Use of MedDRA® in CTCAE and in the Biopharmaceutical Industry

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MedDRA MSSO

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

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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.

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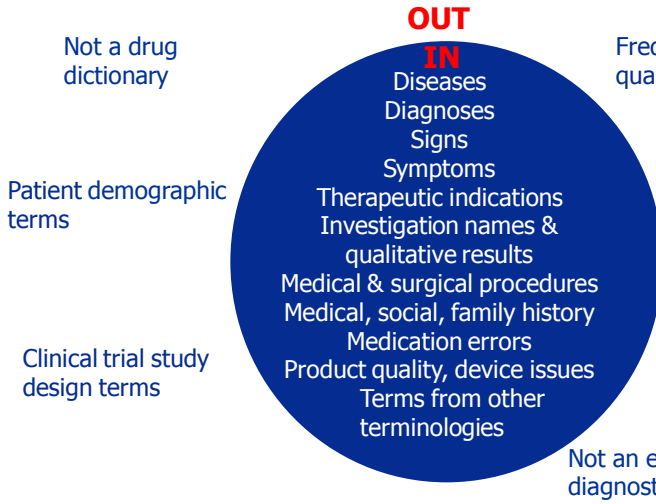
Scope of MedDRA



Not a drug dictionary

Frequency qualifiers

Patient demographic terms

Numerical values for results

Clinical trial study design terms

Severity descriptors

Not an equipment, device, diagnostic product dictionary

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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

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Regulatory Status of Mandate

- 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
- Canada
  - Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products
  - Guidance for Industry - Product Monograph (labeling)

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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

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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

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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

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CTCAE v4.0

General disorders and administration site conditions					
	Grade				
Adverse Event	1	2	3	4	5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal.					

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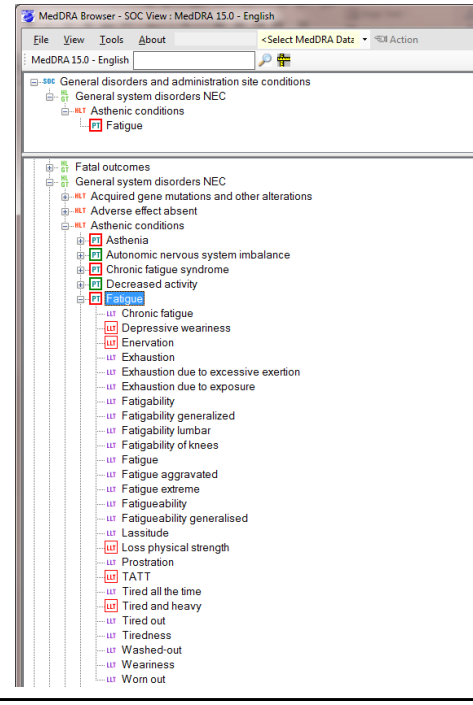

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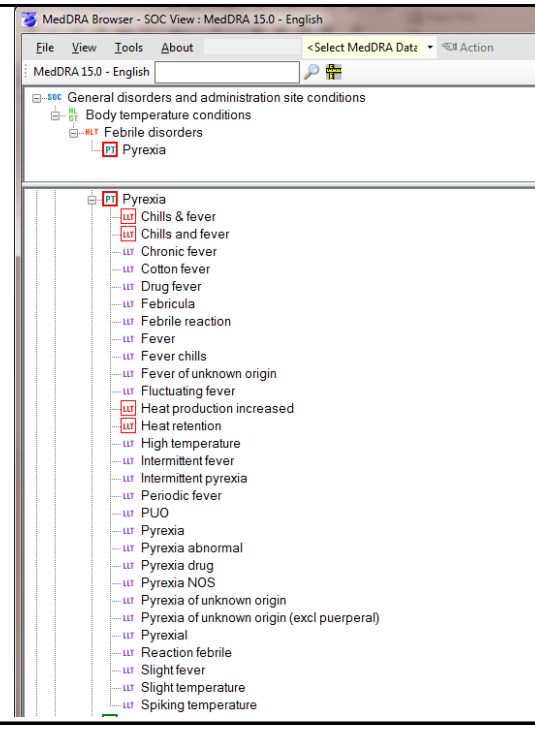

