The Role of MedDRA in Pharmacovigilance Activities

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OVERVIEW

• Governance, development and maintenance of MedDRA
• Regulatory status of MedDRA
• MedDRA and Pharmacovigilance
• WHO and MedDRA
• Helping MedDRA Users
• Long-term benefits of MedDRA
WHAT IS MedDRA?

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

SCOPE of MedDRA

NOT
Not a drug dictionary

IN
Diseases
Diagnoses
Symptoms
Therapeutic indications
Investigation names & qualitative results
Medical & surgical procedures
Medical, social, family history
Medication errors
Product quality, device issues
Terms of other terminologies

OUT
Not an equipment, device, diagnostic product dictionary
ICH MedDRA Management Board

Consists of:

- 6 ICH Parties: EU, EFPIA, FDA, PhRMA, MHLW and JPMA

DEVELOPMENT and MAINTENANCE of MedDRA

- Developed by an ICH Expert Working Group
  - ICH = International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use
  - www.ich.org
- Maintained by the MSSO
  - MSSO = Maintenance and Support Services Organization
  - www.meddramssco.com
MedDRA MSSO

- MedDRA is actively developed and maintained
  - Two releases per year
  - Evolves to meet needs of regulators, industry, other users
  - Success depends on these activities
- ICH contracted MSSO for this purpose
- MSSO activities are governed by ICH MedDRA Management Board

OBJECTIVES of MedDRA’s DEVELOPMENT

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

REGULATORY STATUS – US and JAPAN

- US FDA
  - Used in several FDA databases (AERS, VAERS, and CAERS)
- 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
– 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 (labelling)
    • Preferred terminology for adverse drug reactions
  – Implemented for post-market surveillance (2008)
  – Implemented for pre-market surveillance (2011)
• ICH M4E Guideline on Common Technical Document
  – Recommended in adverse event summary tables

MedDRA and PHARMACOVIGILANCE (1)

• Global public health needs a standardized, multi-lingual, medically validated terminology
• When authorising a product only limited risk data is available (limitations of clinical trials)
• Need post-authorisation surveillance to identify previously unrecognised adverse effects
  – Spontaneous reporting of ADRs to regulatory authorities (e.g. by healthcare professionals, Marketing Authorization Holders, patients)
  – Post-authorisation/marketing studies
  – Published literature
• In the context of pre- and post-authorisation, a recognised terminology is an **essential requirement**
MedDRA and PHARMACOVIGILANCE (2)

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.


MedDRA and PHARMACOVIGILANCE (3)


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
WHO and MedDRA (1)

- MedDRA is 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

WHO and MedDRA (2)

- WHO Uppsala Monitoring Centre (UMC) receives most of its ICSRs coded in MedDRA
- WHO 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
HELPING MedDRA USERS

- Since 1999, ICH MedDRA Points to Consider (PTC) Working Group produces
  - 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

MedDRA SOFTWARE TOOLS

- MedDRA comes with software tools
- Browsers (Desktop and Web-based) to review and search the terminology
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:
- Acute renal failure
- Haemolytic disorders
- Retroperitoneal fibrosis

SMQ – EXAMPLE

- **SMQ Lactic acidosis**

  **Definition**: Lactic acidosis is a form of high anion gap metabolic acidosis. Intracellular contractility may be depressed, but myocardial function can be normal because of catecholamine release. Periphereral arteriolar vasodilation 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 lactic acidosis in which the anion gap is increased and arterial pH may be normal.


  **Note**: Testing is two regulatory databases confirmed that the term list is adequate, as one regulatory database, the term “acidosis” identified cases, but this may be a phenomenon of database characteristics (coding of vocabulary terms under different terminology or coding conventions).
FREE MedDRA TRAINING

• MSSO offers 2 free training courses to all subscribers
  – Coding and analysis/SMQs
  – Have been offered in EU, US, Canada, China
• MedDRA Board is happy 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 – benefit from sharing one single regulatory language
- One regulatory language removes need for multiple terminologies
- Facilitate data exchange between various parties
- Enables data mining/signal detection using large databases (e.g., FDA AERs, WHO Vigibase)
- Reduces impact on environment!

Useful information:
- ICH website: www.ich.org
- MSSO site: www.meddramsso.com
- MSSO Help Desk: mssohelp@ngc.com

Acknowledgement:
WHO Adverse Reaction Terminology (WHO-ART), Copyright© World Health Organization Collaborating Centre for International Drug Monitoring
QUESTIONS?

Thank You!