



MedDRA SMQs Data Analysis Signal Detection with MedDRA

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Overview

- Implementation of SMQs in the EudraVigilance Data Analysis System
- MedDRA Multiaxiality implemented in the EudraVigilance Data Analysis System
- Using MedDRA for coding Indications and Risks in the Interface between the EU-RMP and EudraVigilance
- “Serious Event” List implemented in the EudraVigilance Data Analysis System
- “Paediatric Terms” List



The Standard MedDRA Queries

- SMQs are distributed in two files
 - SMQ_LIST: List of Standard MedDRA Queries (SMQs)
 - SMQ_CONTENT: Map the SMQs to a standard MedDRA hierarchy
- SMQs can have multiple levels of analysis
 - From one to five levels of analysis
- SMQs can have a narrow and a broad scope



Implementation of SMQs in the EudraVigilance Data Analysis System

- SMQs have been implemented in the EudraVigilance Data Analysis System as SMQ hierarchy table:
 - Five levels are always supported
 - When a level is not available in a SMQ, it is populated with the highest level available for that SMQ
 - The hierarchy is always connected at the level of LLT to the E2B(M) “reaction” section
 - Each SMQ has been duplicated with a “(Broad)” or “(Narrow)” qualifier to implement the broad and narrow scope
 - The relationship between SMQs and the E2B(M) “reaction” is many to many



Implementation of SMQs an example...

SMQ Level 3 SMQ Level 2 SMQ Level 1

<input type="checkbox"/>	Depression and suicide/self-injury (SMQ) (Broad)
<input type="checkbox"/>	Depression and suicide/self-injury (SMQ) (Broad)
<input type="checkbox"/>	Suicide/self-injury (SMQ) (Broad)
<input type="checkbox"/>	Depression and suicide/self-injury (SMQ) (Narrow)
<input type="checkbox"/>	Depression and suicide/self-injury (SMQ) (Narrow)
<input type="checkbox"/>	Suicide/self-injury (SMQ) (Narrow)
<input type="checkbox"/>	Embololic and thrombotic events (SMQ) (Broad)
<input type="checkbox"/>	Embololic and thrombotic events (SMQ) (Broad)
<input type="checkbox"/>	Embololic and thrombotic events, arterial (SMQ) (Broad)
<input type="checkbox"/>	Embololic and thrombotic events, venous (SMQ) (Broad)
<input type="checkbox"/>	Embololic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ) (Broad)
<input type="checkbox"/>	Embololic and thrombotic events (SMQ) (Narrow)
<input type="checkbox"/>	Embololic and thrombotic events (SMQ) (Narrow)
<input type="checkbox"/>	Embololic and thrombotic events, arterial (SMQ) (Narrow)
<input type="checkbox"/>	Embololic and thrombotic events, venous (SMQ) (Narrow)
<input type="checkbox"/>	Haematopoietic cytopenias (SMQ) (Broad)
<input type="checkbox"/>	Haematopoietic cytopenias (SMQ) (Broad)
<input type="checkbox"/>	Cytopenia and haematopoietic disorders affecting more than one type of blood cell (SMQ) (Broad)
<input type="checkbox"/>	Erythropenia (SMQ) (Broad)
<input type="checkbox"/>	Leukopenia (SMQ) (Broad)
<input type="checkbox"/>	Thrombocytopenia (SMQ) (Broad)

SMQs - Running an analysis

An example...

