Use of MedDRA® in CTCAE and in the Biopharmaceutical Industry

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MedDRA MSSO

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

MedDRA was developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA Management Board, which is composed of the six ICH parties, the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, and The World Health Organization, and is chaired by the IFPMA.
Objectives

- Demonstrate the relationship of CTCAE to MedDRA
- Illustrate use of MedDRA for CTCAE ‘Other, specify’ terms
- Application of MedDRA in data retrieval, presentation, and analysis
  - Standardised MedDRA Queries (SMQs)
- MSSO free training

MedDRA Definition

MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.
Scope of MedDRA

- Not a drug dictionary
- Patient demographic terms
- Clinical trial study design terms
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
- Not an equipment, device, diagnostic product dictionary

MedDRA Structure

- System Organ Class (SOC) (26)
- High Level Group Term (HLGT) (335)
- High Level Term (HLT) (1,713)
- Preferred Term (PT) (19,550)
- Lowest Level Term (LLT) (70,177)

MedDRA Version 15.0
Regulatory Status of Mandate

- **US FDA**
  - Used in several FDA databases (AERS, VAERS, and CAERS)
- **Japanese Ministry of Health, Labour and Welfare**
- **Canada**
  - Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products
  - Guidance for Industry - Product Monograph (labeling)

Regulatory Status of Mandate

- **European Union EudraVigilance database**
  - New PV legislation (Directive and Regulation) effective July 2012 broadens AR definition:
    - Occurring in context of medication errors
    - With uses outside terms of marketing authorization
    - Misuse and abuse
    - In context of occupational exposures
Regulatory Status of Mandate (cont)

- European Union (cont)
  - Interface between EudraVigilance and EU Risk Management Plan
  - Summary of Product Characteristics guideline
    - MedDRA to be used throughout; in particular for Contraindications, Special warnings and precautions for use, and Undesirable effects sections
- ICH M4E Guideline on Common Technical Document
  - Recommended in adverse event summary tables

CTCAE v4.0

- Utilizes a small subset of MedDRA terms that are common in oncology practice
- Terms are recognized by the ICH community as practice standards
- Lists MedDRA LLTs organized by SOCs
- ‘Other, specify’ allows submission of verbatim
# CTCAE v4.0

## General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Fatigue relieved by rest</td>
<td>Fatigue not relieved by rest, limiting instrumental ADL</td>
<td>Fatigue not relieved by rest, limiting self care ADL</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.

<table>
<thead>
<tr>
<th>Fever</th>
<th>&lt;38.0 degrees C (100.4 F)</th>
<th>&gt;38.0 - 40.0 degrees C (100.4 - 104.0 F)</th>
<th>&gt;40.0 degrees C (104.0 F) for &lt;24 hrs</th>
<th>&gt;40.0 degrees C (104.0 F) for &gt;24 hrs</th>
<th>Death</th>
</tr>
</thead>
</table>

**Definition:** A disorder characterized by elevation of the body's temperature above the upper limit of normal.

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![Diagram of Adverse Events]

**Diagram:**

- **General disorders and administration site conditions**
- **General system disorders NEC**
  - **Anergic conditions**
    - **Fatigue**
    - **Drowsiness**
      - **Depressive awareness**
      - **Enervation**
      - **Exhaustion**
      - **Exhaustion due to excessive exertion**
      - **Fatigue**
      - **Fatigue generalized**
      - **Fatigue limbic**
      - **Fatigue of knees**
      - **Fatigue**
      - **Fatigue aggravated**
      - **Fatigue extreme**
      - **Fatigue unmanageable**
      - **Fatigue generalized**
      - **Lassitude**
      - **Loss of physical strength**
      - **Prostration**
      - **TATT**
      - **Tired all day long**
      - **Tired and heavy**
      - **Tired out**
      - **Tiredness**
      - **Wasted out**
      - **Weakness**
      - **Worn-out**
### CTCAE v4.0

