MedDRA®: Safety Data Analysis and SMQs
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 (EU, EFPIA, MHLW, J PMA, FDA, PhRMA), the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, the Health Canada, and the WHO (as Observer).
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Course Overview

In this course, we will cover:

- MedDRA overview
- *MedDRA Data Retrieval and Presentation: Points to Consider* document
- Developing queries using MedDRA
- Examples and hands-on exercises
Course Overview (cont)

- In this course, we will cover (cont):
  - SMQ background and definition
  - SMQs development status
  - SMQ data characteristics
  - SMQ testing and production maintenance
  - SMQ versioning
  - SMQ applications
  - Customized searches
MedDRA Overview
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)

- **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
  - EudraVigilance database
    • Clinical trial SUSARs (Suspected Unexpected Serious Adverse Reactions) and post-authorization Individual Case Safety Reports (ICSRs) – use MedDRA LLTs (current version or the one previous to it)
  - Volume 9A (To be retired in 2012)
    • MedDRA required for adverse reactions in Periodic Safety Update Report
    • Standardised MedDRA Queries (SMQs) recommended for signal detection
Regulatory Status of Mandate (cont)

• European Union (cont)
  – 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
  – Implementing measures include use of international terminologies, standards, and formats (MedDRA specifically mentioned)
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
Scope of MedDRA

**IN**
- Diseases
- Diagnoses
- Signs
- Symptoms
- Therapeutic indications
- Investigation names & qualitative results
- Medical & surgical procedures
- Medical, social, family history
- Medication errors
- Product quality, device issues
- Terms from other terminologies

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

SOC = Respiratory, thoracic and mediastinal disorders

HLGT = Respiratory tract infections

HLT = Viral upper respiratory tract infections

PT = Influenza

SOC = Infections and infestations

HLGT = Viral infectious disorders

HLT = Influenza viral infections
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
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)
MedDRA Version Analysis Tool (MVAT)

- Web-based (https://mssotools.com/mvat)
- Free to all subscribers
- Allows for comparison of any two versions
- Features
  - Version Report Generator (produces exportable report comparing any two versions)
  - Data Impact Report (identifies changes to a specific set of MedDRA terms or codes uploaded to MVAT)
  - Search Term Change (identifies changes to a single MedDRA term or code)
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
Browser Demonstration

SOC View
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
Quality of Source Data

• High quality data output is dependent on maintaining quality of original information reported by using consistent and appropriate term selection (Refer to MedDRA Term Selection: Points to Consider document)

• Method of conversion of data into MedDRA might impact retrieval and presentation - legacy data conversion using verbatims or coded terms
Documentation of Data Retrieval and Presentation Practices

- Organization-specific guidelines
  - Consistent with Points to Consider documents
  - Coding conventions
  - Data retrieval and output strategies (including SMQs)
  - Quality assurance procedures
  - MedDRA version used for search
  - Search strategy methods
  - Version update processes
  - Processes for customized MedDRA queries
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
Organization-Specific Data Characteristics

- Database structure (storage and use of hierarchy)
- Data storage (level of term, synonym/reported term)
- Data conversion (if applicable)
- Coding practices over time
- Limitations/restrictions (inability to view secondary SOCs)
- Term selection principles
  - More than one term selected increases counts
  - Diagnosis term only selected reduces counts
Impact of MedDRA’s Characteristics – Grouping Terms

• HLGTs and HLTs provide clinically relevant groupings
  – HLGT *Cardiac arrhythmias*
    • HLT *Cardiac conduction disorders*
    • HLT *Rate and rhythm disorders NEC*
    • HLT *Supraventricular arrhythmias*
    • HLT *Ventricular arrhythmias and cardiac arrest*
Impact of MedDRA’s Characteristics – Grouping Terms (cont)

• Caution - ensure all terms are relevant to output
  - HLT *Vascular tests NEC (incl blood pressure)*
    • PT *Blood pressure decreased*
    • PT *Blood pressure increased*

• Caution - related PTs in different locations in SOC
  - HLT *Bullous conditions*
    • PT *Stevens-Johnson syndrome*
  - HLT *Exfoliative conditions*
    • PT *Dermatitis exfoliative*
## Which Level? – SOC Investigations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v15.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>PT Aspartate aminotransferase increased</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>PT Alanine aminotransferase increased</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>PT Gamma-glutamyltransferase increased</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood creatine phosphokinase increased</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PT Blood alkaline phosphatase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood glucose increased</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PT Blood lactate dehydrogenase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Lipase increased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT White blood cell count decreased</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Amylase increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Faecal fat increased</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported.
### Which Level? – SOC Investigations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v15.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>PT Blood pressure increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Blood urea increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Occult blood positive</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Liver function test abnormal</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Monocyte count decreased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Protein urine present</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported.
### Which Level? – SOC Investigations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v15.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>HLT Liver function analyses</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>HLT Tissue enzyme analyses NEC</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>HLT Digestive enzymes</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HLT White blood cell analyses</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HLT Skeletal and cardiac muscle analyses</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>HLT Carbohydrate tolerance analyses (incl diabetes)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HLT Faecal analyses NEC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HLT Vascular tests NEC (incl blood pressure)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HLT Renal function analyses</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HLT Urinalysis NEC</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported.
### Which Level? – SOC Investigations (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v15.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Investigations</td>
<td>13 (29.5%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>HLGT Hepatobiliary investigations</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>HLGT Enzyme investigations NEC</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>HLGT Gastrointestinal investigations</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>HLGT Haematology investigations (incl blood groups)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HLGT Renal and urinary tract investigations and urinalyses</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>HLGT Metabolic, nutritional and blood gas investigations</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HLGT Cardiac and vascular investigations (excl enzyme tests)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported.
## Granularity

