Farmakovijilans ve MedDRA
Pharmacovigilance and MedDRA
FARMAKOVİJİLANS ve FARMAKOVİJİLANS UYGULAMALARI
23-24 EKİM 2003

Dr. Tomás Moraleda
Agenda

1. What is MedDRA?
2. Conditions before MedDRA
3. MedDRA Structure
4. MedDRA Implementation
5. The constant change of MedDRA
6. Why your data look different?: Analysis with MedDRA
What is MedDRA?
Med = Medical
D = Dictionary for
R = Regulatory
A = Activities
Objectives for MedDRA development

- Provide a classification for a wide range of clinical information, able to support for multiple medical product areas
- Within an international multi-lingual frame
- To standardize communication between industry and regulators
- That can be used through all phases of the development cycle
- Thus saving time, resources, and money …
Regulatory Communications Goal

INTERNATIONAL STANDARDS

EMEA  FDA  MHLW

EFPIA  PhRMA  JPMA

IFPIA - INDUSTRY
ICH EDI Coordination

**M2 (ESTRI)**
- the transport vehicle and format definitions

**M1**
*Medical Terminology*

**E2b**
*Clinical Safety Data Management: Content of Report*

**Regulatory Authority**

**Electronic Standards for the Transfer of Regulatory Information**

**Pharmaceutical Company**

**RX**
### MedDRA History

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall 1994</td>
<td>International decision to further develop MEDDRA under the ICH</td>
</tr>
<tr>
<td>March 1995</td>
<td>ICH Meeting - decision to request thorough U.S. scientific review of MEDDRA</td>
</tr>
<tr>
<td>February 1996</td>
<td>Release of MEDDRA 1.5 for review</td>
</tr>
<tr>
<td>July 1997</td>
<td>ICH approval and signing of the International Medical Terminology</td>
</tr>
<tr>
<td>December 1997</td>
<td>IFPMA releases tender for the MSSO</td>
</tr>
<tr>
<td>November 24, 1998</td>
<td>Contract signed</td>
</tr>
<tr>
<td>March 1, 1999</td>
<td>MedDRA 2.1 available from MSSO</td>
</tr>
</tbody>
</table>
MedDRA Subscriptions
Percent by Region

- JMO/Japan: 36%
- EU: 22%
- US: 35%
- Other: 7%
MedDRA Subscriptions Percent by Category

- Pharmaceutical: 40%
- CRO: 32%
- Biotechnology: 10%
- Academic: 3%
- Regulator: 10%
- Other: 5%
Conditions before MedDRA
Conditions before MedDRA

- Use of different types of terminologies
- Use of terminologies for different phases of regulatory cycle
- Resulting use of non-standard terminologies developed “in-house”
- Lack of specificity of terms
- Limited data retrieval options
- Resulting high cost and time investment
MedDRA Structure
Scope of MedDRA

OUT
Drug product terms
Numerical values for results
Severity descriptors
Patient demographic terms

IN
Diseases
Diagnoses
Signs
Symptoms
Therapeutic indications
Investigation names & qualitative results
Medical & surgical procedures
Medical, social, family history

Terms from:
COSTART
WHO-ART®
HARTS
J-ART

Device failure terms
Equipment, device, diagnostic product terms
Clinical trial study design terms
Population-level qualifiers

FARMAKOVIJILANS ve FARMAKOVIJILANS UYGULAMALARI, 23-24 EKİM 2003
MedDRA Hierarchy

- System Organ Class (SOC)
- High Level Group Term (HLGT)
- High Level Term (HLT)
- Preferred Term (PT)
- Lowest Level Term (LLT)

