The Role of MedDRA in Pharmacovigilance Activities

28 April 2011 | Korea

TOPICS

- MedDRA: its governance and maintenance
- Regulatory status of MedDRA
- WHO and MedDRA
- MedDRA's Use for Pharmacovigilance
- Facilitating use of MedDRA
- Long-term benefits of MedDRA

WHAT IS MedDRA?

Med = Medical

D = Dictionary for

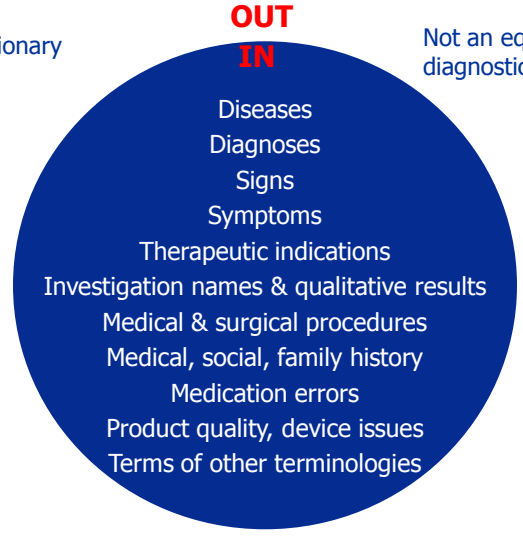
R = Regulatory

A = Activities

SCOPE of MedDRA

Not a drug dictionary

Not an equipment, device, diagnostic product dictionary



DEVELOPMENT and MAINTENANCE of MedDRA

- Developed by an ICH Expert Working Group
  - ICH = **I**nternational **C**onference on **H**armonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use
  - www.ich.org
- Maintained by the MSSO
  - MSSO = **M**aintenance and **S**upport **S**ervices **O**rganization
  - www.meddramsso.com

ICH MedDRA Management Board

Consists of:

MedDRA MSSO

- MedDRA is actively maintained and developed
  - Success depends on these activities
  - Evolves to meet needs of regulators, industry, other users
  - Twice yearly releases
- ICH contracted an MSSO for this purpose
- All operations of MSSO governed by ICH MedDRA Management Board

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OBJECTIVES of MedDRA's DEVELOPMENT

- International multi-lingual terminology
  - Used in 60 countries
  - Available in 11 languages
- Standardized communication between industry and regulators
- Supports electronic submissions
  - Unique 8-digits codes for all terms
  - For data fields in e- submission types (e.g., E2B)
- Application through all phases of development
- Classifies a wide range of clinical information
- Supports multiple medical product areas

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MedDRA and PHARMACOVIGILANCE (1)

- Global public health needs a standardized, multi-lingual, medically validated terminology
- At authorization, limited risk data available (limitations of clinical trials)
- Need post-authorization surveillance to identify previously unrecognized adverse effects
  - Spontaneous reporting of ADRs to regulatory authorities (e.g., by healthcare professionals, Marketing Authorization Holders, patients)
  - Post-authorization/marketing studies
  - Published literature
- In both pre- and post-authorization situations, a recognized terminology is an **essential requirement**

MedDRA and PHARMACOVIGILANCE (2)

Vellozzi, C et al**. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010.**

*In this study, reports to the vaccine adverse event reporting system (VAERS), a US spontaneous reporting system, were reviewed to identify potential rare events or unusual adverse event (AE) patterns after 2009-H1N1 vaccination. These AE reports are coded using **MedDRA**. Analysis of these **MedDRA**-coded data showed that the adverse event profile after 2009-H1N1 vaccine in VAERS (over 10,000 reports) was consistent with that of seasonal influenza vaccines, although the reporting rate was higher after 2009-H1N1 than seasonal influenza vaccines.*

Vaccine 2010 Oct 21;28(45):7248-55

MedDRA and PHARMACOVIGILANCE (3)

Basaria, S et al. **Adverse events associated with testosterone administration**

*In this study of elderly men with limited mobility and low serum testosterone, subjects were randomly assigned to receive placebo or testosterone for 6 months. Adverse events were categorized using **MedDRA**. Based on analysis of specific groups of cardiovascular event **MedDRA** terms, the data and safety monitoring board for this study recommended that the trial be discontinued early because of a higher rate of adverse cardiovascular events in the testosterone group than in the placebo group.*

N Engl J Med 2010;363:109-22

REGULATORY STATUS – US and JAPAN

- US FDA
  - Used in several FDA databases (AERS, VAERS, and CAERS)
  - Proposed Rule for Safety Reporting Requirements (2003): MedDRA for postmarketing safety reports
- Japanese Ministry of Health, Labour and Welfare
  - Mandatory use for electronic reports
  - Used in Periodic Infection and Safety Reports
  - For medical devices with biological components, infections to be described with MedDRA terms

REGULATORY STATUS – EUROPEAN UNION

- Clinical trial SUSARs (Suspected Unexpected Serious Adverse Reactions)
- Volume 9A (all authorized medicinal products)
  - Individual Case Safety Reports (ICSRs)
  - For adverse reactions in Periodic Safety Update Report
  - Standardised MedDRA Queries (SMQs) recommended for signal detection
- Interface between EudraVigilance and EU Risk Management Plan (indications, risks, interactions)
- Summary of Product Characteristics guideline
  - For Contraindications, Special warnings and precautions for use, and Undesirable effects sections

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REGUL ATORY STATUS – CANADA, other ICH