<table>
<thead>
<tr>
<th>Other Terminology Preferred Terms</th>
<th>No. of Events</th>
<th>MedDRA Version 15.0 Preferred Terms</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTION</td>
<td>15</td>
<td>Upper respiratory tract infection</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasopharyngitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower respiratory tract infection</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin infection</td>
<td>1</td>
</tr>
</tbody>
</table>
Multi-Axiality

• Primary SOC allocation rules affect the way data are distributed across the terminology
• Impact on frequencies of medical condition of interest should be considered
• Example: for hepatic abnormality search in SOC Hepatobiliary disorders, SOC Investigations (laboratory test terms), SOC Surgical and medical procedures (e.g., PT Liver transplant)
## Condition vs. Test Result

<table>
<thead>
<tr>
<th>Reported event (% subjects)</th>
<th>Other terminology</th>
<th>MedDRA Version 15.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coded term (% subjects)</td>
<td>Body System/ SOC (% subjects)</td>
</tr>
<tr>
<td>Hyperglycemia (4.1)</td>
<td>Hyperglycemia (10.5)</td>
<td>Metabolism and nutritional disorders (10.5)</td>
</tr>
<tr>
<td>Increased blood sugar (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose was high (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing glucose (0.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multi-Axiality (cont)

- Main presentation is by Primary SOC
- Secondary SOCs used for alternate views and presentation of data
### Primary SOC Analysis – SOC Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v15.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Infections and infestations</td>
<td>14 (31.8%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>PT Upper respiratory tract infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PT Sinusitis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Viral infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Bronchitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Influenza</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Localised infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PT Lower respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Tooth abscess</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported.
Secondary SOC Analysis –
SOC *Infections and infestations*

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v15.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Upper respiratory tract infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PT Sinusitis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PT Bronchitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Influenza</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Lower respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PT Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>SOC Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Viral infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PT Localised infection</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
Secondary SOC Analysis – SOC *Infections and infestations* (cont)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA v15.0)</th>
<th>25 mg MyDrug (N=44)</th>
<th>Placebo (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOC Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Urinary tract infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>SOC Ear and labyrinth disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Ear infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>SOC Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT Tooth abscess</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients may have more than one event reported
MedDRA Versioning

- MedDRA is updated twice a year
  - 1 March X.0 release (all levels)
  - 1 September X.1 release (LLT and PT levels only)

- Version used in data retrieval and presentation should be documented

- Resources:
  - “What’s New” document
  - Version report
  - MedDRA Version Analysis Tool (MVAT)

- Terms used for queries should be in same version as data being queried
### MedDRA Versioning (cont) - Effect of PT Demotion

<table>
<thead>
<tr>
<th></th>
<th>MedDRA Version 14.1</th>
<th>Number of Events at PT Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative haemorrhage (PT)</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Procedural haemorrhage</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MedDRA Version 15.0</th>
<th>Number of Events at PT Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative haemorrhage (no longer a PT)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Procedural haemorrhage</td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>
MedDRA Versioning (cont) - Effect of Primary SOC Change

<table>
<thead>
<tr>
<th>MedDRA Version 14.1</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Respiratory, thoracic and mediastinal disorders</td>
<td>20</td>
</tr>
<tr>
<td>PT Diaphragmatic hernia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MedDRA Version 15.0</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC Respiratory, thoracic and mediastinal disorders</td>
<td>0</td>
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<tr>
<td>SOC Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>PT Diaphragmatic hernia</td>
<td>20</td>
</tr>
</tbody>
</table>
General Queries and Retrieval

• General Principles
  - Data retrieval performed for multiple purposes; analysis of clinical trial data, pharmacovigilance, etc.
  - Various strategies, methods, and tools
  - Update previously used searches
  - Identify safety issues prior to retrieval
  - Consider data analysis plan
  - Group related events
  - Document strategy
  - Evaluate search results against original question
General Queries and Retrieval (cont)

- Types of searches
  - Overview of safety profile in summary reports
  - Comparison of frequency of ADR/AE (spontaneous reports or incidence for studies)
  - Analysis of a specific safety concern
  - Identification of patient subpopulations at risk
    - Searching medical history information
    - Pediatric and gender-specific data (see MSSO and JMO Web sites for adverse event term lists)
Overall Presentation of Safety Profiles

- Highlight overall distribution of ADRs/AEs
- Identify areas for in-depth analysis (focused searches)
- Approaches: full listing of terms to sophisticated statistical methods
- Standard approach: present by SOC and PTs
  - This approach not always optimal due to unique characteristics of MedDRA
Overview by Primary SOC

• Use Internationally Agreed Order of SOCs when applicable (see DRP: PTC or MedDRA Introductory Guide)
• Consider use of HLTs and HLGTs for large data sets
• Line listings, tables, graphs
• Benefits - Broad overview, PTs displayed only once
• Limitations - Incomplete groupings, lengthy output
Primary SOC Graphical Display Example

