MedDRA, SMQs, and Signal Detection

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MSSO/ICH

MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
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 Conference on Harmonisation 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

<table>
<thead>
<tr>
<th>Region</th>
<th>Members</th>
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<tbody>
<tr>
<td><strong>Europe</strong></td>
<td><strong>EC</strong> - European Commission – European Union (EU)</td>
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<td><strong>EFPIA</strong> - European Federation of Pharmaceutical Industries and Associations</td>
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<td><strong>Japan</strong></td>
<td><strong>MHLW</strong> - Ministry of Health, Labour and Welfare</td>
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<td><strong>JPMA</strong> - Japan Pharmaceutical Manufacturers Association</td>
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<td><strong>United States</strong></td>
<td><strong>FDA</strong> - Food and Drug Administration</td>
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<td><strong>PhRMA</strong> - Pharmaceutical Research and Manufacturers of America</td>
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<td><strong>Observers</strong></td>
<td><strong>WHO</strong> – World Health Organization</td>
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<td>Health Canada</td>
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<td><strong>EFTA</strong> - European Free Trade Association</td>
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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

- **US**: 34%
- **EU**: 36%
- **Japan**: 22%
- **Others**: 8%

**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®

- 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
- Immune system disorders
- Allergic conditions
  - Allergic conditions NEC
  - Allergies to foods, food additives, drugs and other chemicals
- Anaphylactic responses
  - Anaphylactic reaction
  - Anaphylactic shock
    - Anaphylactic shock due to adverse food reaction
    - Anaphylactic shock due to crustaceans
    - Anaphylactic shock due to eggs
    - Anaphylactic shock due to fish
    - Anaphylactic shock due to food additives
    - Anaphylactic shock due to fruits and vegetables
    - Anaphylactic shock due to milk products
    - Anaphylactic shock due to other specified food
    - Anaphylactic shock due to peanuts
    - Anaphylactic shock due to tree nuts and seeds
    - Anaphylactic shock due to unspecified food
    - Anaphylactic shock, not elsewhere classified
    - Drug shock
    - Penicillin shock
- Anaphylactic anaphylactoid
  - Anaphylactic transfusion reaction
  - Anaphylactoid reaction
  - Anaphylactoid shock
  - Anaphylactoid syndrome of pregnancy
  - First use syndrome

- Angiokeratoma
- Atopic disorders
- Urticarias
- Autoimmune disorders
- Immune disorders NEC
- Immunodeficiency syndromes
- Infections and infestations
- 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

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 verbatim to terms of an older terminology or other coding conventions).

Narrow Terms
- Blood lactic acid increased
- Hyperlactacidemia
- 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
  - Periperal neuropathy
  - Rhabdomyolssis/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 (EMEA, 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