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CTCAE v4.0

General disorders and administration site conditions					
	Grade				
Adverse Event	1	2	3	4	5
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

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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

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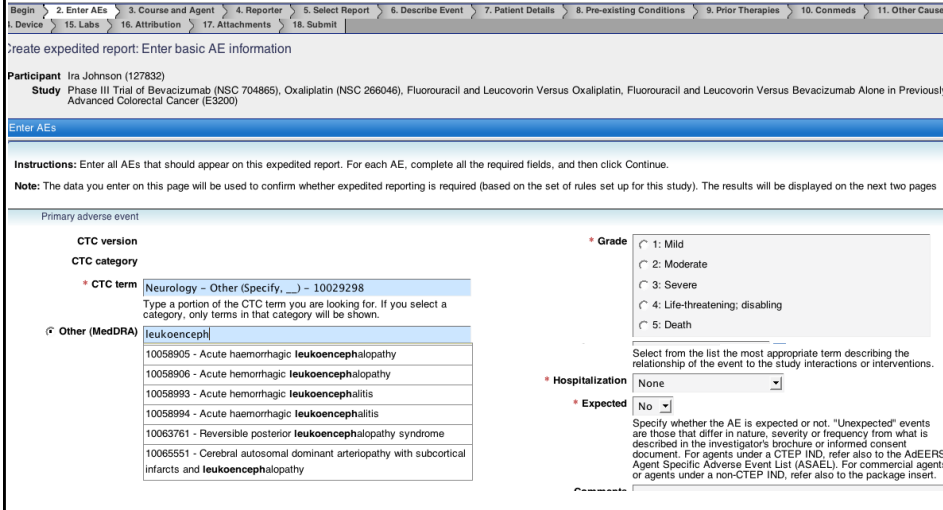
Example of MedDRA & CTCAE 'Other, specify'



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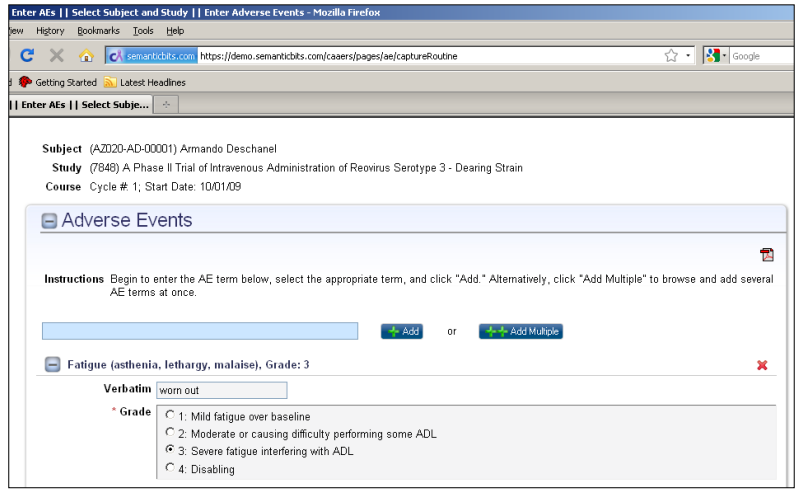
Example of MedDRA & CTCAE 'Other, specify'



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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
- Current version available on MedDRA MSSO Web site (http://www.meddramsso.com/subscriber_library_ptc.asp)

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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

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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

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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

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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