![Graph showing relative frequency of SOC categories](image-url)
Small Dataset PT Display Example

Most Frequent On-Therapy Adverse Events
PTs sorted by relative risk
Primary SOC Output Listing Example

SOC Nervous system disorders 8

   HLGT Mental impairment disorders
      HLT Mental impairment (excl dementia and memory loss)
         PT Disturbance in attention 1

   HLGT Movement disorders (incl Parkinsonism)
      HLT Dyskinesias and movement disorders NEC
         PT Psychomotor hyperactivity 2
      HLT Tremor (excl congenital)
         PT Tremor 3

   HLGT Neurological disorders NEC
      HLT Disturbances in consciousness NEC
         PT Somnolence 1
      HLT Neurological signs and symptoms NEC
         PT Dizziness 1
Focused Searches

Useful when further investigating concepts of interest

• Secondary SOC assignments
  – Programming required if database does not allow automated output by secondary SOC
  – Benefits - more comprehensive view of medically related events
  – Limitations - display by primary and secondary SOC could lead to double counting

• Grouping terms (HLGT/HLT)

• SMQ

• Customized search
  – Modified SMQ
  – Ad hoc query
## Programming a List of PTs in Primary and Secondary SOC Locations

**SOC Eye disorders**
- HLGT Vision disorders
  - HLT Visual field disorders
    - PT Hemianopia
    - PT Hemianopia heteronymous
    - PT Hemianopia homonymous
    - PT Scotoma (primary SOC location)
    - PT Tunnel vision
    - PT Uhthoff’s phenomenon
    - PT Visual field defect

*6 of 7 PTs are primary to SOC Nervous system disorders*
Secondary SOC Graphical Display Example
Use of MedDRA at the FDA

Acknowledgement: Dr. Chuck Cooper, Office of Translational Sciences, CDER, FDA
Developing Queries Using MedDRA: Query Strategy Tips
General Principles

• Define the medical condition
• Develop inclusion/exclusion criteria
• Know your data, e.g., how specific coding conventions impact retrieval strategy
• Good browser is key component
  – Flexible search capabilities
  – Ability to view secondary SOC assignments
Query Strategy Tips

1. ALWAYS search the “non-multi-axial” SOC
   - Investigations
   - Surgical and medical procedures
   - Social circumstances
Query Strategy Tips (cont)

2. Consider looking at the following SOCs

- *General disorders and administration site conditions*
- *Congenital, familial and genetic disorders*
- Remaining “Other/Support” SOCs as needed
Query Strategy Tips (cont)

3. Take your time and do a broad, inclusive search. If you find a term you like, go up and down the hierarchy and consider the term’s “neighbors,” including the term’s multi-axial linkages. (“Top-down” and “Bottom-up” searches).
Query Strategy Tips (cont)

4. Use the “grouping terms” in the hierarchy (HLGTs, HLTs) when applicable. If all PTs in an HLT are pertinent except for one, use the HLT and “exclude” that particular PT
Query Strategy Tips (cont)

5. Avoid the use of LLTs in queries. These terms were designed to be the “entry-level” into the terminology and NOT designed for useful data retrieval.

NOTE: SOC *Infections and infestations* is an exception to this tip: specific species information is found at the LLT level.
Query Strategy Tips (cont)

6. When you think you’re done, you’re NOT – always recheck your work…
Additional Points About Query Development

- Periodically review queries to determine possible impact of new MedDRA versions, e.g., PT term demotion, LLT currency changes, renaming of HLT/HLGTs, remapping of terms, etc.
- Set aside enough time – a thorough, well-constructed query takes time, but it is well worth the effort
- Recycle! If a query worked for one product, it could be applicable to others
Connect the DOTSSS!

- **Diagnosis/disease terms**
- **Operations** (Surgical and medical procedures)
- **Tests** (Investigations)
- **Support SOCs (Other…)**
- **Signs & symptoms**
- **Social circumstances**
Examples and Hands-on Exercises
Example

Cardiac arrhythmias
Example – Cardiac Arrhythmias

• Obvious starting point – HLGT Cardiac arrhythmias ("Top-down" search)
• Also use “Arrhythmia” terms as starting point of “Bottom-up” search
• What about non-multi-axial SOCs?
Example – Cardiac Arrhythmias (cont)

• SOC Investigations
  – PTs subordinate to HLT ECG investigations and HLT Heart rate and pulse investigations should be reviewed
    • Example: PT Heart rate irregular
Example – Cardiac Arrhythmias (cont)

• SOC *Surgical and medical procedures*
  Important to review:
  – PTs subordinate to HLT *Cardiac device therapeutic procedures*
    • Example: PT *Implantable defibrillator insertion*
  – PTs subordinate to HLT *Cardiac therapeutic procedures NEC*
    • Example: PT *Cardioversion*

*Note: Pacemaker and other cardiac therapeutic procedure terms were not included in SMQ *Cardiac arrhythmias*
Example – Cardiac Arrhythmias (cont)

• Because arrhythmias may produce various signs and symptoms, you may wish to review PTs subordinate to the following HLTs:
  - HLT *Disturbances in consciousness NEC*
  - HLT *Neurological signs and symptoms NEC*
  - HLT *Cardiac disorders NEC*
  - HLT *Cardiac signs and symptoms NEC*
  - HLT *Dyspnoeas*
Example – Cardiac Arrhythmias (cont)

