Coding with MedDRA®

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

Course Overview

- MedDRA background
- MedDRA's structure, scope, and characteristics
- MedDRA maintenance
- Coding conventions
- Synonym lists
- QA of coding
- *MedDRA Term Selection: Points to Consider* document
- Hands-on coding exercises

MedDRA Background

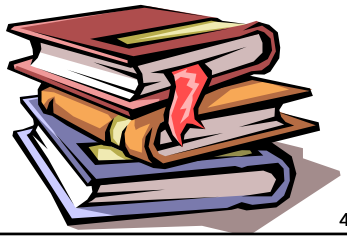
What is MedDRA?

Med = Medical

D = Dictionary for

R = Regulatory

A = Activities



Why MedDRA?

- MedDRA has been developed by an ICH Working Group to provide:
  - Standardized communication between regulators and industry/sponsors of clinical trials
    - Within regions and between regions
  - An international, multi-lingual, medical terminology
    - Medical personnel can code ADR data in their native language
      - Safer – less likely to miscode data

Objectives for MedDRA Development

Result of an ICH initiative (M1)

To provide:

- An international multi-lingual terminology
- Standardized communication between industry and regulators
- Support of electronic submissions
- Application through all phases of the development cycle

Objectives for MedDRA Development (cont)

To provide (cont):

- Classification for a wide range of clinical information
- Support for multiple medical product areas
- A terminology that saves time, resources, and money

MedDRA & I C H

Development of MedDRA under the auspices of **I C H**

INTERNATIONAL **C**ONFERENCE ON **H**ARMONIS/ZATION

of

Technical Requirements for the Registration of Pharmaceuticals for Human Use

http://www.ich.org

MedDRA Management Board

- 6 ICH Parties: **EU**, **EFPIA**, **FDA**, **PhRMA**, **MHLW** and **JPMA**
- **MHRA** (Medicines and Healthcare products Regulatory Agency of the UK)
- **Health Canada**
- **WHO** (participates as a non-voting Observer)
- **IFPMA** acts as a non-voting Observer, and chairs the Board

Maintenance & Development

- MedDRA is actively maintained and developed
  - ❑Success of the terminology depends on its long-term maintenance and development
  - ❑MedDRA evolves to meet needs of both regulators, industry and other users
- ICH contracted a MedDRA Maintenance and Support Services Organization (MSSO)
  - ❑All operations of MSSO governed by the ICH MedDRA Management Board

MedDRA and the MSSO

- International support and development of terminology
- Foster use of MedDRA through communications and educational offerings
- “Custodians”, not owners, of the terminology
- JMO (partner organization for Japanese-language MedDRA)
- Governed by a Management Board (industry, regulators, multi-national, other interested parties)

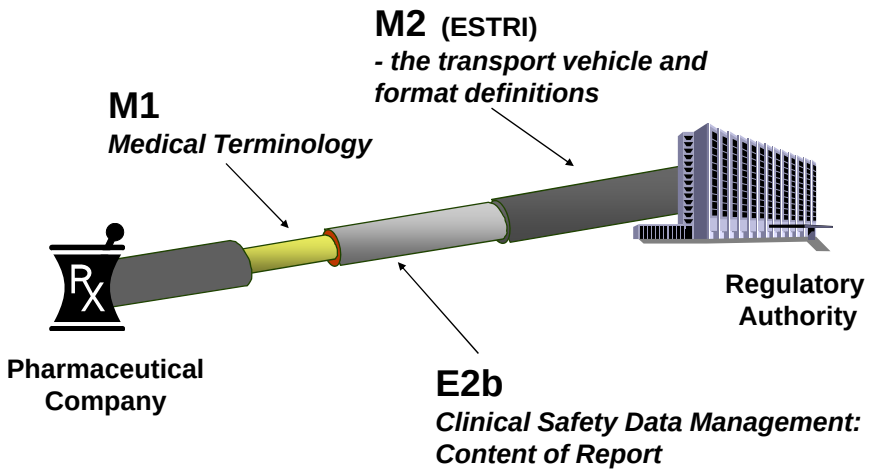
e-Reporting

- Transmission of individual case safety reports currently relies in many countries on paper-based formats or electronic media (usually by on-line access, tape or file transfer)
- **Electronic** reporting is becoming the main route for exchanging adverse event/reaction reports between companies, sponsors of clinical trials and regulators worldwide

e-Reporting

- E2B is the electronic standard for transfer of safety information (ICSRs) which has been developed by ICH, MedDRA being a required component of it
- Work is underway with ISO (International Organization for Standardization) to develop ICSRs (E2B) as an international electronic standard

ICH EDI Coordination



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.

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
  - 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 of Mandate (cont)

- European Union
  - Clinical trials
    - SUSARs (Suspected Unexpected Serious Adverse Reactions) – use MedDRA LLTs (current or previous version)
  - Volume 9A (all authorized medicinal products, including OTC)
    - Individual Case Safety Reports (ICSRs) – use MedDRA LLTs (current or previous version)
    - For adverse reactions in Periodic Safety Update Report
    - Standardised MedDRA Queries (SMQs) recommended for signal detection

Regulatory Status of Mandate (cont)

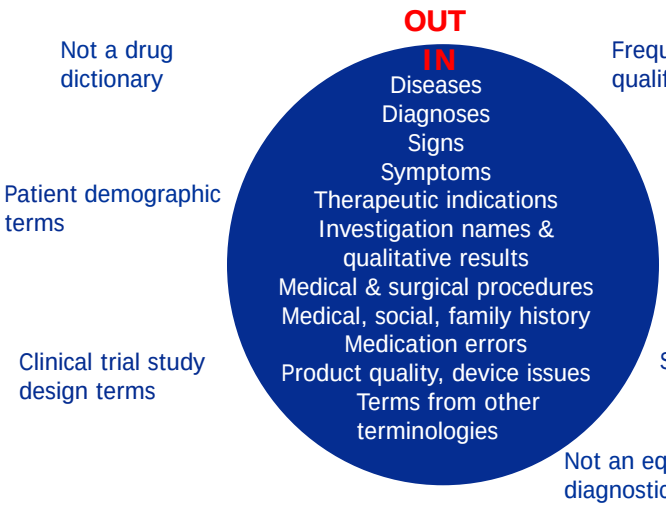
- European Union (cont)
  - Interface between EudraVigilance and EU Risk Management Plan
    - To code indications, risks, interactions (potential and identified)
  - Summary of Product Characteristics guideline
    - MedDRA to be used throughout; in particular for Contraindications, Special warnings and precautions for use, and Undesirable effects sections