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SMQ Resources

- Refer to MSSO Web site for information on SMQs

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

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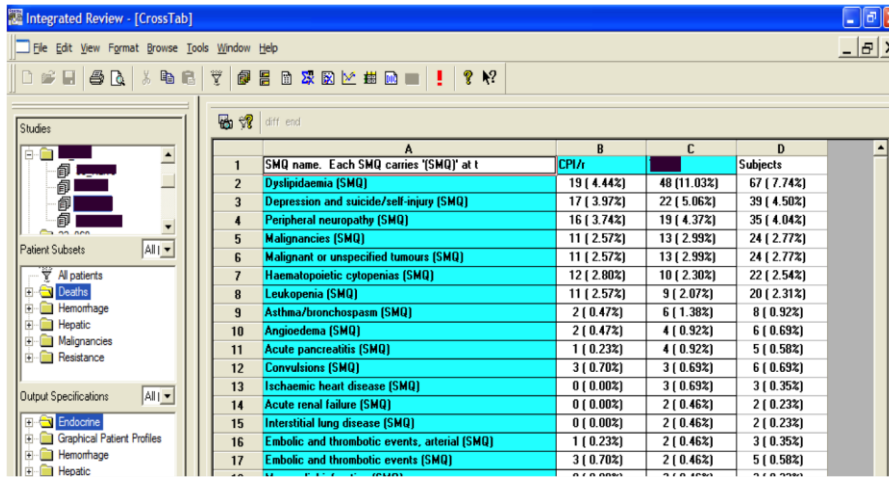
Use of SMQs at the FDA



	A	B	C	D
1	SMQ name. Each SMQ carries '(SMQ)' at t	CPI/r	[redacted]	Subjects
2	Dyslipidaemia (SMQ)	19 (4.44%)	48 (11.03%)	67 (7.74%)
3	Depression and suicide/self-injury (SMQ)	17 (3.97%)	22 (5.06%)	39 (4.50%)
4	Peripheral neuropathy (SMQ)	16 (3.74%)	19 (4.37%)	35 (4.04%)
5	Malignancies (SMQ)	11 (2.57%)	13 (2.99%)	24 (2.77%)
6	Malignant or unspecified tumours (SMQ)	11 (2.57%)	13 (2.99%)	24 (2.77%)
7	Haematopoietic cytopenias (SMQ)	12 (2.80%)	10 (2.30%)	22 (2.54%)
8	Leukopenia (SMQ)	11 (2.57%)	9 (2.07%)	20 (2.31%)
9	Asthma/bronchospasm (SMQ)	2 (0.47%)	6 (1.38%)	8 (0.92%)
10	Angioedema (SMQ)	2 (0.47%)	4 (0.92%)	6 (0.69%)
11	Acute pancreatitis (SMQ)	1 (0.23%)	4 (0.92%)	5 (0.58%)
12	Convulsions (SMQ)	3 (0.70%)	3 (0.69%)	6 (0.69%)
13	Ischaemic heart disease (SMQ)	0 (0.00%)	3 (0.69%)	3 (0.35%)
14	Acute renal failure (SMQ)	0 (0.00%)	2 (0.46%)	2 (0.23%)
15	Interstitial lung disease (SMQ)	0 (0.00%)	2 (0.46%)	2 (0.23%)
16	Embolic and thrombotic events, arterial (SMQ)	1 (0.23%)	2 (0.46%)	3 (0.35%)
17	Embolic and thrombotic events (SMQ)	3 (0.70%)	2 (0.46%)	5 (0.58%)

