reports
- **Assigned safety reviewer checks retrieved cases regularly**
- **Case alert may trigger full search and review**

Case awareness tool



Case ID	Case Type	Protocol ID	Project ID	Country (Admin Loc)	Age (Gender	Case Outcome	Primary Suspect Drug	Other Suspect Drugs	Events	Receipt Dates for Company, Safety Dept (Tracking Memo)	Case Reviewed
B0631075A	S			GB (B)	21Y (M)	Resolved	Atracurium besylate	Morphine	Anaphylactic reaction	04Feb2010, 04Feb2010	☐
B0627706A	S			US (B)	25Y (F)	Fatal	Methadone	Morphine,	Death,Cardio-respirator	18Jan2010, 18Jan2010	☐
B0627739A	S			US (B)	46Y (M)	Fatal	Methadone	Morphine, Cocaine,	Drug	18Jan2010, 18Jan2010	☐
B0627765A	S			US (B)	37Y (F)	Fatal	Methadone	Morphine	Drug	18Jan2010, 18Jan2010	☐

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**
  - those requiring medical intervention to prevent a regulatory serious outcome
  - such cases require expedited reporting to regulators
- **For consistency, company may maintain list of MedDRA terms that are always serious**
  - Manual check against list in some companies
  - 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
- **http://eudravigilance.ema.europa.eu/human/textforIME.asp**

Industry – regulator interface in EU

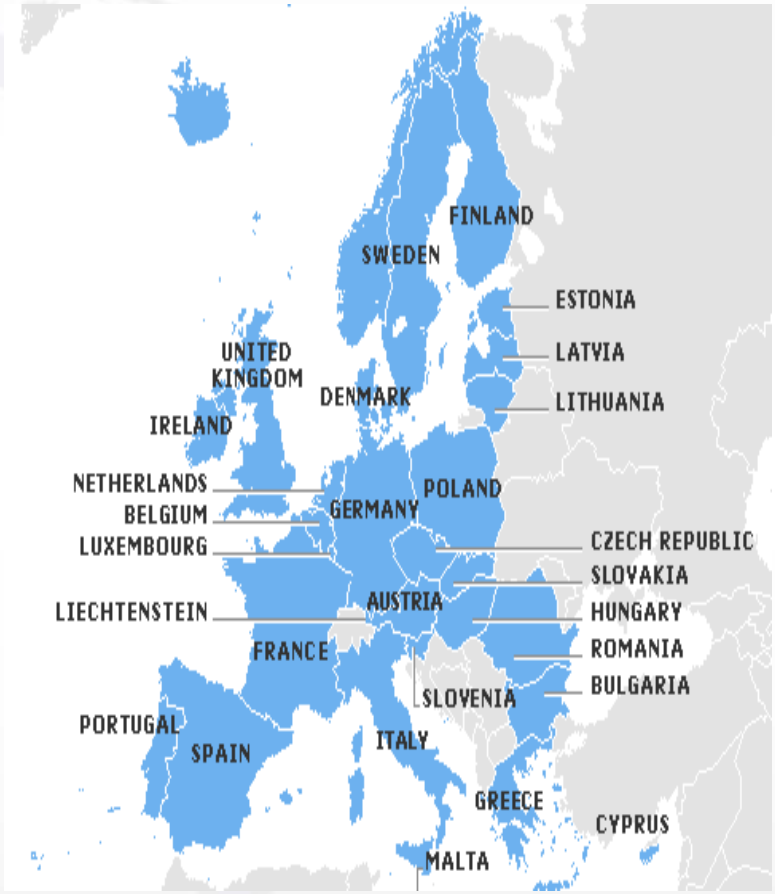
- **Eudravigilance database**
- **EVWEB – Eudravigilance web application**

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 competant 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**
  - 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**
  - Registration and training is required

ICH
harmonisation for better health

Thank You!