Regulatory Status of Mandate (cont)

- ICH M4E Guideline on Common Technical Document
  - Recommended in adverse event summary tables
- Canada
  - Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products
    - Recommended as standard for adverse reaction reports
  - Guidance for Industry - Product Monograph (labeling)
    - Preferred terminology for adverse drug reactions

MedDRA Overview

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

MedDRA Structure

System Organ Class (SOC) (26)

High Level Group Term (HLGT) (335)

High Level Term (HLT) (1,710)

Preferred Term (PT) (19,086)

Lowest Level Term (LLT) (69,019)

MedDRA Version 14.0

MedDRA Term Level Definitions

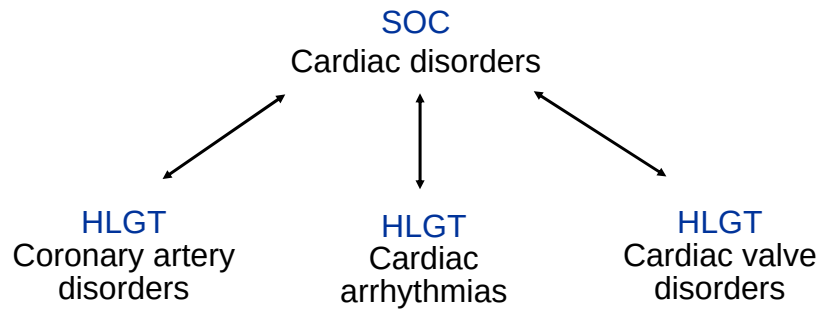
- **SOC** - Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose
- **HLGT** - Subordinate to SOC, superordinate descriptor for one or more HLTs
- **HLT** - Subordinate to HLGT, superordinate descriptor for one or more PTs
- **PT** - Represents a single medical concept
- **LLT** - Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym (Note: All PTs have an identical LLT)

System Organ Classes

- 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
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

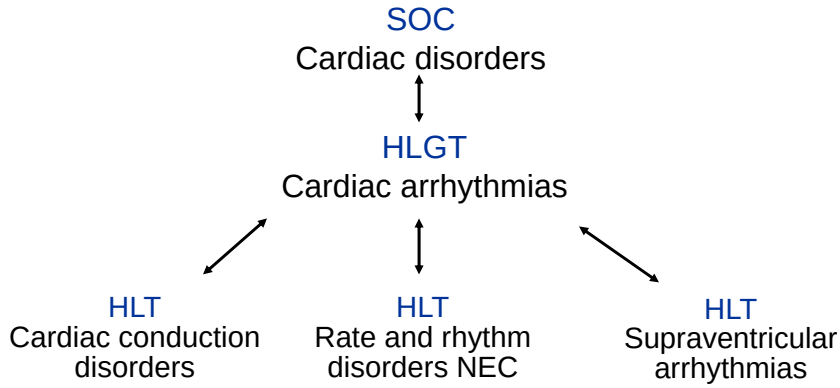
High Level Group Term

Subordinate only to SOCs and superordinate descriptor for one or more HLTs

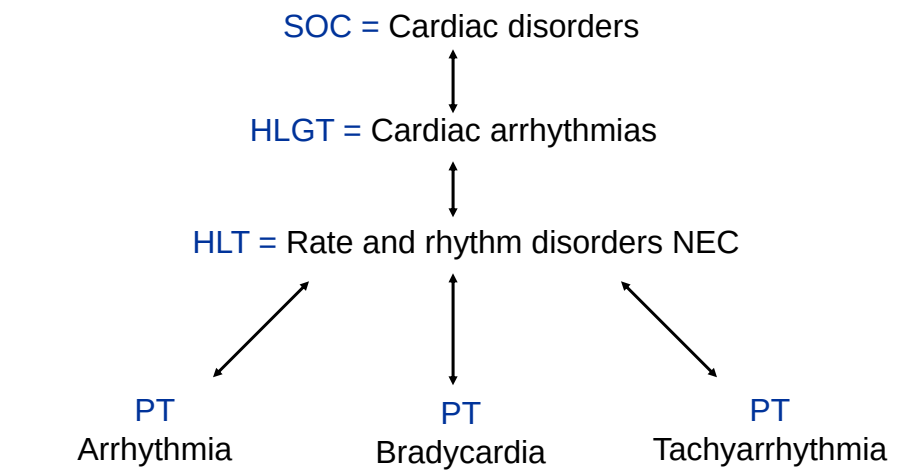


High Level Term

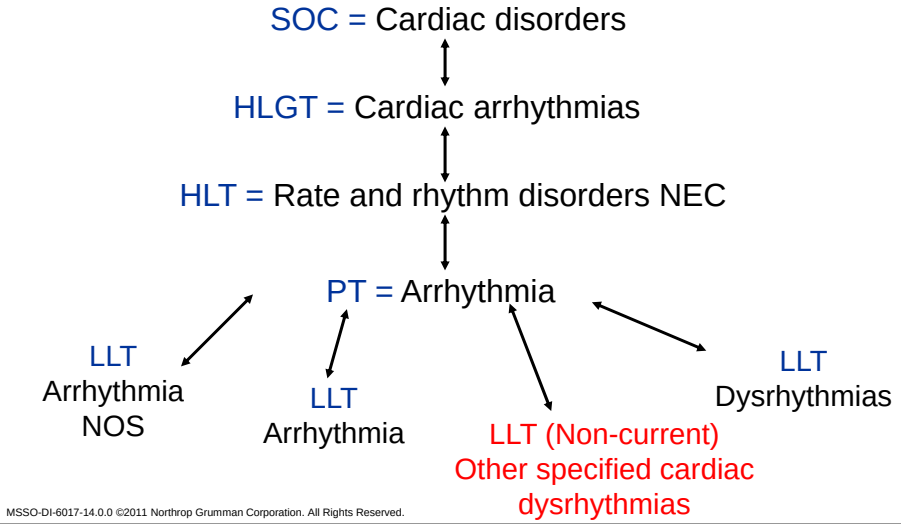
Subordinate to HLGTs and superordinate descriptor for the PTs linked to it