• Lastly…
  – PTs subordinate to HLT *Death and sudden death* (under SOC *General disorders and administration site conditions*) should be reviewed
    • Example: PT *Cardiac death*
Example

Pancreatitis
Example - Pancreatitis

• Obvious starting point in SOC Gastrointestinal disorders:
  – HLT *Acute and chronic pancreatitis* (“Top-down”)
    • Example: PT *Alcoholic pancreatitis*
    • Example: PT *Pancreas infection*

• Also use “Pancrea” terms in “Bottom-up” search

*Note: SMQ *Acute pancreatitis* is focused on acute pancreatitis, not chronic pancreatitis. This exercise includes both conditions.*
Example – Pancreatitis (cont)

• Consider including SOC *Investigations* in your query
  - HLT *Digestive enzymes*
    • Example: PT *Amylase increased*
    • Example: PT *Lipase abnormal*
    • Example: PT *Pancreatic enzymes increased*
Example – Pancreatitis (cont)

• Review other groupings
  – HLT *Pancreatic disorders NEC*
    • Example: PT *Pancreatic necrosis*
  – HLT *Cystic pancreatic disorders*
    • Example: PT *Pancreatic pseudocyst*
  – HLT *Pancreatic therapeutic procedures*
    • Example: PT *Pancreatic pseudocyst drainage*
Developing Queries – Lessons Learned

• MedDRA is a potentially powerful tool for data retrieval, BUT it requires:
  – Solid medical knowledge
  – Solid MedDRA knowledge

• Size and complexity of MedDRA overcome lack of specificity of other terminologies, but may require a more “creative” approach to data retrieval

• WELL WORTH THE EFFORT to develop, share, and store in-house queries
Topic: Cardiac failure

- Build a query with a set of PTs relevant to this condition
- Consider:
  - Diagnosis terms
  - Signs and symptoms
  - Investigations
  - Surgical and medical procedures
  - Other…
- Can you identify cases of interest in a dataset?
Exercises

Develop queries for the following concepts:

- Chronic renal failure
- Hypoglycemia
- Hypotension
- Depression

- Describe how you developed the query, including use of a definition/reference as starting point
- Describe the inclusion/exclusion criteria (etiologies and risk factors are typically excluded)
- Note the main SOCs, HLGTs and HLTs used in your query, as well as examples of specific PTs
Standardised MedDRA Queries (SMQs)
Background of SMQ Development
CIOMS and SMQs

- CIOMS (Council for International Organizations of Medical Sciences): An international, non-governmental, non-profit organization established jointly by World Health Organization (WHO) and United Nations Educational, Scientific and Cultural Organization (UNESCO)
- CIOMS and ICH have established terms of reference for cooperative development of SMQs
- Maintenance of SMQs is the joint responsibility of the user community (through MSSO Change Request process) and the MSSO
CIOMS SMQ Working Group (WG)

- 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
CIOMS SMQ WG (cont)

- ICH Advisory Panel
  - Includes representatives from industry and regulators from the three ICH regions, MHRA, Health Canada and WHO (as an observer)
  - ICH oversight for the development of SMQs
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
SMQ Definition
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 Development Status
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 Production and Development List

- Refer to MSSO Web site for current status of SMQs in production and development

http://www.meddramsso.com/subscriber_smq.asp
SMQ Data Characteristics
SMQ Data Characteristics

- MedDRA term inclusion
- SMQ naming convention
- Broad/narrow
- Algorithms
- Hierarchy
- SMQ status/term status within an SMQ
- Term versioning in an SMQ
- Distributed data includes text data
- Distributed file structure
MedDRA Term Inclusion

- SMQs are constructed at MedDRA PT level
- LLTs that are subordinate to an included PT are also included
SMQ Naming Convention

- SMQ titles have “(SMQ)” appended to the end to ensure there is no name conflict with existing MedDRA terms
- E.g., “Agranulocytosis (SMQ)”
- Each SMQ has a unique 8-digit code starting with “2”
Narrow and Broad Searches

- “Narrow” scope – specificity (cases highly likely to be condition of interest)
- “Broad” scope – sensitivity (all possible cases)
- “Broad search” = All broad + all narrow terms
- MedDRA term can be broad or narrow depending on SMQ
  - Example: PT Renal failure acute
    - Narrow in Acute renal failure (SMQ)
    - Broad in Rhabdomyolysis/myopathy (SMQ)
Narrow vs. Broad Example

Lactic acidosis (SMQ)

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).
Algorithmic SMQs

- Some SMQs are designed to utilize algorithms
- Better case identification among broad search terms may result if cases are selected by a defined combination of selected terms
Algorithmic SMQ Example

- **Anaphylactic reaction (SMQ):**
  - A case with any of the following PTs:
    - Anaphylactic reaction
    - Anaphylactic shock
    - Anaphylactic transfusion reaction
    - Anaphylactoid reaction
    - Anaphylactoid shock
    - Circulatory collapse
    - First use syndrome
    - Kounis syndrome
    - Shock
    - Type I hypersensitivity

(Narrow search terms = Category A)
Algorithmic SMQ Example (cont)

