Introduction to MedDRA – An ICH Product
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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.
Agenda

• What is MedDRA?
  o MedDRA – an ICH product

• Why MedDRA?
  o An ICH standard
  o A drug safety terminology
  o Features of MedDRA
  o ICH-endorsed guides for users
  o Active maintenance
  o Support for users
MedDRA

Med = Medical
D = Dictionary for
R = Regulatory
A = Activities

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MedDRA Is Developed under the Auspices of ICH

INTERNATIONAL CONFERENCE ON HARMONISATION of Technical Requirements for the Registration of Pharmaceuticals for Human Use

http://www.ich.org

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What is ICH?

- ICH is a unique harmonisation project involving the regulators and research-based industries of US, EU and Japan
  - started in 1990
    - WHO, Canada, and EFTA are observers
- Well-defined objectives:
  - To improve efficiency of new drug development and registration process
  - To promote public health, prevent duplication of clinical trials in humans and minimise the use of animal testing without compromising safety and effectiveness
- Accomplished through the development and implementation of harmonised guidelines and standards

ICH Accomplishments

- 60+ harmonised guidelines on technical requirements (quality, safety, efficacy)
- Electronic standards (ESTRI, E2B)
- Common format and electronic specification for marketing applications: CTD and eCTD
- MedDRA – ICH’s standard for electronic safety data exchange

→ 2010 marked the 20th Anniversary of ICH
The ICH Members

Europe
- EC – European Commission – European Union (EU)
- EFPIA - European Federation of Pharmaceutical Industries and Associations

Japan
- MHLW - Ministry of Health, Labour and Welfare
- JPMA - Japan Pharmaceutical Manufacturers Association

United States
- FDA - Food and Drug Administration
- PhRMA - Pharmaceutical Research and Manufacturers of America

Observers
- WHO – World Health Organization
- Health Canada
- EFTA – European Free Trade Association

...Expanding beyond ICH regions

Protect Public Health

• Drug approval – evaluate and decide
  o Is the drug safe and effective?
  o What should the label contain?
  o Does the method of manufacturing preserve the drug's identity, strength, quality, and purity

• THE THALIDOMIDE TRAGEDY
  o An estimated 10,000 human birth deformities
  o Dr. Frances Kelsey, the Medical Officer of the Food and Drug Administration, rejected the drug firm's application to market Kevadon (thalidomide) in the United States
The Need for MedDRA

Before MedDRA:
- Impossible for electronic communication
- Some used WHO-ART, COSTART, ICD-9, ICD-9 CM, HARTS etc
- Some used their own customised versions of these
- Some used their in-house developed dictionary
- Inadequacies of previous terminologies
  - Not enough medical terms - low specificity
  - Not medically valid
  - Poor or no maintenance - addition of terms
  - Poor hierarchies hinder retrieval of grouped data

• In both pre- and post-authorization situations, a recognized terminology is an essential requirement

• For protection of global public health: need for an international, standardized, multi-lingual, robust, medically validated terminology which facilitates electronic communication.

⇒ MedDRA
ICH “Multidisciplinary” Expert Working Group 1 developed MedDRA

- Made up of drug safety experts from regulatory authorities and industry
- UK's Medicines Control Agency (current MHRA) terminology – MedDRA – used as the basis
- Capability testing conducted by US FDA and others
- Produced the final product - MedDRA

(Mozzicato, P. “MedDRA – Past and Future” Dec 2006, RAJ Pharma, p797)
MedDRA Management Board
Purpose & Responsibilities

- Oversees financial and technical operations of the MSSO
  - Examples: Review MSSO costs and fee structure
- Ensures the continued development and viability of MedDRA
- Ensures that MedDRA is easy to use and accessible to all
- Ensures MSSO is meeting the needs of users

IFPMA
International Federation of Pharmaceutical Manufactures and Associations

- Non-Profit, Non-Governmental Organisation
- Represents national industry associations & R&D companies from developed & developing countries
- Hosts the ICH Secretariat
- Holds ownership of MedDRA, as a trustee of ICH
- Contracts the maintenance organization of MedDRA (MSSO) on behalf of ICH
ICH Management Structure of MedDRA (cont)

MedDRA Management Board
(Six ICH parties, Canada, UK MHRA & WHO as Observer)

ICH Steering Committee

Others (Future)