SMQ Level 1	Metrics	PRR (-)	PRR	PRR (+)	CHI^2	# Cases
Acute pancreatitis (SMQ) (Broad)		1.20	1.25	1.31	116.4710	2,141
Acute pancreatitis (SMQ) (Narrow)		0.75	0.87	1.02	2.8035	159
Acute renal failure (SMQ) (Broad)		1.25	1.34	1.44	68.6131	790
Acute renal failure (SMQ) (Narrow)		1.28	1.40	1.53	56.8554	511
Agranulocytosis (SMQ) (Broad)		1.31	1.39	1.49	106.9384	959
Agranulocytosis (SMQ) (Narrow)		1.28	1.40	1.52	60.9715	552
Anaphylactic reaction (SMQ) (Broad)		1.04	1.07	1.11	18.7577	3,313
Anaphylactic reaction (SMQ) (Narrow)		0.83	0.93	1.03	2.0766	355
Angioedema (SMQ) (Broad)		0.97	1.02	1.08	0.7897	1,304
Angioedema (SMQ) (Narrow)		1.01	1.09	1.18	4.8970	632
Asthma/bronchospasm (SMQ) (Broad)		1.06	1.18	1.31	9.3958	357
Asthma/bronchospasm (SMQ) (Narrow)		0.86	1.01	1.19	0.0249	154
Cholestasis and jaundice of hepatic origin (SMQ) (Broad)		1.35	1.50	1.67	53.7653	332
Congenital, familial and genetic disorders (SMQ) (Broad)		0.47	0.58	0.72	25.9135	88
Congenital, familial, neonatal and genetic disorders of the liver (SMQ) (Broad)		0.09	0.35	1.39	2.4356	2
Convulsions (SMQ) (Broad)		0.72	0.79	0.87	24.4710	444
Convulsions (SMQ) (Narrow)		0.71	0.78	0.86	25.9154	436
Cytopenia and haematopoietic disorders affecting more than one type of blood cell (SMQ) (Broad)		0.88	0.99	1.12	0.0090	253
Cytopenia and haematopoietic disorders affecting more than one type of blood cell (SMQ) (Narrow)		0.93	1.06	1.20	0.7260	237
Depression and suicide/self-injury (SMQ) (Broad)		1.13	1.22	1.31	26.0643	687
Depression and suicide/self-injury (SMQ) (Narrow)		1.15	1.26	1.38	22.9513	441



SMQs Implementation

- The difficulty encountered is to structure the SMQ tables as they are distributed in hierarchy tables
- A distribution of SMQs as single table hierarchy should be taken into account by the MedDRA MSSO
- Adjustment of the analytical tools to work with many to many relationships is necessary (otherwise the results are not correct)



MedDRA: The strength and the problems of multiaxiality

- SOCs, HLGTS, HLTs, PTs are connected through many to many relationships
- This approach reflects how the medical terms work
- To transform MedDRA in a hierarchy with only one to many relationships between its levels, MedDRA uses the concept of "Primary SOC"
- Analysis only at the primary SOC only can limit signal detection
- Analysis taking into account MedDRA multiaxiality must be carefully implemented as it can generate 'wrong' calculations

Adjusting PRR for many to many relationships

Reactions

Drugs

	R1	R2	(...)	Rj	(...)	Rm
D1	$a_{1,1}$	$a_{1,2}$	(...)	$a_{1,j}$	(...)	$a_{1,m}$
D2	$a_{2,1}$	$a_{1,2}$	(...)	$a_{2,j}$	(...)	$a_{2,m}$
(...)	(...)	(...)	(...)	(...)	(...)	(...)
Di	$a_{i,1}$	$a_{i,2}$	(...)	$a_{i,j}$	(...)	$a_{i,m}$
(...)	(...)	(...)	(...)	(...)	(...)	(...)
Dn	$a_{n,1}$	$a_{n,2}$	(...)	$a_{n,j}$	(...)	$a_{n,m}$

Adjusting PRR for many to many relationships (cont)

Totals for each event	Totals for each drug	Totals for the database
$a_{0,1}$	$a_{1,0}$	$a_{0,0}$
$a_{0,2}$	$a_{2,0}$	
(...)	(...)	
$a_{0,m}$	$a_{n,0}$	



Adjusting PRR for many to many relationships (cont)

$$PRR(i, j) = \frac{a_{i,j} / a_{i,0}}{(a_{0,j} - a_{i,j}) / (a_{0,0} - a_{i,0})}$$



Adjusting the PRR for many to many relationships (cont)

- Need to run four separate queries whilst using the primary SOC it is sufficient to calculate the drug x reaction table and the other tables can be calculated at the same time with subtotals
- Matches the “medical sense” of MedDRA
- Extensible to SMQs as they have many to many relationships

Example of Multiaxial Analysis

Reaction SOC	Reaction HLGT	Reaction HLT	Reaction PT	Metrics	PRR (SOC)	PRR (HLGT)	PRR (HLT)	PRR (PT)
Psychiatric disorders (Maximum)					1.38	2.20	2.20	3.47
Suicidal and self-injurious behaviours NEC (Maximum)					1.38	2.20	2.20	3.47
Suicidal and self-injurious behaviour (Maximum)					1.38	2.20	2.20	3.47
Completed suicide					1.38	2.20	2.20	3.47
Intentional self-injury					1.38	2.20	2.20	1.46
Self-injurious ideation					1.38	2.20	2.20	0.84
Self injurious behaviour					1.38	2.20	2.20	0.59
Suicidal behaviour					1.38	2.20	2.20	0.42
Suicidal ideation					1.38	2.20	2.20	1.19
Suicide attempt					1.38	2.20	2.20	1.95
Injury, poisoning and procedural complications (Maximum)					1.96	4.16	4.31	48.90
Medication errors (Maximum)					1.96	2.43	3.80	48.90
Overdoses (Maximum)					1.96	2.43	3.80	6.33
Accidental overdose					1.96	2.43	3.80	4.24
Intentional overdose					1.96	2.43	3.80	3.79
Multiple drug overdose					1.96	2.43	3.80	4.70
Multiple drug overdose accidental					1.96	2.43	3.80	4.42
Multiple drug overdose intentional					1.96	2.43	3.80	6.33
Overdose					1.96	2.43	3.80	3.42