<table>
<thead>
<tr>
<th>Category B - Upper airway/ Respiratory</th>
<th>Category C - Angioedema/ Urticaria, etc.</th>
<th>Category D - Cardiovascular/ Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure</td>
<td>Allergic oedema</td>
<td>Blood pressure decreased</td>
</tr>
<tr>
<td>Asthma</td>
<td>Angioedema</td>
<td>Blood pressure diastolic decreased</td>
</tr>
<tr>
<td>Bronchial oedema</td>
<td>Erythema</td>
<td>Blood pressure systolic decreased</td>
</tr>
</tbody>
</table>

- Case = A (Narrow terms)
- Or Term from Category B and term from Category C
- Or Term from either Category B or Category C plus Term from Category D
Hierarchical SMQs

- Some SMQs may develop as set of queries related to one another in a hierarchical relationship
- Not related to MedDRA standard hierarchy
- One or more subordinate SMQs combined to create a superordinate, more inclusive SMQ
Hierarchical SMQ Example

- Haematopoietic cytopenias
  - Haematopoietic cytopenias affecting more than one type of blood cell
  - Haematopoietic erythropenia
  - Haematopoietic leukopenia
  - Haematopoietic thrombocytopenia
SMQ Status/Term Status

• Each SMQ has a status (Active/Inactive)
• Similar in concept to MedDRA currency
• Terms assigned to an SMQ also have a status flag
  – Once a term is added to an SMQ, it will always be included in the SMQ but the status may be inactive
Term Versioning in an SMQ

- Each term included in an SMQ has version fields
  - Term addition – version of MedDRA when the term was added to the SMQ
  - Term last modified – version of MedDRA when a change was made to the term in the SMQ (e.g. status, scope)

- Allows user to know the maintenance history of the SMQ
Text Data Included in SMQ

• Description field
  – Additional information about each SMQ (from SMQ Introductory Guide)

• Source field
  – Medical references used in development/maintenance

• Development note
  – Pertinent notes for proper use
  – Description of algorithm (if applicable), and definition of categories
Development Note

Example from SMQ *Pseudomembranous colitis*

- PTs *Diarrhoea* and *Diarrhoea haemorrhagic*
  - in the narrow search if the compound is an antibiotic
  - in the broad search if the compound is not an antibiotic

- PT *Clostridial infection* includes LLTs for non-specific “clostridial” descriptions, as well as non-C. difficile species
  - cases should be carefully reviewed for relevance
SMQ Distributed File Structure

- SMQs are distributed in two data files
  - **SMQ_List.asc** – provides general information about each SMQ
  - **SMQ_Content.asc** – provides general information about included MedDRA terms as well as subordinated SMQs

- Both data files are
  - ASCII format
  - “$” delimited
SMQ Files and Documents

• MedDRA distributed files unchanged by inclusion of SMQ files
• SMQ Introductory Guide
  – Recommended reading for optimal utilization of SMQs
  – Details of individual SMQs
  – Notes for implementation and/or expectation of results
• Production SMQ Spreadsheet
  – SMQs and included terms (.xls)
• SMQ changes: “What’s New” document, Version Report, MVAT
• Original CIOMS Working Group documentation
Browser Demonstration

SMQ View
How to “Run” SMQs

- IT perspective of SMQs = stored queries
- Code at LLT level; most organizations store coded data as LLTs
- SMQ ASCII files include PTs and LLTs
- Load SMQs into a query tool; run query against coded MedDRA terms in safety or clinical trial database for “Hits”
- Use SMQ options, if applicable
  - Narrow/broad search
  - Algorithms
  - Hierarchy
How to “Run” SMQs (cont)
SMQ Narrow Search Results Example

Asthma/bronchospasm (SMQ) Cases – Narrow Search
(since 1-JAN-2008)

<table>
<thead>
<tr>
<th>ID</th>
<th>MedDRA_PT</th>
<th>REPORT_VERBATIM</th>
<th>DATE_CREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>045</td>
<td>Asthma</td>
<td>Asthma attack</td>
<td>01-APR-2008</td>
</tr>
<tr>
<td>063</td>
<td>Asthma</td>
<td>Severe asthma</td>
<td>10-JUN-2008</td>
</tr>
<tr>
<td>060</td>
<td>Asthma exercise induced</td>
<td>Asthma when exercising</td>
<td>30-MAY-2008</td>
</tr>
<tr>
<td>091</td>
<td>Bronchospasm</td>
<td>Spasms, bronchial</td>
<td>12-AUG-2008</td>
</tr>
<tr>
<td>074</td>
<td>Bronchospasm</td>
<td>Bronchoconstriction</td>
<td>03-JUL-2008</td>
</tr>
<tr>
<td>100</td>
<td>Bronchial hyperreactivity</td>
<td>Airways hyperreactive</td>
<td>20-SEP-2008</td>
</tr>
<tr>
<td>069</td>
<td>Bronchial hyperreactivity</td>
<td>Reactive airways disease</td>
<td>21-JUN-2008</td>
</tr>
</tbody>
</table>
### Asthma/bronchospasm (SMQ) Cases – Broad Search
(since 1-JAN-2008)