MSSO
Development
Implementation
Communication

Maintenance
User Support

User Communities
Regulatory Authorities
WHO

Regulated Industries
Others

JMO
(MedDRA Japanese)

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MSSO
Maintenance and Support Services Organization

- Contracted by ICH (Nov. 1998 - )
- Activities directed by the MedDRA Management Board
- Maintains/develops & distributes MedDRA (twice a year)
- Support Subscribers with Help Desk support and training
- MSSO activities self-funded through MedDRA subscriptions
  - Free for all Regulators worldwide
  - Free for all Healthcare providers and academics
  - Sliding scale subscription rates for commercial organizations
  - Special licenses to provide access to low revenue users

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**JMO**

**Japanese Maintenance Organization**

- MedDRA MSSO partner (Nov. 1998 - )
- Operated by Pharmaceutical and Medical Device Regulatory Science Society of Japan
- Maintains & distributes Japanese MedDRA translation (MedDRA/J) to companies headquartered in Japan
  - Works with MSSO to ensure consistency of MedDRA/J with original English version
- Supports MedDRA/J users with Help Desk support and training in Japanese
- Activities self-funded through MedDRA/J subscriptions

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**Interest from Beyond the ICH Regions**

- November 2010 MB special session at Fukuoka included representatives from
  - SFDA (中国)
  - APEC (亚太经济合作组织)
  - ASEAN (东盟)
  - SADC (南部非洲发展共同体)
  - GCC (Gulf Cooperation Countries)
  - KFDA (南韩)
  - HSA (新加坡)
  - Chinese Taipei Department of Health
MedDRA Subscriber Worldwide

2847 organizations as of 31 March 2011

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Why MedDRA?
ICH Standard Terminology

For better protection of global public health

• Speaking the same language in product safety
  o No matter where you are
    - FDA (AERS, VERS, CAERS) – MedDRA
    - Health Canada (Canada Vigilance) – MedDRA
    - EMA (EudraVigilance) – MedDRA
      • EU national regulatory authorities
    - MHLW (MHLW database of pharmaceutical ADR reports) – MedDRA
    - WHO/UMC (Vigibase) – MedDRA
    - Regulated industry

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WHO & MedDRA

• As of March 2008, MedDRA has been implemented in WHO’s Global Safety Database (Vigibase)
  o WHO National Centres can review data and conduct analyses in both WHO-ART and MedDRA
    - Data can be sent/entered in either MedDRA or WHO-ART
    - Reports generated in either MedDRA or WHO-ART

• With Vigibase containing >6 million ICSRs, it now provides a global repository of MedDRA-coded safety data:
  o Substantial tool for pharmacovigilance
  o Of significant benefit to global patient safety

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WHO & MedDRA

- WHO Uppsala Monitoring Centre (UMC) has developed with ICH/MSSO a “bridge” or mapping from WHO-ART to MedDRA:
  - Allows conversion of legacy data from WHO-ART to MedDRA
  - Maintained current with every version release of WHO-ART and MedDRA
  - Does not work in the other direction since MedDRA is more granular than WHO-ART

- WHO UMC receives most of ICSRs coded in MedDRA

ICH Standard Terminology (cont)

- Speaking the same language in product safety (cont)
  - Applicable through all phases of development, from clinical trials to the post-marketing period
  - Applicable for a range of medicinal products
    - Drugs
    - Biologics
    - Vaccines
    - Medicine/devices combination products
  - Available in 11 languages
    - Chinese, Czech, Dutch, English, French, German, Hungarian, Italian, Japanese, Portuguese, Spanish
ICH Standard Terminology (cont)

• Clear and accurate communication of drug safety
  o Regulator – regulator (drug safety alert)
  o Regulator – industry (regulatory submissions)
  o Industry – industry (collaboration)

• Eliminate potential mistranslation from one terminology to another
  o Comparison with other drugs of the same class or therapeutic indication
  o Drug approval by multiple regulatory authorities

ICH Standard Terminology (cont)

• Work together with other ICH standards for electronic submission:
  o ICH E2B form: data elements for transmission of ICSR