Examples of PTs



Examples of LLTs



Non-Current Terms

- Non-current terms are flagged at the LLT level within MedDRA
- Not recommended for continued use
- Retained within the terminology to preserve historical data for retrieval and analysis
- Terms that are vague, ambiguous, out-dated, truncated, or misspelled
- Terms derived from other terminologies that do not fit MedDRA rules

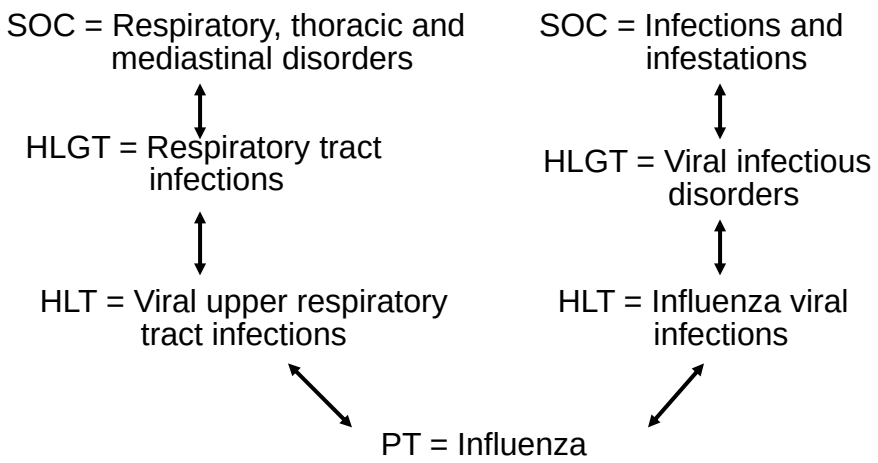
MedDRA Codes

- Each MedDRA term assigned an 8-digit numeric code
- The code is non-expressive
- Codes can fulfill a data field in various electronic submission types (e.g., E2B)
- Initially assigned alphabetically by term starting with 10000001
  - New terms are assigned sequentially
- Supplemental terms are assigned codes

A Multi-Axial Terminology

- Multi-axial = the representation of a medical concept in multiple SOCs
  - Allows grouping by different classifications
  - Allows retrieval and presentation via different data sets
- Purpose of Primary SOC
  - Determines which SOC will represent a PT during cumulative data outputs
  - Is used to support consistent data presentation for reporting to regulators

A Multi-Axial Terminology (cont)



A Multi-Axial Terminology (cont)

PTs in the following SOCs only appear in that particular SOC and not in others, i.e., they are not multi-axial

- *Investigations*
- *Surgical and medical procedures*
- *Social circumstances*

Rules for Primary SOC Allocation

- PTs for diseases, signs and symptoms are assigned to prime manifestation site SOC
- Congenital and hereditary anomalies terms have SOC *Congenital, familial and genetic disorders* as Primary SOC
- Neoplasms terms have SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* as Primary SOC
  - **Exception:** Cysts and polyps have prime manifestation site SOC as Primary SOC
- Infections and infestations terms have SOC *Infections and infestations* as Primary SOC

Primary SOC Priority

If a PT links to more than one of the exceptions, the following priority will be used to determine primary SOC:

- *1st: Congenital, familial and genetic disorders*
- *2nd: Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
- *3rd: Infections and infestations*

Cardiac disorders vs. Vascular disorders

PT	HLT	HLGT	SOC
Arteritis coronary	Coronary artery disorders NEC	Coronary artery disorders	Cardiac disorders (P)
	Arterial inflammations	Vascular inflammations	Vascular disorders

SOC *Congenital, familial and genetic disorders* - Example

PT	HLT	HLGT	SOC
Congenital HIV infection	Viral infections congenital	Infections and infestations congenital	Congenital, familial and genetic disorders (P)
	Congenital neonatal infections	Neonatal and perinatal conditions	Pregnancy, puerperium and perinatal conditions
	Retroviral infections	Viral infectious disorders	Infections and infestations
	Acquired immunodeficiency syndromes	Immunodeficiency syndromes	Immune system disorders

Conditions vs. Investigations

PT	HLT	HLGT	SOC
Pregnancy test positive	Reproductive hormone analyses	Endocrine investigations (incl sex hormones)	Investigations
Pregnancy	Normal pregnancy, labour and delivery	Pregnancy, labour, delivery and postpartum conditions	Pregnancy, puerperium and perinatal conditions

Be careful to distinguish between a condition and an investigation or a result of an investigation

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

SMQs in Production - Examples

- As of Version 14.0, a total of 85 in production (One is inactive)

- 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 Applications

- Clinical trials
  - Where safety profile is not fully established, use multiple SMQs on routine basis as screening tool
  - Selected SMQs to evaluate previously identified issue (pre-clinical data or class effect)
- Postmarketing
  - Selected SMQs to retrieve cases for suspected or known safety issue
  - Signal detection (multiple SMQs employed)
  - Single case alerts
  - Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)

SMQ Resources

- Refer to MSSO Web site for information on SMQs

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

MedDRA Maintenance

MedDRA Maintenance

- MedDRA is a user responsive terminology
- Subscribers may submit change requests to the MSSO for consideration
  - Core and basic subscribers: 100 change requests (CRs) per month
  - For simple changes (PT and LLT levels), notification of supplemental change within 7-10 working days
  - Weekly supplemental changes posted on MSSO Web site
  - Complex changes above PT level received all year round. Posted for subscribers' comments mid-year.

MedDRA Maintenance (cont)

- Twice yearly official updates
  - 1 September X.1 release (Simple changes only)
  - 1 March X.0 release (Complex and simple changes)

WebCR

- Web-based tool for Change Requests (CR)
  - URL: https://mssotools.com/webcr/
  - Via the Change Request Information page
- Ability to submit CRs online
- Immediate confirmation
- Review unsubmitted CRs online
- Ability to query CR history back to v5.1

Change Request Justification Statements

- Justification statement always required
- Inadequate justification – "Term does not exist in MedDRA"
- Adequate justification – statement of need
- Support with definitions and references (PDFs preferred)
- Examples of need:
  - Term needed to code an indication
  - Concept is being reported in a clinical trial

Proactive MedDRA Maintenance

- What is the proactive approach?
  - Corrections/improvements made internally by the MSSO
  - General changes suggested by users
- Submitting ideas
  - Send to MSSO Help Desk. Justification is helpful.
  - Example: Consider consolidation of HLTs with only one PT
- Evaluation of proposals
  - MSSO is not obligated to respond
  - Proactive approach does not replace usual CR process

MSSO's MedDRA Browsers

- MedDRA Desktop Browser
  - Download from MSSO Web site
  - View/search MedDRA and SMQs
  - Export functionality
- MedDRA Web-Based Browser
  - https://www.meddrabrowser.org/dsnavigator/
  - Requires specific user ID and password
  - Access to all MedDRA versions in English and available EU languages (and Chinese, if subscribed)
  - View/search MedDRA and SMQs
  - Export functionality

MedDRA Browser Demonstration and Instruction

Coding Exercises

Exercise 1

The patient states she has been experiencing headaches, dizziness and vertigo.