<table>
<thead>
<tr>
<th>ID</th>
<th>MedDRA_PT</th>
<th>REPORT_VERBATIM</th>
<th>DATE_CREATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>023</td>
<td>Allergic respiratory disease</td>
<td>Respiratory (allergy) disorder</td>
<td>18-FEB-2008</td>
</tr>
<tr>
<td>045</td>
<td>Asthma</td>
<td>Asthma attack</td>
<td>01-APR-2008</td>
</tr>
<tr>
<td>063</td>
<td>Asthma</td>
<td>Severe asthma</td>
<td>10-JUN-2008</td>
</tr>
<tr>
<td>060</td>
<td>Asthma exercise induced</td>
<td>Asthma when exercising</td>
<td>30-MAY-2008</td>
</tr>
<tr>
<td>016</td>
<td>Bronchial obstruction</td>
<td>Bronchial obstruct.</td>
<td>16-JAN-2008</td>
</tr>
<tr>
<td>039</td>
<td>Bronchial obstruction</td>
<td>Bronchus obstruction</td>
<td>14-MAR-2008</td>
</tr>
<tr>
<td>091</td>
<td><strong>Bronchospasm</strong></td>
<td>Spasms, bronchial</td>
<td>12-AUG-2008</td>
</tr>
<tr>
<td>074</td>
<td><strong>Bronchospasm</strong></td>
<td>Bronchoconstriction</td>
<td>03-JUL-2008</td>
</tr>
<tr>
<td>100</td>
<td>Bronchial hyperreactivity</td>
<td>Airways hyperreactive</td>
<td>20-SEP-2008</td>
</tr>
<tr>
<td>069</td>
<td>Bronchial hyperreactivity</td>
<td>Reactive Airways Disease</td>
<td>21-JUN-2008</td>
</tr>
<tr>
<td>088</td>
<td>Obstructive Airways Disorder</td>
<td>Obstructive Airways Disorder</td>
<td>29-JUL-2008</td>
</tr>
</tbody>
</table>
SMQ vs. MedDRA Grouping Terms

• Data retrieved using HLTs and HLGTs may differ from those retrieved by a related SMQ

• Example:
  - HLGT *Cardiac arrhythmias* vs. SMQ *Cardiac arrhythmias*
  - SMQ likely to retrieve more events than HLGT because SMQ includes additional terms from other SOCs
## SMQ Acute renal failure – Sources of Terms

<table>
<thead>
<tr>
<th>PT (Example)</th>
<th>HLT</th>
<th>HLGT</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema due to renal disease</td>
<td>Oedema NEC</td>
<td>General system disorders NEC</td>
<td>General disorders and administration site conditions</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>Renal function analyses</td>
<td>Renal and urinary tract investigations and urinalyses</td>
<td>Investigations</td>
</tr>
<tr>
<td>Protein urine present</td>
<td>Urinalysis NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output decreased</td>
<td>Urinary tract function analyses NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercreatininaemia</td>
<td>Metabolic disorders NEC</td>
<td>Metabolism disorders NEC</td>
<td>Metabolism and nutrition disorders</td>
</tr>
<tr>
<td>Nephritis</td>
<td>Nephritis NEC</td>
<td>Nephropathies</td>
<td>Renal and urinary disorders</td>
</tr>
<tr>
<td>Nephropathy toxic</td>
<td>Nephropathies and tubular disorders NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure acute</td>
<td>Renal failure and impairment</td>
<td>Renal disorders (excl nephropathies)</td>
<td></td>
</tr>
<tr>
<td>Azotaemia</td>
<td>Renal failure complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal tubular necrosis</td>
<td>Renal vascular and ischaemic conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Urinary abnormalities</td>
<td>Urinary tract signs and symptoms</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>Haematological therapeutic procedures NEC</td>
<td>Haematological and lymphoid tissue therapeutic procedures</td>
<td>Surgical and medical procedures</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>Renal therapeutic procedures</td>
<td>Renal and urinary tract therapeutic procedures</td>
<td></td>
</tr>
</tbody>
</table>
SMQ Testing and Production Maintenance
SMQ Development Summary

• Pre-release testing by CIOMS Working Group members
  – Typically, at least one company and one regulator database
  – Cases retrieved reviewed for relevance
  – Fine-tuning of SMQ may require several iterations
  – Reviewed and approved by CIOMS WG

• Production Phase: continue to be fine-tuned through the MSSO maintenance process
SMQ Production Maintenance

- Essentially a change request process
- Final disposition is not time limited
- MSSO reviews all new terms in new release for inclusion in existing SMQs
- MSSO reviews existing terms for impact of demotions, moves, etc.
- All SMQ change requests reviewed by CI OMS WG after 18-24 months in production
SMQ Production Maintenance (cont)

- SMQ change requests undergo the same process as other MedDRA change requests
  - SMQ change requests are considered simple change requests
  - SMQ change requests are part of the 100 allotted change requests for each core subscriber
SMQ Production Maintenance (cont)

- Types of SMQ Change Requests
  - **Add a new SMQ** - with or without detail of included terms
  - **Rename an SMQ**
  - **Change status of an SMQ** - active or inactive
  - **Merge an SMQ**
  - **Move an SMQ** - change the hierarchy
  - **Update SMQ description** - in the distributed ASCII text file
  - **Update SMQ note**
SMQ Production Maintenance (cont)

- Types of SMQ Change Requests (cont)
  - Add a MedDRA term to an SMQ
  - Change a MedDRA term status in an SMQ
  - Update MedDRA Term Scope field - broad to narrow, or narrow to broad
  - Update MedDRA term category
SMQ Versioning
SMQ Versioning