Acknowledgement: Dr. Chuck Cooper, Office of Translational Sciences, CDER, FDA

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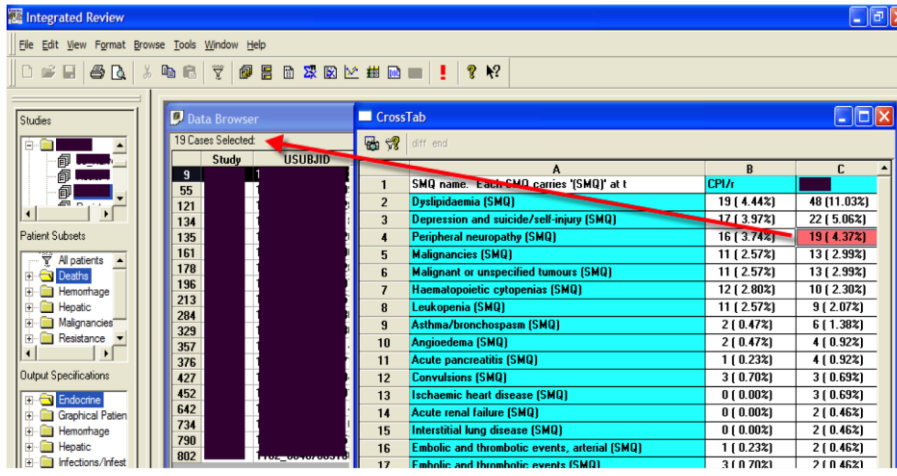
Use of SMQs at the FDA (cont)



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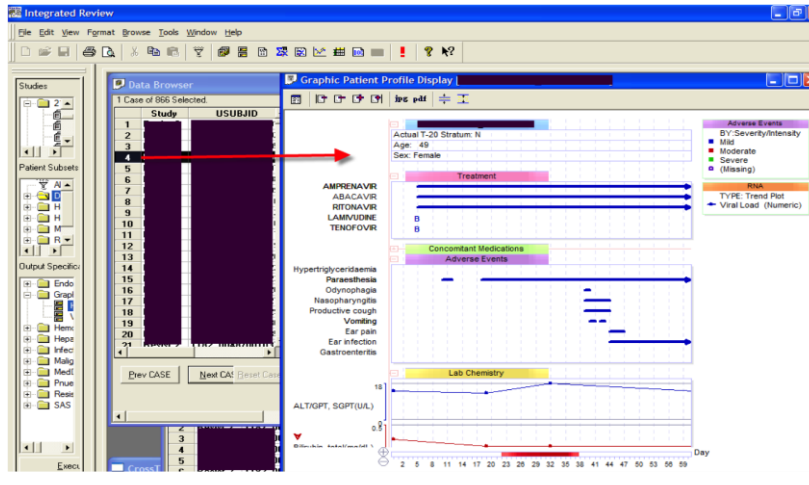
Use of SMQs at the FDA (cont)



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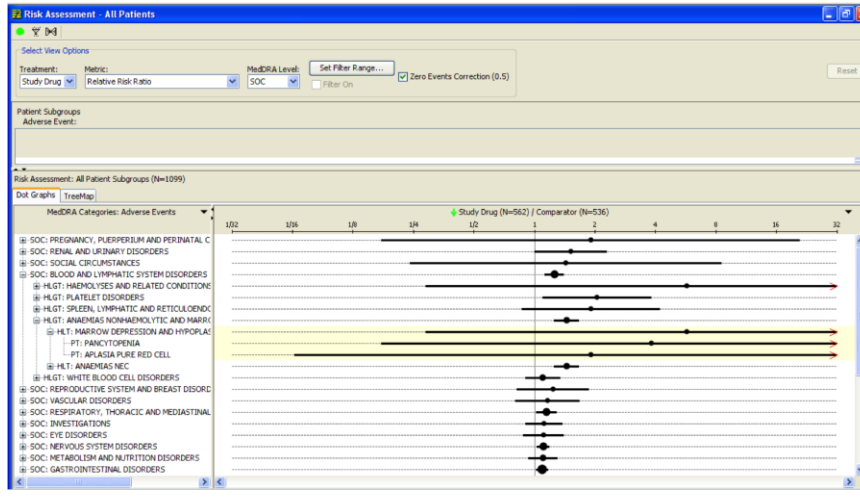
Use of MedDRA at the FDA



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MedDRA Training Resources

Free Training	Open Registration Webinars
Coding with MedDRA	What's New in MedDRA
MedDRA Safety Data Analysis and SMQs	MedDRA Versioning
Webinar-MedDRA Coding Basics	Introduction to MedDRA
Webinar-Introduction to MedDRA Data Analysis and SMQs for Physicians	Medication Errors and Product Quality Issue Concepts in MedDRA

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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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