_____ LLT → _____ PT
_____ LLT → _____ PT
_____ LLT → _____ PT

Exercise 2

Lab results indicate an increase in erythrocytes.

_____ LLT → _____ PT

Exercise 3

LJ, a 55 year old female, is a heavy smoker and suffers from alcohol abuse.

_____ LLT → _____ PT

_____ LLT → _____ PT

Exercise 4

Drug was contaminated with Staphylococcus.

_____ LLT → _____ PT

Exercise 5

A three year old boy was admitted for loratadine toxicity after accidentally ingesting the remaining tablets in the bottle.

_____ LLT → _____ PT
_____ LLT → _____ PT

Exercise 6

A 32 year old female had a contraceptive implant in her left arm. On a follow-up visit, the insertion site was noted to be infected.

_____ LLT → _____ PT

Exercise 7

The patient's insulin pump was noted to be broken.

_____ LLT → _____ PT

Coding with MedDRA

What Is “Coding”?

Code

1 : a systematic statement of a body of law; especially one given statutory force

2 : a system of principles or rules <moral code>

3 a : *a system of signals or symbols for communication*

b : a system of symbols (as letters or numbers) used to represent assigned and often secret meanings

4 : genetic code

5 : a set of instructions for a computer

Why Do We Code?

- Retrieve
- Present
- Analyze
- Communicate

Role of a Terminology

- Provides a TOOL to represent data/ concepts using “place-holder” terms
- Assists in retrieval, analysis, and comprehension of data

What Does MedDRA Offer?

- Size and specificity (“granularity”)
- Hierarchy/grouping terms
- “Support” SOCs widen data collection/analysis options
- Up-to-date and medically rigorous
- User-responsive
- STANDARDIZATION

Why Do We Need Coding Conventions?

- Differences in medical aptitude of coders
- Consistency concerns (many more "choices" to manually code terms in MedDRA compared to older terminologies)
- Even with an autoencoder, may still need manual coding

Can I Make Coding Conventions Specific to My Company/Product?

- MedDRA may reduce the need to do this because:
  - Increased size/granularity will result in better (i.e., more accurate) representation of data
  - Secondary SOC allocations allow for different "views" of the data
- This type of approach should be done cautiously

Synonym Lists

- Can be derived from existing term lists or directly from verbatims
- For recurring, but unusual, verbatims – one-time assignment to a MedDRA term
- Enforces consistency by limiting choices once MedDRA term is assigned
- Increases likelihood of autoencoding “hit”
- Natural outgrowth of a legacy data conversion
- Maintenance required

Synonym List Maintenance

- For new MedDRA versions, run synonyms against new MedDRA LLTs
  - Identify new non-current LLTs that are on synonym list; flag for recoding
- Run synonyms against new MedDRA LLT list
  - Identify possible new current direct matches

Synonym List Maintenance (cont)

- Remaining challenge is to determine if “better medical matches” have been added (essentially, a manual process)
- Communicate results to users of synonym list

QA Reports

- Allows reviewers to check for consistency (both auto-encoded and human-coded terms)
- Check for adherence to/deviation from coding conventions
- Check for emerging drifts/biases
- Multiple data views (verbatims to coded terms; coded term to verbatims; by SOC, etc.)

QA Sample Report

SOC	HLT	PT	Verbatim	Count
Respiratory, thoracic and mediastinal disorders				
	Bronchospasm and obstruction			
		Wheezing		
			WHEEZING	16
			Wheeze	5
			INCREASED WHEEZING	1
			Breathing suppressed wheezing	1
			HYPERREACTIVITY AND WHEEZING	1
			wheeze in chest	1
	Laryngeal and adjacent sites disorders NEC (excl infections and neopla			
		Vocal cord disorder		
			SPASMODIC DYSTONIA OF THE VOCAL CORDS	1
	Newborn respiratory disorders NEC			
		Transient tachypnoea of the newborn		
			Transient hazy vision	1
			Transient tachypnea, neonatal	1
			Tachypnea of the newborn, transient	1

QA Sample Report

SOC	HLT	PT	Verbatim	Count
Metabolism and nutrition disorders				
	Potassium imbalance			
		Hyperkalaemia		
			Hyperkalemia	58
			HYPERKALAEMIA	9
			Rebound perioperative hyperkalemia	6
			HYPERPOTASSEMIA	4
			Increased Potassium	1
			Increased serum potassium/Hyperkalemia	1
		Hypokalaemia		
			Hypokalemia	164
			Hypokalaemia	49
			HYPOPOTASSEMIA	15
			SUPPLEMENTATION FOR RITODRINE-INDUCED HYPOKALEMIA	6
			Present hypokalemia	2
			Hypokalemia trend	1
			hypokaliaemia	1
			TRANSIENT HYPOKALEMIA	1
			HYPOKALEMIA SEVERE	1
			HYPOKALIEMIA PROPHYLAXIS	1

Legacy Data Conversion – Comparing Verbatim to Coded Term Approach

Verbatim	MedDRA PT (based on verbatim)	Orig coded term (COSTART)	MedDRA PT (based on orig COSTART term)
(R) knee effusion	*Joint effusion*	ARTHROSIS	*Osteoarthritis*
Common cold	*Nasopharyngitis*	INFECTION	*Infection*
Periorbital edema	*Periorbital oedema*	FACE EDEMA	*Face oedema*
Seasonal allergies	*Seasonal allergy*	ALLERGIC REACTION	*Hypersensitivity*
Skin injury	*Skin injury*	SKIN DISORDER	*Skin disorder*