---

2. GUIDELINE: CONTENT OF THE DATA ELEMENTS.........................................................4
   A. Administrative and Identification Information .....................................................4
      A.1 Identification of the case safety report .........................................................4
      A.2 Primary source(s) of information .................................................................8
      A.3 Information on sender and receiver of case safety report .............................9
   B. Information on The Case .................................................................................10
      B.1 Patient characteristics .................................................................................10
      B.2 Reaction(s)/event(s) ....................................................................................14
      B.3 Results of tests and procedures relevant to the investigation of the patient ......16
      B.4 Drug(s) information ....................................................................................17
      B.5 Narrative case summary and further information .......................................23
ICH Standard Terminology (cont)

- Work together with other ICH standards for electronic submission:
  - ICH Common Technical Document (eCTD): Common format for drug registration
    - M4E Guideline: MedDRA is recommended in adverse event summary tables
    - Mandated in EU and Japan
    - Recommended in US and Canada
  
A. Module 1 Administrative Information and Prescribing Information Folder
   1. eCTD backbone document information files
   2. Cover letter (optional)
   3. Labeling
   4. Advertisements and promotional material
   5. Marketing annual reports
   6. Information amendments

B. Module 2 Summary Folder
C. Module 3 Quality Folder
D. Module 4 Safety Folder
   1. Study reports
   2. Literature references
   3. Datasets

E. Module 5 Clinical Study Reports Folder
   1. Tabular listing of all clinical studies
   2. Study reports
   3. Case report forms
   4. Datasets
   5. Periodic safety update reports
   6. Literature references

MedDRA

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FDA: eCTD Submission Specifications (October 2005)
http://www.fda.gov/RegulatoryInformation/Guidances/ucm126959.htm

A Drug Safety Terminology

- Developed by a group of international drug safety experts (ICH M1 EWG)
  - Experts from regulatory authorities
    - Regulatory perspective
  - Experts from pharmaceutical industries
    - Industry perspective
  - Lessons learned from other terminologies
    - Limited scope
    - Limited granularity
    - Lack of analytical capability
Features of MedDRA

• **Widened scope**
  - Diseases, diagnoses, signs/symptoms, therapeutic indications
  - Investigations, procedures, social/family history
  - Medication errors
  - Product quality issues
  - Device issues
  - Pharmacogenetic/pharmacogenomic terms (new)

• **Increased granularity and specificity**
  - About 70,000 terms

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Features of MedDRA (cont)

• **MedDRA analytical features**
  - Five levels of hierarchy

```
系统器官分类 (SOC) (26)  
高位组语 (HLGT) (335)  
高位语 (HLT) (1,710)  
首选语 (PT) (19,086)  
低位语 (LLT) (69,019)  
```

SOC = 心脏器官疾病
HLGT = 心律失常类疾病
HLT = 心率和节律异常（不另分类）
PT = 心律不齐
LLT = 心律不齐
Features of MedDRA (cont)

- 26 System Organ Classes

  -血液及淋巴系统疾病
  -心脏器官疾病
  -内分泌系统疾病
  -代谢及营养类疾病
  -免疫系统疾病
  -感染及侵染类疾病
  -耳及迷路类疾病
  -神经系统疾病
  -血液系统疾病
  -肝脏系统疾病
  -败血症及感染类疾病
  -异常性反应及给药部位各种反应
  -急性及慢性或长期的反应
  -恶性及良性肿瘤(包括囊状和息肉状)
  -生殖系统及乳腺疾病
  -感染及侵染类疾病
  -全身性疾病及给药部位各种反应
  -血管与淋巴管类疾病
  -皮肤及皮下组织类疾病
  -关节与关节炎疾病
  -各类损伤、中毒及手术并发症
  -精神类疾病

- Multi-axiality and primary SOC

  SOC = 呼吸系统、胸及膈隔疾病
  HLGT = 各类呼吸道感染
  HLT = 各种病毒性上呼吸道感染
  PT = 流行性感冒

  SOC = 感染及侵染类疾病 (Primary)
  HLGT = 传染性病毒感染
  HLT = 流行性病毒感染

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Features of MedDRA (cont)

- **Standardised MedDRA Queries (SMQs)**
  - Groupings of terms from one or more MedDRA System Organ Classes (SOCs) related to defined medical condition or area of interest
  - Included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc., related to medical condition or area of interest
  - Intended to aid in case identification and signal detection

An SMQ Example

*Lactic acidosis (SMQ)* 乳酸中毒 (SMQ)

**Definition**
Lactic acidosis is a form of high anion gap metabolic acidosis. Intracranial cardiac contractility may be depressed, but isotropic function can be normal because of catecholamine release. Peripherally arterial vasoconstriction and central vasoconstriction can be present. Central nervous system function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Glucose intolerance may occur. Characterized by an increase in plasma l-lactate. Acidosis is seldom significant unless blood lactate exceeds 5 mmoL/L. Clinical presentation: type B lactic acidosis: Symptoms: hyperpnea, tachycardia, hypotension, and abdominal pain. Onset of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness.