- It is recommended that organizations use the SMQs with data coded with the same version of MedDRA
  - Match the MedDRA version of the SMQ with the MedDRA version of the coded data
  - Mismatches of SMQ and MedDRA coded data could produce unexpected results
SMQ Versioning (cont)

- Examples of PTs added to SMQs in MedDRA Version 15.0:
  - PT *Prerenal failure* in SMQ *Acute renal failure*
  - PT *Ovarian vein thrombosis* in SMQ *Embolic and thrombotic events, venous*

- Using version 14.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 15.0
SMQ Applications
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)
Practical Application of SMQs

SMQ Acute central respiratory depression

• Example shows:
  – Number of events/cases retrieved by single PT vs. narrow search vs. broad search
  – Use of positive and negative control compounds
  – Review and verification of relevant cases
  – Decisions made for final term list
SMQ Acute central respiratory depression (cont)

- Pharmaceutical company safety database
- All spontaneous reports up to 31 December 2005
- Coded in MedDRA Version 8.1
- Compound 1: opiate (positive control)
  - 1278 events in 432 cases
- Compound 2: topical product (negative control)
  - 2093 events in 802 cases
- Query for PT Respiratory depression alone
  - Compound 1: 15 cases
  - Compound 2: 0 cases
# Narrow Search Results

<table>
<thead>
<tr>
<th>PT</th>
<th>Compound 1 No. of reports (Relevant cases)</th>
<th>Compound 2 No. of reports (Relevant cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnoea</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>2 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>15 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory rate decreased</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>106 events in 21 cases</strong></td>
<td><strong>0 events in 0 cases</strong></td>
</tr>
</tbody>
</table>

PTs that did not retrieve any cases are omitted from table.
## Broad Search Results

<table>
<thead>
<tr>
<th>PT</th>
<th>Compound 1 No. of reports (Relevant cases)</th>
<th>Compound 2 No. of reports (Relevant cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Cardio-respiratory arrest</td>
<td>32 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>3 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Oxygen saturation decreased</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total (Broad search alone)</strong></td>
<td><strong>160 events in 46 cases</strong></td>
<td><strong>28 events in 2 cases</strong></td>
</tr>
<tr>
<td><strong>Total (Narrow and broad)</strong></td>
<td><strong>184 events in 50 cases</strong></td>
<td><strong>28 events in 2 cases</strong></td>
</tr>
</tbody>
</table>
Review of Cases Retrieved

• Narrow search
  
  – PT *Respiratory arrest*
    
    • Retrieved 2 cases related to seizure
    • Despite this, PT is medically relevant; retained in SMQ
  
  – PT *Respiratory rate decreased*
    
    • Retrieved a relevant case
    • Not on original SMQ term list, but added based on this result
Review of Cases Retrieved (cont)

• Broad search
  - PT *Cardiac arrest* and PT *Cardio-respiratory arrest*
    • Did not retrieve relevant cases
    • Retained in SMQ but may be “noisy”
  - PT *Acute respiratory failure*
    • Not on original SMQ term list, but retrieved a relevant case
    • Added to SMQ based on this result
Use of SMQs at the FDA

<table>
<thead>
<tr>
<th>SMQ name (SMQ)</th>
<th>CPI1</th>
<th>CPI2</th>
<th>CPI3</th>
<th>CPI4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidaemia</td>
<td>19(4.44%)</td>
<td>48(11.03%)</td>
<td>67(7.74%)</td>
<td></td>
</tr>
<tr>
<td>Depression and suicide/self-injury</td>
<td>17(3.97%)</td>
<td>22(5.06%)</td>
<td>39(4.50%)</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy (SMQ)</td>
<td>16(3.74%)</td>
<td>19(4.37%)</td>
<td>35(4.04%)</td>
<td></td>
</tr>
<tr>
<td>Malignancies (SMQ)</td>
<td>11(2.57%)</td>
<td>13(2.99%)</td>
<td>24(2.77%)</td>
<td></td>
</tr>
<tr>
<td>Malignant or unspecified tumours (SMQ)</td>
<td>11(2.57%)</td>
<td>13(2.99%)</td>
<td>24(2.77%)</td>
<td></td>
</tr>
<tr>
<td>Haematopoietic cytopenias (SMQ)</td>
<td>12(2.60%)</td>
<td>10(2.30%)</td>
<td>22(2.54%)</td>
<td></td>
</tr>
<tr>
<td>Leukopenia (SMQ)</td>
<td>11(2.57%)</td>
<td>9(2.07%)</td>
<td>20(2.31%)</td>
<td></td>
</tr>
<tr>
<td>Asthma/bronchospasm (SMQ)</td>
<td>2(0.47%)</td>
<td>6(1.38%)</td>
<td>8(0.92%)</td>
<td></td>
</tr>
<tr>
<td>Angioedema (SMQ)</td>
<td>2(0.47%)</td>
<td>4(0.92%)</td>
<td>6(0.69%)</td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis (SMQ)</td>
<td>1(0.23%)</td>
<td>4(0.92%)</td>
<td>5(0.58%)</td>
<td></td>
</tr>
<tr>
<td>Convulsions (SMQ)</td>
<td>3(0.70%)</td>
<td>3(0.69%)</td>
<td>6(0.69%)</td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease (SMQ)</td>
<td>0(0.00%)</td>
<td>3(0.69%)</td>
<td>3(0.35%)</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure (SMQ)</td>
<td>0(0.00%)</td>
<td>2(0.46%)</td>
<td>2(0.23%)</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease (SMQ)</td>
<td>0(0.00%)</td>
<td>2(0.46%)</td>
<td>2(0.23%)</td>
<td></td>
</tr>
<tr>
<td>Embolic and thrombotic events, arterial (SMQ)</td>
<td>1(0.23%)</td>
<td>2(0.46%)</td>
<td>3(0.35%)</td>
<td></td>
</tr>
<tr>
<td>Embolic and thrombotic events (SMQ)</td>
<td>3(0.70%)</td>
<td>2(0.46%)</td>
<td>5(0.58%)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Acknowledgement: Dr. Chuck Cooper, Office of Translational Sciences, CDER, FDA
Case study at EMA