WHO and MedDRA

- As of March 2008, MedDRA has been implemented in WHO's Global Safety Database (Vigibase)
  - ❑WHO National Centres can review data and conduct analyses in both WHO-ART and MedDRA
    - ❑Data can be sent/entered in either MedDRA or WHO-ART
    - ❑Reports generated in either MedDRA or WHO-ART
- With Vigibase containing >5.5 million ICSRs, it now provides a global repository of MedDRA-coded safety data:
  - ❑Substantial tool for pharmacovigilance
  - ❑Of significant benefit to global patient safety

WHO and MedDRA

- WHO Uppsala Monitoring Centre (UMC) has developed with ICH/MSSO a "bridge" or mapping from WHO-ART to 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 the other direction since MedDRA is more granular than WHO-ART
- WHO UMC receives most of ICSRs coded in MedDRA

ICH-endorsed Guide for users

- Establishment of the ICH MedDRA Points to Consider (PtC) Working Group in 1999
- ICH MedDRA Points to Consider Documents:
  - ❑ How to best classify the data? *MedDRA Term Selection document*
  - ❑ How to best retrieve and present the data? *MedDRA Data Retrieval and Presentation document*
  - ❑ Both updated with Users feedback for every release of MedDRA

MedDRA Points to Consider

http://www.ich.org

MedDRA Term Selection: Points to Consider (MTS:PTC)

- An ICH-endorsed guide for MedDRA users
- Developed to promote medically accurate and consistent use of MedDRA in exchange of data (ultimately, for "medically meaningful" retrieval and analysis)

MedDRA Term Selection: PTC (cont)

- Developed by a working group of the ICH Steering Committee
  - Regulators and industry representatives
  - EU, Japan, USA
  - Canadian observer, MSSO, JMO
- Current version available on MedDRA MSSO Web site (http://www.meddramsso.com/subscriber_library_ptc.asp)

MedDRA Term Selection: PTC (cont)

- In some cases with more than one option for selecting terms, a “preferred option” is identified but this does not limit MedDRA users to applying that option. Organizations should be consistent in their choice of option.
- Section 4.1 – Versioning (Appendix)
  - 4.1.1 Versioning methodologies
  - 4.1.2 Timing of version implementation

General Term Selection Principles

- Quality of Source Data
- Quality Assurance
- Do Not Alter MedDRA
- Always Select a Lowest Level Term
- Select Only Current Lowest Level Terms
- When to Request a Term
- Use of Medical Judgment in Term Selection
- Selecting More than One Term
- Check the Hierarchy
- Select Terms for All Reported Information, Do Not Add Information

Quality of Source Data Quality Assurance

- Quality of original information impacts quality of output
- Obtain clarification of data
- Can be optimized by careful design of data collection forms and proper training of staff
- Organizations' coding guidelines should be consistent with MTS:PTC
- Review of term selection by qualified individuals
- Human oversight of automated coding results

Do Not Alter MedDRA

- MedDRA is a standardized terminology with a pre-defined term hierarchy
- Users must not make *ad hoc* structural alterations, including changing the primary SOC allocation
- If terms are incorrectly placed, submit a change request to the MSSO

Always Select a Lowest Level Term Select Only Current LLTs

- Lowest Level Term that most accurately reflects the reported verbatim information should be selected
- Degree of specificity may be challenging
  - Example: "*Abscess on face*" → select "*Facial abscess*," not simply "*Abscess*"
- Select current LLTs only
  - Non-current terms for legacy conversion/historical purposes

When to Request a Term Use of Medical Judgment

- Avoid company-specific "work-arounds" for MedDRA deficiencies. If concept not adequately represented in MedDRA, submit Change Request to MSSO.
- If no exact match in MedDRA, use medical judgment to match to an existing term that adequately represents the concept

Selecting More than One Term Check the Hierarchy

- Can select more than one LLT to represent reported information. Document procedures.
  - Selecting one term may lead to loss of specificity
  - Selecting more than one term may lead to redundant counts
- Check the hierarchy above a selected LLT (PT, HLT, HLGT, SOC) to ensure placement accurately reflects meaning of reported term

Select Terms for All Reported Information

- Select terms for every AR/AE reported, regardless of causal association
- Select terms for device-related events, product quality issues, medication errors, medical and social history, investigations and indications as appropriate
- If diagnosis reported with characteristic signs and symptoms, preferred option is to select term for diagnosis only

Do Not Add Information

- Do not make diagnosis if only signs/symptoms reported

Reported	LLT Selected	Comment
Abdominal pain, increased serum amylase, and increased serum lipase	Abdominal pain	It is inappropriate to assign an LLT for diagnosis of "pancreatitis"
	Serum amylase increased	
	Lipase increased	

FDA-Defined Coding Errors

- Missed Concepts
  - All medical concepts described after the product is taken should be coded
  - Example: "*The patient took drug X and developed alopecia, increased LFTs and pancreatitis*". Manufacturer only codes alopecia and increased LFTs (missed concept of pancreatitis)
  - Example: "*The patient took drug X and developed interstitial nephritis which later deteriorated into renal failure*". Manufacturer only codes interstitial nephritis (missed renal failure concept)

Acknowledgement: Dr. Toni Piazza-Hepp, Office of Surveillance and Epidemiology, CDER

FDA-Defined Coding Errors (cont)

- "Soft Coding"
  - Selecting a term which is both less specific and less severe than another MedDRA term is "soft coding"
  - Example: "*Liver failure*" coded as hepatotoxicity or increased LFTs
  - Example: "*Aplastic anemia*" coded as unspecified anemia
  - Example: "*Rash subsequently diagnosed as Stevens Johnson syndrome*" coded as rash

Acknowledgement: Dr. Toni Piazza-Hepp, Office of Surveillance and Epidemiology, CDER

Term Selection Points

- Diagnoses and Provisional Diagnoses with or without Signs and Symptoms
- Death and Other Patient Outcomes
- Suicide and Self-Harm
- Conflicting/Ambiguous/Vague Information
- Combination Terms
- Age vs. Event Specificity
- Body Site vs. Event Specificity
- Location Specific vs. Microorganism Specific Information
- Modification of Pre-existing Conditions
- Exposures During Pregnancy and Breast Feeding
- Congenital Terms
- Neoplasms
- Medical and Surgical Procedures