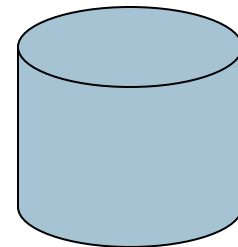
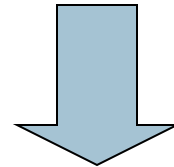
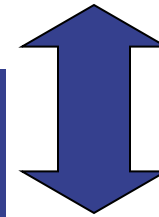
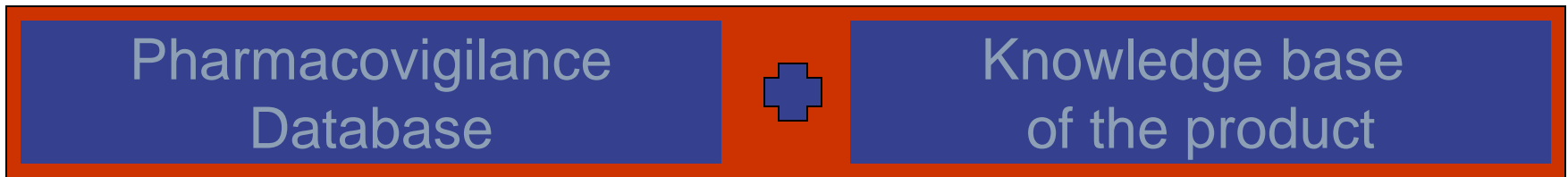


MedDRA and EU Risk Management Plans

- Interface between EudraVigilance and the EU risk Management Plan (EU-RMP)
- MedDRA used to code:
 - Indications
 - Risks (Potential and Identified)
 - Interactions (Potential and Identified)



EU-RMP and EudraVigilance a Knowledge Base for Medicinal Products



**Interface between EU-RMP
and EudraVigilance**



MedDRA and EU Risk Management Plans

To query the pharmacovigilance database, the information from the safety specification section has to be structured based on standard terminology

- Risks = MedDRA
- Indications = MedDRA
- Products = EudraVigilance Medicinal Product Dictionary (EVMPD)
- Substances = EVMPD



Multiple levels of MedDRA

- To simplify the coding of the risks and indications with MedDRA, terms from the following levels of the MedDRA hierarchy can be chosen:
 - SMQs (Standard MedDRA Queries)
 - SOCs (System Organ Classes)
 - HLGTs (High Level Group Terms)
 - HLTs (High Level Terms)
 - PTs (Preferred Terms)



Indications and Risks coded in MedDRA

- It is possible to code only the high level indication of the medicinal product with exception of:
 - Line of treatment
 - Concomitant conditions/treatments/therapies
- Risks should be integrated with:
 - Concomitant conditions/treatments/therapies



Serious Events

- In the EudraVigilance Data Analysis System it is possible to discriminate events that should always be considered serious
- Based on CIOMS V serious events list
- These events should always be monitored independently of quantitative signal detection calculations



Serious Events

- The EudraVigilance Expert Working Group (EV-EWG) in liaison with the MedDRA MSSO has reviewed the initial CIOMS V list
- The CHMP PhVWP has been invited to comment on the revised draft list as prepared by the EV-EWG
- The EV-EWG will submit a request to the MedDRA Management Board for the maintenance of the 'Serious Events' list
 - PT level grouped by Primary SOC including MedDRA codes



Paediatric Terms List

- The EV-EWG in liaison with the MedDRA MSSO is in a process of drafting a paediatric specific adverse event list
- This relates specifically to the requirements laid down in the Guideline on the Conduct of Pharmacovigilance for Medicines used by the Paediatric Population (EMA/CHMP/235910/05 Rev 1; June 2006)
- Requirement to monitor specifically detect paediatric ADRs e.g. those related to growth, development, sexual maturation



Paediatric Terms List

- The Paediatrics Working Group at the EMEA has been invited to comment on the draft list
- The EV-EWG will submit a request to the MedDRA Management Board for the maintenance of the 'Paediatric Terms' list



Questions

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