**Source**

**Note**
Testing in two regulatory databases confirmed that the term list is adequate, in one regulatory database, the term “acidosis” identified cases, but this may be a phenomenon of the database characteristic (coding of infections in terms of an older terminology or other coding conventions).
Features of MedDRA (cont)

- Sample SMQ topics
  - Agranulocytosis
  - Anaphylactic reaction
  - Cerebrovascular disorders
  - Convulsions
  - Depression and suicide/self-injury
  - Hepatic disorders
  - Ischaemic heart disease
  - Lack of efficacy/effect
  - Peripheral neuropathy
  - Pregnancy and neonatal topics
  - Pseudomembranous colitis
  - Rhabdomyolysis/myopathy
  - Severe cutaneous adverse reactions
  - Systemic lupus erythematosus

- SMQs – case identification

Clinical Trial Database
Safety Database

Features of MedDRA (cont)

- Available in Chinese
  - MedDRA Chinese translation – since 2009
    - Linked to English MedDRA via MedDRA code
  - Originally translated by Pfizer (辉瑞)
    - In MedDRA v7.1
    - Transferred to ICH
  - Updated by the MSSO
    - From v7.1 to v12.1
    - Translated SMQs, MedDRA documents, such as
Features of MedDRA (cont)

• Available in Chinese (cont)
  o Translation validation
    - MedDRA term translation rules
    - Translation correctness of terms and documents
      • Selected terms and documents
      • Eight subscribing companies participated
        • Volunteer physicians - native Chinese from local Chinese branch offices
        • MedDRA users
        • Based on medical specialty

ICH-Endorsed Guides for Users

• Developed by an ICH Expert Working Group
• Current versions available on MedDRA MSSO Web site (http://www.meddramsso.com/subscriber_library_ptc.asp)

  Or the ICH Web site:

• Promote the standard use of MedDRA: two Points to Consider (PTC) documents
  o PTC: MedDRA Term Selection
  o PTC: MedDRA Data Retrieval and Presentation
Active Maintenance

• MedDRA is actively maintained – user responsive
  o Need a new term in MedDRA?
  o Need to modify the links in MedDRA?
  o MSSO change request process
  o MedDRA Expert Panel

• Bi-annual release
  o March 1
  o September 1

Support for Users

Available with MSSO subscription:

• Free MedDRA Browsers
  o MedDRA Desktop Browser (MDB)
  o MedDRA Web-Based Browser (WBB)

• Free MedDRA Version Analysis tool
  o To help users assess the impact of a new version on their data
    - Changes identified between any two MedDRA versions
    - Users to decide whether to re-code based on information provided
  o To be available in late 2011
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Support for Users (cont)

• Free training sessions by the MSSO
  o 2010 Beijing free training
    - 20th and 21st May 2010
    - Day one (Coding With MedDRA) - 64
    - Day two (Safety Data Analysis and SMQs) – 62
  o 2011 Shanghai free training
    - 10th and 11th May 2011
    - Day one (Coding With MedDRA)
    - Day two (Safety Data Analysis and SMQs)

• Timely MSSO Help Desk service
  o Available by email and phone
  o English and Chinese
  o mssohelp@ngc.com

Support for Users (cont)

• Chinese MedDRA User Group (CMUG)
  o Volunteer group
  o 50 members (22 organizations)
  o Help to organize free training
  o User feedback
  o CMUG web page
  o Continue CMUG activities in 2011 and beyond

• MSSO User Group Meetings
  o 20th May 2010 – in Beijing
    - The Use of MedDRA in Clinical Trial Data Management and EDC (Electronic Data Capture)
    - Practical experience in MedDRA coding and analysis
    - The challenges of using MedDRA in clinical practice
  o 10th May 2011 – in Shanghai
Acknowledgement

- SFDA – workshop logistics
- ICH Secretariat – program assistance
- MedDRA Management Board – program support
Thank You!