Term Selection Points (cont)

- Investigations
- Medication/Administration Errors and Accidental Exposures
- Transmission of Infectious Agent via Medicinal Product
- Overdose, Toxicity and Poisoning
- Device-related Terms
- Drug Interactions
- No Adverse Effect and “Normal” Terms
- Unexpected Therapeutic Effect
- Modification of Effect
- Social Circumstances
- Medical and Social History
- Indication for Product Use
- Off Label Use
- Product Quality Issues

Diagnoses and Provisional Diagnoses

SINGLE DIAGNOSIS	
DEFINITIVE DIAGNOSIS	**PROVISIONAL DIAGNOSIS**
Single diagnosis without signs and symptoms •Diagnosis (only possible option)	Single provisional diagnosis without signs and symptoms •Provisional diagnosis (only possible option)
Example: *"Myocardial infarction"* → select *"Myocardial infarction"*	Example: *"Possible myocardial infarction"* → select *"Myocardial infarction"* (select term as if definitive diagnosis)

Similar principles apply for multiple diagnoses

Diagnoses and Provisional Diagnoses (cont)

SINGLE DIAGNOSIS	
DEFINITIVE DIAGNOSIS	**PROVISIONAL DIAGNOSIS**
Single diagnosis with signs/ symptoms •Preferred: Diagnosis only	Single provisional diagnosis with signs/symptoms •Preferred: Provisional diagnosis and signs/symptoms
Example: *"Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm"* → select *"Anaphylactic reaction"*	Example: *"Possible myocardial infarction with chest pain, dyspnea, diaphoresis"* → select *"Myocardial infarction"* *"Chest pain"*, *"Dyspned"*, and *"Diaphoresis"*

Similar principles apply for multiple diagnoses

Diagnoses and Provisional Diagnoses (cont)

SINGLE DIAGNOSIS	
DEFINITIVE DIAGNOSIS	**PROVISIONAL DIAGNOSIS**
Single diagnosis with signs/ symptoms •Alternate: Diagnosis and signs/symptoms	Single provisional diagnosis with signs/symptoms •Alternate: Signs/symptoms only (as provisional diagnosis may change
Example: *"Anaphylactic reaction with rash, dyspnea, hypotension, and laryngospasm"* → select *"Anaphylactic reaction"*, *"Rash"*, *"Dyspned"*, *Hypotension"*, and *"Laryngospasm"*	Example: *"Possible myocardial infarction with chest pain, dyspnea, diaphoresis"* → select *"Chest pain"*, *"Dyspned"*, and *"Diaphoresis"*

Similar principles apply for multiple diagnoses

Diagnoses and Provisional Diagnoses (cont)

- Always include signs/symptoms not associated with diagnosis

Reported	LLT Selected
Myocardial infarction, chest pain, dyspnea, diaphoresis, ECG changes and jaundice	Myocardial infarction Jaundice (note that jaundice is not typically associated with myocardial infarction)

Death and Other Patient Outcomes

- Death is an outcome and is not usually considered an AR/AE

Reported	LLT Selected	Comment
Death due to myocardial infarction	Myocardial infarction	Record death as an outcome in an appropriate data field
Constipation, ruptured bowel, peritonitis, sepsis; patient died	Constipation Perforated bowel Peritonitis Sepsis	

Death and Other Patient Outcomes (cont)

- If only information reported is death, select most specific death term available

Reported	LLT Selected
Patient was found dead	Found dead
Patient died in childbirth	Maternal death during childbirth

Death and Other Patient Outcomes (cont)

- Hospitalization, disability and other patient outcomes are not generally considered ARs/AEs

Reported	LLT Selected	Comment
Hospitalisation due to congestive heart failure	Congestive heart failure	Record hospitalisation as an outcome
Patient was hospitalised	Hospitalisation	If only information reported is patient outcome, select most specific term available

Suicide and Self-Harm

- Accurate and consistent term selection for reports of suicide attempts, completed suicides, and self-harm is necessary for data retrieval and analysis
- If suicide attempt is fatal, select term reflecting outcome instead of attempt only

Reported	LLT Selected	Comment
Suicide attempt resulted in death	Completed suicide	Record death as an outcome

Conflicting/Ambiguous/Vague Information

- First, try to obtain more specific information

Reported	LLT Selected	Comment
Hyperkalemia with a serum potassium of 1.6 mEq/L	Serum potassium abnormal	LLT *Serum potassium abnormal* covers both of the reported concepts (note: serum potassium of 1.6 mEq/L is a low result, not high)
GU pain	Pain	"GU" could be either "genito-urinary" or "gastric ulcer". Since "pain" is definite, select LLT *Pain.*
Congestion	Unevaluable event	"Congestion" reported alone is vague; this can refer to multiple organs and physiologic processes

What Term to Select?

- Clinical complication of IUD
  - IUD complication (PT Medical device complication)?
  - Intra-uterine death (PT Intra-uterine death)?
  - Unevaluable event?
- Hypoglycemia (blood glucose = 200 mg/dL)
  - Blood glucose abnormal?
  - Blood glucose increased?
  - Hypoglycemia?

Combination Terms

- One condition is more specific than the other

Reported	LLT Selected
Arrhythmia due to atrial fibrillation	Atrial fibrillation

- A MedDRA combination term is available

Reported	LLT Selected
Retinopathy due to diabetes	Diabetic retinopathy

Combination Terms (cont)

- If splitting provides more clinical information, select more than one term
- In all cases of combination terms, apply medical judgment

Reported	LLT Selected
Diarrhea and vomiting	Diarrhea Vomiting
Wrist fracture due to fall	Wrist fracture Fall

What Term to Select?

- Unwitnessed sudden death; found pulseless and apneic

  Sudden death?

  Unattended death?

  Sudden death, cause unknown?

  Pulseless?
- Stiff neck and shoulders

  Stiff neck? (PT *Musculoskeletal stiffness*)

  Stiffness shoulder? (PT *Musculoskeletal stiffness*)

  Musculoskeletal stiffness?

Body Site vs. Event Specificity

- MedDRA term includes body site and event information

Reported	LLT Selected
Skin rash on face	Rash on face

- No MedDRA term that includes body site and event. Event information has priority.

Reported	LLT Selected	Comment
Skin rash on chest	Skin rash	In this instance, there is no available term for a skin rash on the chest

Body Site vs. Event Specificity (cont)

- No MedDRA term that includes body site and event. Exercise judgment; body site may take priority.