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Other, specify</td>
<td>Asymptomatic or mild symptoms, clinical or diagnostic observations only</td>
<td>Moderate; minimal, local or noninvasive intervention indicated, limited age-appropriate instrumental ADL</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
CTCAE v3.0 Analysis Prior to MedDRA Harmonization

- CTCAE v3.0
  - Routine reporting (Phase 1, 2) ~ 383,000
  - Expedited reporting (All Phases) ~ 66,000
  - ‘Other, specify’ ~ 6,000

- ‘Other, specify’ Verbatim & MedDRA
  - Match 41%
  - Algorithmic match 23%
  - No match 36%

Setser, A. 2009 CTCAE Boot Camp Presentations

Example of MedDRA & CTCAE ‘Other, specify’

Instructions: Enter all AEs that should appear on this expedited report. For each AE, complete all the required fields, and then click Continue.

Note: The data you enter on this page will be used to confirm whether expedited reporting is required (based on the set of rules set up for this study). The results will be displayed on the next two pages.
Example of MedDRA & CTCAE ‘Other, specify’

MedDRA Data Retrieval and Presentation: Points to Consider
MedDRA Data Retrieval and Presentation: Points to Consider

- An ICH-Endorsed Guide for MedDRA users on Data Output
- Developed by an ICH Expert Working Group
- Provides data retrieval and presentation options for industry or regulatory purposes
- Objective is to promote understanding of implications that various options for data retrieval have on accuracy and consistency of final output

Data Retrieval PTC Points Addressed

- General Principles
  - Quality of Source Data
  - Documentation of Data Retrieval and Presentation Practices
  - Do Not Alter MedDRA
  - Organization-Specific Data Characteristics
  - Characteristics of MedDRA that Impact Data Retrieval and Analysis
  - MedDRA Versioning
- General Queries and Retrieval
- Standardised MedDRA Queries
- Customized Searches
Standardised MedDRA Queries (SMQs)

Definition of SMQ

- Result of cooperative effort between CIOMS and ICH (MSSO)
- 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
SMQ Benefits and Limitations

• Benefits
  – Application across multiple therapeutic areas
  – Validated reusable search logic
  – Standardized communication of safety information
  – Consistent data retrieval
  – Maintenance by MSSO/JMO

• Limitations
  – Do not cover all medical topics or safety issues
  – Will evolve and undergo further refinement even though they have been tested during development

SMQs in Production - Examples

• As of Version 15.0, a total of 86 in production
  • 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
SMQ Resources

- Refer to MSSO Web site for information on SMQs

http://www.meddramsso.com/subscriber_smq.asp

Use of SMQs at the FDA

Acknowledgement: Dr. Chuck Cooper, Office of Translational Sciences, CDER, FDA
Use of SMQs at the FDA (cont)

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Use of MedDRA at the FDA

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MedDRA Training Resources

<table>
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<tr>
<th>Free Training</th>
<th>Open Registration Webinars</th>
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<tbody>
<tr>
<td>Coding with MedDRA</td>
<td>What’s New in MedDRA</td>
</tr>
<tr>
<td>MedDRA Safety Data Analysis and SMQs</td>
<td>MedDRA Versioning</td>
</tr>
<tr>
<td>Webinar-MedDRA Coding Basics</td>
<td>Introduction to MedDRA</td>
</tr>
<tr>
<td>Webinar-Introduction to MedDRA Data Analysis and SMQs for Physicians</td>
<td>Medication Errors and Product Quality Issue Concepts in MedDRA</td>
</tr>
</tbody>
</table>
Summary

In this presentation, we:

- Demonstrated the relationship of CTCAE to MedDRA
- Briefly reviewed the structure and scope of MedDRA
- Illustrated how CTCAE ‘Other, specify’ verbatim reported as MedDRA could facilitate data retrieval, presentation and analysis
- Were introduced to MedDRA Standardized MedDRA Queries (SMQs)
- Presented options for MedDRA training

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