Special Search Category level
System Organ Classes

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

SOC = Psychiatric disorders

HLGT = Dissociative disorders

HLT = Dissociative states

PT = Dissociative identity disorders

LLT = Multiple personality disorders
A Multi-Axial Terminology

SOC = Respiratory, thoracic and mediastinal disorders

HLGT = Upper respiratory tract infections

HLT = Viral upper respiratory tract infections

SOC = Infections and Infestations

HLGT = Viral Diseases

HLT = Influenza viral infection

PT = Influenza

And its LLTs
A Multi-Axial Terminology

SOC = Cardiac disorders

HLGT = Congenital cardiac disease

HLT = Congenital valve disorders

SOC = Psychiatric disorders

HLGT = Cognitive and attention disorders and disturbances

SO = Nervous system disorders

HLGT = Mental Impairment disorders

SOC = Congenital and familial/genetic disorders

HLGT = Musculoskeletal, connective tissue and bone disorders congenital

SOC = Musculoskeletal, connective tissue and bone disorders

HLT = Non-site specific musculoskeletal disorders congenital NOS

PT = Rubenstein-Taybi syndrome

And its LLTs

Primary SOC
A Multi-Axial Terminology
A Multi-Axial Terminology

- 15,149 PTs in MedDRA 4.1
- 5,396 (36%) are multi-axial

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diencephalic syndrome of infancy</td>
<td>6</td>
</tr>
<tr>
<td>Behcet's syndrome</td>
<td>6</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Foetal hydantoin syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Hepato-lenticular degeneration</td>
<td>5</td>
</tr>
<tr>
<td>Osteoporosis-pseudoglioma syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Reiter's syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Trisomy 22</td>
<td>5</td>
</tr>
<tr>
<td>Wolman's disease</td>
<td>5</td>
</tr>
<tr>
<td>Toxic oil syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Pseudoxanthoma syndrome</td>
<td>5</td>
</tr>
<tr>
<td>Porphyria acute</td>
<td>5</td>
</tr>
<tr>
<td>Phakomatosis</td>
<td>5</td>
</tr>
</tbody>
</table>
Primary SOC Allocation (cont.)

• Purpose of Primary SOC:
  – Determines *which SOC will represent a PT during cumulative data outputs*
  – Is used to support consistent data presentation for reporting to regulators

• Secondary SOCs are used for alternative presentations of data
MedDRA Implementation
Impact of MedDRA

MedDRA is used to generate data on clinical research SAFETY…

... But actually it will be also used for OTHER clinical research DATA

☑ Medical history
☑ Complete physical exam
☑ Selection criteria
☑ Chemistry and hematology
☑ Non-Pharmacological Treatment/Procedure(s)

But also in OTHER regulatory aspects …

▪ new therapeutic indications
▪ absorption
▪ administration
▪ interactions

MedDRA will influence SAFETY report in the PMK surveillance (data mining and signal detection) ….

But also in OTHER clinical research DATA

rega

Patient: Peoni Wright
Peeright Plus 500 mg
Take 1 q/day
Drink 40 oz. water and eat one banana per day

Data migration
Communication and Coordination

• **Different groups** within an organization will want to implement on **different timelines**
  - Coordinated by a single **group** with a leader
  - **Senior management** champion support

• **MedDRA** will force a review/update of **coding conventions**

• **MedDRA** often provides an **opportunity to review/improve existing processes**
MedDRA big **size, multiaxiality and frequent update needs software** tools to support different functions:
- Autoencoding
- Browsing
- Terminology maintenance

Software tool selection should consider:
- **needs from all parts of the user community:** Clinical, Safety, IT, Regulatory, Legal …
- Commercial **system compatibility**
Training

• Identification of appropriate
  – Staff to be trained
  – Method of training
    • Enterprise training program
    • Train the trainer
    • Computer Based Training (CBT)
  – Timing of training
Implementation Benefits

- Saves valuable time, money and resources
- No need for development of in-house or modified terminologies
- Relieves time delays and loss or distortion of data during conversion (especially with multi-national companies)
- Increases granularity (augmenting both specificity and sensitivity)
- Decreases “guess work” with increased specificity of terms
- Standardization of data set content and structure facilitates electronic communication
  - Decreases paperwork
  - Decreases processing time
The constant change of MedDRA: Maintenance, statistics, versioning policy ...
In short! ...

- Something **AMBITIOUS**
- Result of an **AGREEMENT**
MSSO

M = Maintenance
S = Support
S = Services
O = Organization
Maintenance Organization Structure

ICH Steering Committee

M.S.S.O.
- Development
- Maintenance
- Implementation
- User Support
- Communication

JMO
- Maintains and distributes MedDRA/J
- Assists MSSO in providing MedDRA related information and services in Japan

Regulated Industries, Regulatory Authorities, User Communities, WHO, Others...

User Groups (meetings)

Northrop Grumman (Health Care dept.)