Reported	LLT Selected	Comment
Cyanosis at injection site	Injection site reaction	Cyanosis implies a generalized disorder. In this example, selecting LLT *Cyanosis* would result in loss of important medical information and miscommunication.

Body Site vs. Event Specificity (cont)

- If event reported at multiple body sites and all LLTs link to same PT, select a single LLT; the event information has priority

Reported	LLT Selected	Comment
Skin rash on face and neck	Skin rash	LLT *Rash on face* and LLT *Neck rash* both link to PT *Rash*

Location Specific vs. Microorganism Specific Infection

- MedDRA term includes microorganism and anatomic location

Reported	LLT Selected	Comment
Pneumococcal pneumonia	Pneumococcal pneumonia	In this example, the implied anatomic location is the lung

Location Specific vs. Microorganism Specific Infection (cont)

- No MedDRA term that includes both microorganism and anatomic location. Preferred option is to select a term for the microorganism specific infection.

Reported	LLT Selected	Comment
Respiratory chlamydial infection	Chlamydial infection	Preferred option. Represents microorganism specific infection.
	Respiratory infection	Represents location-specific infection
	Chlamydial infection Respiratory infection	Represents both microorganism specific infection and anatomic location

What Term to Select?

- Viral infection of vestibular apparatus

  Labyrinthitis?

  Viral infection?

  Viral labyrinthitis?

- Soft tissue mycosis

  Soft tissue infection?

  Infection mycotic?

  Both terms?

Medical and Surgical Procedures

- Only the procedure is reported

Reported	LLT Selected
Patient had tonsillectomy in childhood	Tonsillectomy

- Procedure and diagnosis are reported

Reported	LLT Selected	Comment
Liver transplantation due to liver injury	Liver injury Liver transplantation	Preferred Option. Selecting term for the procedure may indicate severity of the condition.
	Liver injury	

Investigations

- Medical condition vs. investigation result

Reported	LLT Selected	Comment
Hypoglycemia	Hypoglycemia	LLT *Hypoglycemia* links to SOC *Metabolism and nutrition disorders*
Decreased glucose	Glucose decreased	LLT *Glucose decreased* links to SOC *Investigations*

Investigations (cont)

- Unambiguous investigation result

Reported	LLT Selected	Comment
Glucose 40 mg/dL	Glucose low	Glucose is clearly below the reference range

- Ambiguous investigation result

Reported	LLT Selected	Comment
His glucose was 40	Glucose abnormal	No units have been reported. Select LLT *Glucose abnormal* if clarification cannot be obtained.

Investigations (cont)

- Investigation results consistent with diagnosis

Reported	LLT Selected	Comment
Elevated potassium, K 7.0 mmol/L, and hyperkalemia	Hyperkalemia	It is not necessary to select LLT *Potassium increased*

- Grouped investigation result terms

Reported	LLT Selected	Comment
Increased alkaline phosphatase, increased SGPT, increased SGOT and elevated LDH	Alkaline phosphatase increased SGPT increased SGOT increased LDH increased	Select four individual terms. A single term such as LLT *Liver function tests abnormal* should not be selected.

What Term to Select?

- WBCs markedly increased

  WBC increased?

  Leukocytosis?

  Both terms?
- CSF was positive for Candida spp.

  Candidal meningitis?

  Candida test positive?

What Term to Select?

- Sudden onset of fevers up to 105 F

  Temperature elevation?

  Fever?

  Fever of unknown origin?
- Low hemoglobin and hematocrit

  Anemia?

  Hemoglobin low?

  Hematocrit low?

Medication Errors

See Appendix B of MedDRA Introductory Guide for Concept Descriptions

- Medication error with clinical consequences

Reported	LLT Selected
Patient was administered wrong drug and experienced hypotension	Wrong drug administered Hypotension
Because of similar sounding drug names, the patient took the wrong drug and experienced a rash	Drug name confusion Wrong drug administered Rash

Medication Errors (cont)

Important to record occurrence or potential occurrence of medication error

- Medication error without clinical consequences

Reported	LLT Selected	Comment
Medication was given intravenously instead of intramuscularly without sequelae	Intramuscular formulation administered by other route No adverse effect	If specifically reported that there is no adverse effect, acceptable to select LLT *No adverse effect*
Pharmacist notices that the names of two drugs are similar and is concerned that this may result in a medication error	Circumstance or information capable of leading to medication error	LLT *Drug name confusion* could be an optional additional term to select. Note: this example is a potential medication error.

Transmission of Infectious Agent via Medicinal Product

- Select term for transmission and term for infection, if identified

Reported	LLT Selected
Suspected transmission of Hepatitis C via blood product	Suspected transmission of an infectious agent via a medicinal product Hepatitis C
Confirmed transmission of Hepatitis C via blood product	Transmission of an infectious agent via a medicinal product Hepatitis C

Overdose, Toxicity and Poisoning

If overdose, poisoning or toxicity is explicitly reported, select the appropriate term

- Overdose with clinical consequences

Reported	LLT Selected
Stomach upset from study drug overdose	Stomach upset Overdose

- Overdose without clinical consequences

Reported	LLT Selected	Comment
Patient received an overdose of medicine without any adverse consequences	Overdose No adverse effect	LLT *No adverse effect* can also be selected

Product Quality Issues

See Appendix B of MedDRA Introductory Guide

"Top-down" navigation in HLGT *Product quality issues* is optimal approach for term selection

- Product quality issue with clinical consequences

Reported	LLT Selected
New bottle of drug tablets have unusual chemical smell that made me nauseous	Product odor abnormal Nauseous
I switched from one brand to another of my blood pressure medication, and I developed smelly breath	Product substitution issue brand to brand Smelly breath

Product Quality Issues (cont)

- Product quality issue without clinical consequences

Reported	LLT Selected
Sterile lumbar puncture kit received in broken packaging (sterility compromised)	Product sterile packaging disrupted

What Term to Select?

- Drug injected IM instead of SC; no sequelae
  - Subcutaneous injection formulation administered by other route?
  - Incorrect route of drug administration?
  - No adverse effect?
- Unintended overdose, dispensing error
  - Accidental overdose?
  - Adverse event?
  - Drug dispensing error?
  - Medication error?

What Term to Select?

