



MedDRA, SMQs, and Signal Detection

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MSSO/ICH

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Topics

- MedDRA and ICH
- SMQs' role in Pharmacovigilance
- SMQs development and CIOMS



MedDRA and ICH



MedDRA

Med = Medical

D = Dictionary for

R = Regulatory

A = Activities



Development of MedDRA under the auspices of ICH

International **C**onference on **H**armonisation
of Technical Requirements for Registration
of Pharmaceuticals for Human Use

*Created to make recommendations on ways to
achieve harmonisation in technical requirements
for medicinal product registration in order to
reduce or prevent redundant testing carried out
during the research and development of new
medicines*



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



IFPMA

International Federation of Pharmaceutical Manufacturers & Associations

- Non-Profit, Non-Governmental Organisation
- Represents national industry associations and R&D companies from developed & developing countries
- Provides the ICH Secretariat
- Holds ownership of MedDRA, as a trustee of ICH
- Contracts for the maintenance organization of MedDRA (MSSO)



MSSO

Maintenance and Support Services Organisation

- Contracted by IFPMA, as a trustee of ICH
- Serves as the repository, maintainer, and distributor of MedDRA
 - ⇒ Oversight of MedDRA is the responsibility of an ICH MedDRA Management Board, appointed by the ICH Steering Committee
- Provides MedDRA training

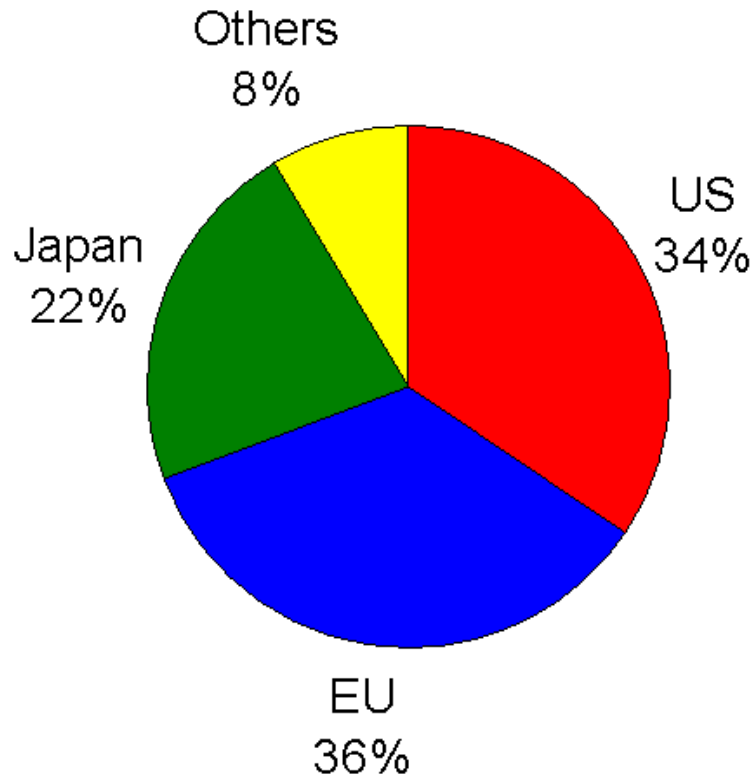


MedDRA Subscription

- Basic subscription: non-profit (FREE subscription)
 - Medical libraries
 - Educational institutes
 - Direct patient care providers
- Core subscription
- Developer subscription
- MedDRA has been implemented in WHO UMC Vigibase and its analytical tools



MedDRA Subscription (cont)



2122 Subscribers
Worldwide

Others (By Country)
Argentina
Australia
Brazil
Canada
China
Dominican Republic
Hong Kong
India
Israel
Malaysia
Mexico
New Zealand
Peru
Singapore
South Africa
South Korea
Taiwan
Thailand