EWGs

Management Board
Board of Directors Staff

I.F.P.M.A.
MedDRA Maintenance Rules

- **9,000 possible changes per year**
- Per core subscriber:
  - 100 routine change requests per month
- **Daily supplemental changes**
- **Twice yearly official updates** (March 1, September 1)
- **Yearly complex changes** (March 1)
Versioning Illustration

v3.0  v3.1  v3.2  v3.3  v4.0

Study 1  Study 1  Data Lock  Study 2  Data Lock  Study 3  Data Lock

PhV*  PhV  PhV  PhV  PhV

*Pharmacovigilance

Integrated analysis: MedDRA v4.0
CRs procedure along time
2.0 – 4.0 – 5.0 versions distribution

![Bar chart with categories and values](image-url)
Why your data look different?: Analysis with MedDRA
<table>
<thead>
<tr>
<th></th>
<th>MedDRA</th>
<th>COSTART</th>
<th>WHO-ART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of terms</strong></td>
<td>3.2</td>
<td>5.0</td>
<td>98.3</td>
</tr>
<tr>
<td><strong>Preferred Term</strong></td>
<td>12,469*</td>
<td>1,184</td>
<td>1,652**</td>
</tr>
<tr>
<td><strong>High Level Term</strong></td>
<td>1,653</td>
<td>165</td>
<td>173</td>
</tr>
<tr>
<td><strong>High Level Group Term</strong></td>
<td>334</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>System Organ Class</strong></td>
<td>26</td>
<td>12</td>
<td>29</td>
</tr>
</tbody>
</table>

* as of MedDRA Version 3.2
** as of WHO-ART Version 98:3
The “Splatter Effect”

• What once fit into one ‘bucket’…

• …now may be in multiple places.
Let us make the most of what we have: Multiaxiality and SOCs “personality”

<table>
<thead>
<tr>
<th>Cerebrovascular and spinal vascular disorders NEC</th>
<th>Central nervous system vascular disorders NEC</th>
<th>Traumatic central nervous system haemorrhages</th>
<th>Cerebrovascular venous and sinus thrombosis</th>
<th>Transient cerebrovascular events</th>
<th>Central nervous system haemorrhages and cerebrovascular accidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disorder NOS</td>
<td>Traumatic intracranial haemorrhage NOS</td>
<td>Cavernous sinus thrombosis</td>
<td>Transient ischaemic attack</td>
<td>Cerebral artery embolism</td>
<td>Cerebral infarction</td>
</tr>
<tr>
<td>Traumatic intracranial haemorrhage NOS</td>
<td>Cavernous sinus thrombosis</td>
<td>Transient ischaemic attack</td>
<td>Cerebral artery embolism</td>
<td>Cerebral infarction</td>
<td>Cerebral infarction</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td></td>
<td>Transient ischaemic attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular and spinal necrosis and vascular insufficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular haemorrhagic disorders</td>
<td>Cerebrovascular and spinal necrosis and vascular insufficiency</td>
<td>Cerebrovascular and spinal vascular disorders NEC</td>
<td>Central nervous system vascular disorders NEC</td>
<td>Traumatic central nervous system haemorrhages</td>
<td>Cerebrovascular venous and sinus thrombosis</td>
</tr>
</tbody>
</table>
What are some of the “hot” safety issues in the biopharm industry?

- QT prolongation
- Pancreatitis
- Lactic acidosis
- Stevens-Johnson syndrome
- Hepatotoxicity/liver failure
- Angioedema
- Neuroleptic malignant syndrome
- Rhabdomyolysis
- Peripheral neuropathy
- Thrombocytopenia
- Agranulocytosis
- Suicide/depression
Contacting MSSO
MSSO Contacts

• Mail
  MSSO
  VAR1/8A/MSSO
  12011 Sunset Hills Road
  Reston, VA 20190-3285
  USA

• Telephone
  – 703.345.7799
  – 877.258.8280 (AT&T toll free)
MSSO Contacts (cont.)

• To Subscribe
  – Send e-mail to subscribe@trw.com
  – Call 703.345.7765
  – Fax 703.345.7755

• Web Page
  – www.meddramsso.com

• Products and Services
  – 703.345.7799
How to get in contact with me ...

- Tomás Moraleda
- Spanish International Medical Officer
- Telephone: +34 91 518 70 13
- Email: tmoraled@teleline.es
Questions & Answers