- Pills do not split correctly along score
  - APACHE II score?
  - Tablet issue?
  - Scored tablet splitting issue?
- Hair was found inside drug blister pack
  - Hair loss?
  - Blister infected?
  - Product blister packaging issue?
  - Product contamination hair?

Points to Consider About MedDRA Term Selection: Points to Consider

- A “living document,” intended to grow and change as MedDRA advances from version to version
- A “companion document” to MedDRA
- Recommended to be used as the basis for individual organizations’ coding conventions

Facilitating the use of MedDRA

Free Training

- MSSO offers two free training courses to MSSO Subscribers, be regulatory authorities or otherwise
  - ❑Basic and Advanced topics
  - ❑Multiple locations around the world
- The MedDRA Board considers requests for training. Considerations based on:
  - ❑Optimally, be regionally-based
  - ❑Leverage existing regional training activities and events

Access to MedDRA

- The ICH Board has developed special licenses to provide access to low revenue companies
  - ❑EMA has a special mechanism for small and medium sized companies to submit ICSRs
    - Includes free access to MedDRA
  - ❑US FDA is developing a similar mechanism for small manufacturers to meet regulatory reporting requirements using MedDRA
- The ICH Board is open to exploring other financing models to fit the local needs and culture

Access to MedDRA (cont)

- MedDRA is available at no charge to
  - ❑Academics
  - ❑Healthcare providers
  - ❑Regulatory authorities
- Commercial organizations pay an annual subscription fee based on annual turnover
  - ❑Subscription rates have been reduced or kept unchanged for the last six years

How Much Does MedDRA Cost?

- Annual subscriptions based on the annual turnover (revenue) of the organization
  - – Basic limited to non-profits/hospitals

MSSO 2011 Pricing

MedDRA Subscription Levels	2011 Annual Subscription Rates	Additional Rates for Japanese Translation (if applicable)	Additional Rates for Chinese Translation (if applicable)
Regulatory Authorities	$0 USD	$0 USD	$0 USD
Basic (Non-profit)	$0 USD	$850 USD	$50 USD
Core Service (Parent Company Annual Revenue or Turnover)			
Core Service 0 (Annual Revenue < $1 Million)	$190 USD	$850 USD	$50 USD
Core Service 1 (Annual Revenue $1-$10 Million)	$804 USD	$850 USD	$50 USD
Core Service 2 (Annual Revenue $10-$500 Million)	$5,529 USD	$850 USD	$150 USD
Core Service 3 (Annual Revenue $500-$1 Billion)	$11,600 USD	$850 USD	$300 USD
Core Service 4 (Annual Revenue $1-$5 Billion)	$47,600 USD	$850 USD	$600 USD
Core Service 5 (Annual Revenue > $5 Billion)	$62,850 USD	$850 USD	$850 USD
Developer	$2,990 USD	$850 USD	$450 USD

Long-term Benefits (cont)

- Reduce impact on environment!

MedDRA users in 60 countries

Argentina
Australia
Austria
Belgium
Brazil
Bulgaria
Canada
Chile
China
Chinese Taipei
Croatia
Cyprus
Czech Republic
Denmark
Dominican Republic
Estonia
Ethiopia
Finland
France
Germany
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Hong Kong
Hungary
Iceland
India
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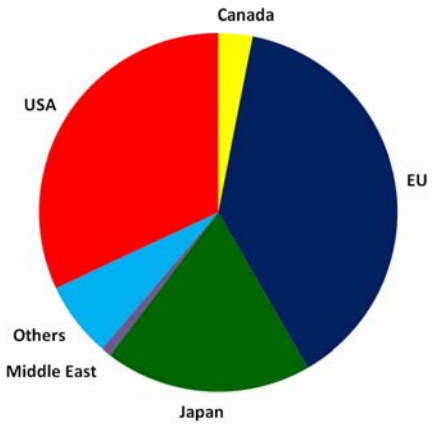
Serbia
Singapore
Slovakia
Slovenia
South Africa
South Korea
Spain
Sweden
Switzerland
Thailand
Ukraine
United Arab Emirate
United Kingdom
United States

Multi-lingual terminology

- MedDRA maintained simultaneously in 10 languages
  - English (1999)
  - Japanese (1999)
  - French (2002)
  - German (2002)
  - Portuguese (2002)
  - Spanish (2002)
  - Dutch (2003)
  - Italian (2005)
  - Czech (2007)
  - Mandarin Chinese (2009)
  - *Future availability – Hungarian (2011)*
- Translation includes terms and supporting documentation

MedDRA Worldwide Subscriptions



Over 2,800 Organizations in over 60 countries

Course Summary

- In this course, we covered:
  - A review of MedDRA's structure, including primary SOC allocation rules
  - Scope of MedDRA (with practice exercises)
  - Coding conventions, synonym lists, and coding QA
  - Introduction to the *MedDRA Term Selection: Points to Consider* document
  - Coding exercises

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Acronyms

- **CTD**: Common Technical Document
- **e-CTD**: electronic Common Technical Document
- **E2B**: Data Elements for Transmission of Individual Case Safety Reports
- **EFTA**: European Free Trade Association
- **EC**: European Commission
- **EFPIA**: European Federation of Pharmaceutical Industries and Associations
- **EU**: European Union

Acronyms

- **FDA US**: Food and Drug Administration United States
- **ICH**: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- **ICSR**: Individual Case Safety Report
- **IFPMA**: International Federation of Pharmaceutical Manufacturers & Associations
- **ISO:** International Organization for Standardization

Acronyms

- **JPMA**: Japan Pharmaceutical Manufacturers Association
- **M1**: Medical Dictionary for Regulatory Activities
- **MedDRA**: Medical Dictionary for Regulatory Activities
- **MHLW**: Ministry of Health, Labour and Welfare
- **MHRA**: Medicines and Healthcare products Regulatory Agency of the UK
- **MSSO**: MedDRA Support Services Organization
- **NCA**: National Competent Authority

Acronyms

- **PhRMA:** Pharmaceutical Research and Manufacturers of America
- **PSUR**: Periodic Safety Update Report
- **SMEs**: Small and Medium Sized Enterprises
- **SMQs**: Standardized MedDRA Queries
- **US**: United States
- **WHO**: World Health Organisation
- **WHO-ART**: World Health Organisation-Adverse Reaction Terminology