- Canada
  - Guidance Document for Industry – Reporting Adverse Reactions to Marketed Health Products
    - Recommended as standard for adverse reaction reports
  - Guidance for Industry – Product Monograph (labeling)
    - Preferred terminology for adverse drug reactions
  - Implemented for post-market surveillance (2008)
  - Implementation for pre-market surveillance (2011)
- ICH M4E Guideline on Common Technical Document
  - Recommended in adverse event summary tables

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WHO and MedDRA (1)

- MedDRA implemented in WHO's Global Safety Database (Vigibase)
  - WHO National Centres can review data, conduct analyses in both WHO-ART and MedDRA
- Vigibase (>5.5 million ICSRs) provides a global repository of MedDRA-coded safety data
  - Substantial pharmacovigilance tool
  - Significant benefit to global patient safety

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WHO and MedDRA (2)

- WHO Uppsala Monitoring Centre (UMC) has developed with ICH/MSSO a mapping bridge, WHO-ART → 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 other direction (MedDRA → WHO-ART) since MedDRA is more granular than WHO-ART
- WHO UMC receives most of its ICSRs coded in MedDRA

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FACILITATING USE of MedDRA

- ICH MedDRA Points to Consider (PTC) Working Group (since 1999)
  - Term selection (coding) of data: *MedDRA Term Selection: Points to Consider*
  - Retrieve and present MedDRA-coded data: *MedDRA Data Retrieval and Presentation: Points to Consider*
  - Documents updated with each MedDRA release based on user feedback
- PTC documents on ICH Web site (http://www.ich.org/products/meddra/meddraptc.html)

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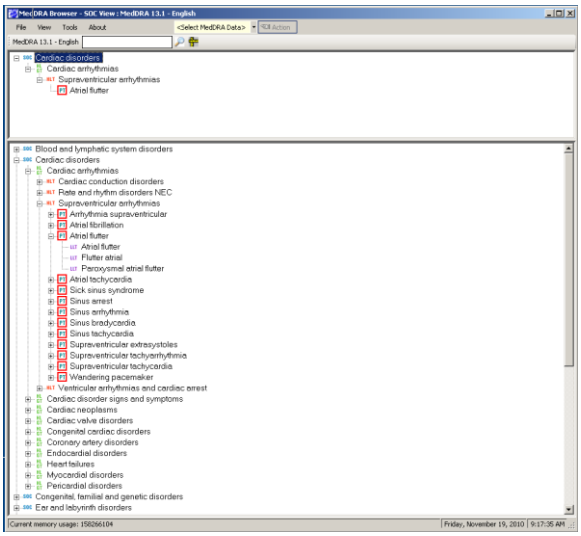
MedDRA SOFTWARE TOOLS

- MedDRA comes with software tools
- Browsers (Desktop and Web-based) to review and search the terminology



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STANDARDISED MedDRA QUERIES (SMQs)

- Over 80 SMQs jointly developed by CIOMS WG on SMQs and ICH/MSSO
  - Important signal detection tools
  - Groupings of MedDRA terms related to a defined medical condition or area of interest
  - Intended to aid in case identification and retrieval
  - Maintained with each version of MedDRA
  - Examples:
    - Anaphylactic reaction
    - Ischaemic heart disease
    - Depression and suicide/self-injury

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SMQ – EXAMPLE

- SMQ *Lactic acidosis*

Definition
Lactic acidosis is a form of high anion gap metabolic acidosis. Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release. Peripheral arterial vasodilatation 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 in type B lactic acidosis: Symptoms: hyperventilation or dyspnea, stupor or coma, vomiting, drowsiness, and abdominal pain. Onset of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness

Source
1. Braunwald E, Fauci A, Kasper D. Harrison's Principles of Internal Medicine. 15th Edition, 2001 pp 285-9
2. Weatherall D, Ledingham J and Warrell D. Oxford Textbood of Medicine. Third edition, 1996; volume 2 pp 1541-44

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 characteristics (coding of verbatims to terms of an older terminology or other coding conventions).

Narrow Terms
Blood lactic acid increased
Hyperlactacidaemia
Lactic acidosis

Broad Terms
Acid base balance abnormal
Acidosis
Anion gap abnormal
Anion gap increased
Blood bicarbonate abnormal
Blood bicarbonate decreased
Blood gases abnormal
Blood lactic acid abnormal
Blood pH abnormal
Blood pH decreased
Coma acidotic
Kussmaul respiration
Metabolic acidosis
PCO2 abnormal
PCO2 decreased
Urine lactic acid increased

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FREE MedDRA TRAINING

- MSSO offers 2 free training courses to all subscribers
  - Coding and analysis/SMQs
  - Have been offered in US, EU, Canada, China
- MedDRA Board is pleased to consider requests for subscriber training in other regions
  - Optimally, to be regionally-based
  - Leverage existing regional training activities and events

ACCESS to MedDRA

- MedDRA is **free** to regulatory authorities, academics, healthcare providers
- Commercial organizations pay annual fee based on revenue/turnover
- Subscription rates have been reduced or remained unchanged for the past 6 years
- Special licenses for access by low revenue companies:
  - EMA has this in place; FDA, under development
- MedDRA Board is currently exploring other models to help facilitate MedDRA's use

LONG-TERM BENEFITS of MedDRA

- Regulators and pharmaceutical companies operate on a global scale – important to speak the same regulatory language
- One regulatory language removes need for multiple terminologies
- Ease of data exchange between various parties
- Enables data mining/signal detection using large databases (e.g., FDA AERs, WHO Vigibase)
- Reduces impact on environment!

QUESTIONS?

- Please contact the ICH MedDRA Management Board: **meddraboard@ich.org**
- Other useful information:
  - ICH website: **www.ich.org**
  - MSSO site: **www.meddramsso.com**
  - MSSO Help Desk: **mssohelp@ngc.com**

Thank You!