Signal detection using SMQ

Hyperglycaemia/new onset diabetes mellitus

Based on work by:
Victoria Newbould
Nick Halsey
Stefano Cappe
Panos Tsintis
Magnus Lerch
and Patricia Mozzicato

Acknowledgement: Jim Slattery, EMEA. Slides used with permission.
EMA Signal Detection Activities (made simple)

- All newly arrived reports are reviewed
- Disproportionality measure – Proportional Reporting Ratio (PRR) – is calculated
- If the lower confidence bound exceeds one and the total number of cases is 3 or more further investigation may be started
Question

• Although not designed primarily for detection of drug safety issues, is it likely that the SMQs will have advantages over other levels of MedDRA in early signalling of new safety problems?
Design of Study

- SMQ *Hyperglycaemia/new onset diabetes mellitus*
- An antipsychotic with known association
- Calculate PRR as function of time
- Compare with PRR from single PTs, HLT, and HLGT
Signal Detection from various Adverse Event Groups

Note: Points marked with a black dot have counts of 3 or more cases
Case Study Conclusions

• There is potential for well thought-out grouping of MedDRA categories to improve signal detection

• In this case narrow was better than broad – thus not simply a matter of amalgamating all clinically related terms

• However, both broad and narrow competed with PTs and higher levels

• In designing SMQs for signal detection we must consider ‘specificity’ to avoid increasing noise
Influence of the MedDRA® hierarchy on pharmacovigilance data mining results

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\textsuperscript{g} Columbia University, New York, NY, USA

MedDRA and Signal Detection (cont)

- **Methodology**
  - Data mining using three algorithms for signals of disproportionate reporting (SDRs) for 26 drugs in FDA’s AERS database
  - Adverse events identified by PTs, HLTs, or SMQs

- **Conclusions**
  - HLTs and SMQs can improve % of unlabeled supported SDRs in data mining
  - Improvement holds for all algorithms tested
  - Trade-off: HLTs, SMQs medically less-specific vs. PTs
  - Need to examine component PTs of each HLT or SMQ that results in an SDR
Customized Searches
Customized Searches – Modified SMQs

- Do not modify SMQ unless there is a compelling reason – makes it non-standard

- “Modified MedDRA query based on an SMQ”
  - To be used to refer to an SMQ that has been modified
  - All modifications must be documented
  - Version updates and maintenance are responsibility of organization that created it
Modified MedDRA Queries Based on SMQs - Examples

• Additional PTs needed
  – Product investigated for possible safety signal of dementia and user wishes to use SMQ *Dementia*
  – For this particular product, PT *Disturbance in attention* may be needed. Document that this PT has been added to SMQ *Dementia*.

• Excluding PTs
  – Antipsychotic investigated for QT prolongation also has association with hypotension/fainting
  – Exclude PT *Syncope* from SMQ *Torsade de pointes/QT prolongation* (broad search) to prevent “noise” in retrieval
Modified MedDRA Queries Based on SMQs – Examples (cont)

• Changing scope of SMQ term
  - Product investigated for severe cutaneous adverse reactions including potential for DRESS syndrome; specific (narrow) search result is required
  - Include PT *Drug rash with eosinophilia and systemic symptoms* (normally a broad search term) with the narrow search terms in SMQ *Severe cutaneous adverse reactions*
Customized Searches – Ad Hoc Queries

• Need medical knowledge
• Need knowledge of structure and characteristics of MedDRA and of your data
• Refer to the *MedDRA Data Retrieval and Presentation: Points to Consider* document for query construction tips
• Save query for future use; maintenance needed for MedDRA version changes
• Consider submitting *ad hoc* query to MSSO via change request for possible development as an SMQ
Exercise

• SMQ *Lack of efficacy/effect* often needs to be modified based on the particular characteristics of a product

• Consider how you would create a Modified MedDRA Query based on SMQ *Lack of efficacy/effect* for:
  
  – An inhaled bronchodilator indicated for use in asthma
  
  – A drug used for migraine prophylaxis

• Remember to document changes!
Course Summary

• In this course, we:
  – Reviewed MedDRA’s scope, structure, and characteristics
  – Reviewed key sections of the *MedDRA Data Retrieval and Presentation: Points to Consider* document
  – Reviewed key points for developing queries using MedDRA
  – Worked on MedDRA query exercises
Course Summary (cont)

• In this course, we:
  – Reviewed SMQ background and definition
  – Reviewed the development status of SMQs
  – Discussed SMQ data characteristics
  – Discussed SMQ testing, production maintenance, and versioning
  – Reviewed SMQ applications
  – Discussed customized searches
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