Scope of MedDRA

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®

- SOC Blood and lymphatic system disorders
- SOC Cardiac disorders
- SOC Congenital, familial and genetic disorders
- SOC Ear and labyrinth disorders
- SOC Endocrine disorders
- SOC Eye disorders
- SOC Gastrointestinal disorders
- SOC General disorders and administration site conditions
- SOC Hepatobiliary disorders
- SOC Immune system disorders
- HL Allergic conditions
 - HL Allergic conditions NEC
 - HL Allergies to foods, food additives, drugs and other chemicals
 - HL Anaphylactic responses
 - PT Anaphylactic reaction
 - PT Anaphylactic shock
 - LT Anaphylactic shock
 - LT Anaphylactic shock due to adverse food reaction
 - LT Anaphylactic shock due to crustaceans
 - LT Anaphylactic shock due to eggs
 - LT Anaphylactic shock due to fish
 - LT Anaphylactic shock due to food additives
 - LT Anaphylactic shock due to fruits and vegetables
 - LT Anaphylactic shock due to milk products
 - LT Anaphylactic shock due to other specified food
 - LT Anaphylactic shock due to peanuts
 - LT Anaphylactic shock due to tree nuts and seeds
 - LT Anaphylactic shock due to unspecified food
 - LT Anaphylactic shock, not elsewhere classified
 - LT Drug shock
 - LT Penicillin shock
 - LT Shock anaphylactic anaphylactoid
 - PT Anaphylactic transfusion reaction
 - PT Anaphylactoid reaction
 - PT Anaphylactoid shock
 - PT Anaphylactoid syndrome of pregnancy
 - PT First use syndrome
 - HL Angioedemas
 - HL Atopic disorders
 - HL Urticarias
- HL Autoimmune disorders
- HL Immune disorders NEC
- HL Immunodeficiency syndromes
- SOC Infections and infestations
- SOC Injury, poisoning and procedural complications



MedDRA

- MedDRA – a classification terminology, it is used for:
 - Indexing (coding)
 - Data presentation
 - Data retrieval
 - Data analysis
- MedDRA – multilingual terminology
 - Czech, Dutch, French, German, Italian, Japanese, Portuguese, Spanish
 - Chinese will be available later 2008



SMQs' role in Pharmacovigilance



SMQ

- SMQ – an additional analytical tool for MedDRA-coded data, it is used for:
 - Case identification
 - Signal detection

A Sample 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 Textbook 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

SMQs in Production - Examples

- As of September 2007 release, a total of 55 in production (Many other SMQs in development)
 - Acute pancreatitis
 - Acute renal failure
 - Adverse pregnancy outcome
 - Agranulocytosis
 - Anaphylactic reaction
 - Cardiac Failure
 - Cerebrovascular disorders
 - Depression and suicide/self-injury
 - Dyslipidaemia
 - Gastrointestinal non-specific inflammation and dysfunction
 - Haematopoietic cytopenias
 - Hepatic disorders
 - Hyperglycaemia/new onset diabetes mellitus
 - Lack of efficacy/effect
 - Lactic acidosis
 - Malignancies
 - Oropharyngeal disorders
 - Peripheral neuropathy
 - Rhabdomyolysis/myopathy
 - Severe cutaneous adverse reactions
 - Shock



Why do we need SMQs?

- Potential scenarios:
 - Regulators to monitor a newly-marketed product with a certain potential safety issue from late Phase III
 - Safety monitors (pre- or post-marketing) could set up “surveillance” parameters in safety system to alert them to incoming cases whose events “belong” to an SMQ of interest



Why do we need SMQs? (cont)

- Potential scenarios (cont):
 - Co-development/marketing safety issues (or potential issues) can be shared and compared readily
 - PSURs (overdose, pregnancy exposure, drug abuse, etc.)
 - Identify cases based on PSUR findings



SMQs and Regulators

- Volume 9A recommends using SMQs for signal detection and retrieving cases of interest
- EMEA and PMDA (Japan) currently testing SMQs for signal detection
- FDA exploring the use of SMQs in new drug review process



Standardised MedDRA Queries (SMQs) development and CIOMS



What is CIOMS?

- International, non-governmental, non-profit organization established jointly by World Health Organization (WHO) and United Nations Educational, Scientific and Cultural Organization (UNESCO)
- Objectives:
 - Facilitate/promote international activities in biomedical sciences
 - Maintain collaborative relations with UN and its specialized agencies
 - Serve scientific interests of international biomedical community
- Has a particular interest in drug safety/adverse event reporting



CIOMS SMQ Working Group (WG)

- CIOMS and ICH have worked to establish terms of reference for cooperative development of SMQs
- Maintenance of SMQs is the joint responsibility of the user community (through feedback to MSSO/Change Request process) and the MSSO



CIOMS SMQ WG (cont)

- Current members of CIOMS WG for SMQs:
 - Senior scientists (as members or observers) from several drug regulatory authorities and other organizations (EMA, BfArM, FDA, Health Canada, MHRA, MPA, TGA, MHLW, Society of Japanese Pharmacopoeia, and WHO)
 - Senior scientists from many pharmaceutical companies
 - Two physicians from MSSO
- WG holds several meetings a year



SMQ Development Summary

- Pre-release: tested on databases available to CIOMS Working Group members; typically, at least one company and one regulator database
 - Assure that each candidate SMQ will identify a reasonable pool of cases
 - Ensure that the intended purpose of the candidate SMQ is met
 - Fine-tuning of the candidate SMQ may require several iterations



SMQ Development Summary (cont)

- Production Phase: continue to be fine-tuned by MedDRA subscribers through the MSSO maintenance process



Thank you