
Standardised MedDRA® Queries: Experience at Roche

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Barcelona 6 March



Learning Objectives



- Understand what SMQs are.
- Understand the basic structures of SMQs.
- Provide some examples of how SMQs have been used at Roche Ltd.

What Are Standardised MedDRA Queries (SMQs)?



- SMQs are:
 - Groupings of MedDRA terms.
 - Usually at the Preferred Term (PT) level.
 - Relate to a defined medical condition or area of interest.
 - Intended to aid in the identification and retrieval of potentially relevant individual case safety reports.

SMQ Design Concepts



- Three (3) Main Designs
 - Narrow and Broad.
 - Algorithm.
 - Hierarchy.

Narrow and Broad Searches



- Narrow search intended to identify cases that are highly likely to represent condition of interest, and is "specific".
- Broad search intended to identify cases that report signs/symptoms potentially related to the condition of interest, and is "sensitive".

Narrow vs. Broad Example



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

1. Braunwald E, Fauci A, Kasper D. Harrison's Principles of Internal Medicine. 15th Edition, 2001 pp 285-9
2. Weatherall D, Ledingham J and Warrell D. Oxford Textbook of Medicine. Third edition, 1996; volume 2 pp 1541-44

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 verbatims to terms of an older terminology or other coding conventions).

Narrow Terms
Blood lactic acid increased
Hyperlactacidaemia
Lactic acidosis

Broad Terms
Acid base balance abnormal
Acidosis
Anion gap abnormal
Anion gap increased
Blood bicarbonate abnormal
Blood bicarbonate decreased
Blood gases abnormal
Blood lactic acid abnormal
Blood pH abnormal
Blood pH decreased
Coma acidotic
Kussmaul respiration
Metabolic acidosis
PCO2 abnormal
PCO2 decreased
Urine lactic acid increased

Algorithm Searches



- Designed to identify cases based on the presence of combinations of event terms suggestive of the condition of interest.

Algorithm Example

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

(Narrow search terms = Category A)

Algorithm Example (continued)

Category B - Upper airway/Respiratory	Category C - Angioedema/ Urticaria, etc.	Category D - Cardiovascular/Hypotension
<i>Acute respiratory Failure</i>	<i>Allergic oedema</i>	<i>Blood pressure decreased</i>
<i>Asthma</i>	<i>Angioedema</i>	<i>Blood pressure diastolic decreased</i>
<i>Bronchial oedema</i>	<i>Erythema</i>	<i>Blood pressure systolic decreased</i>

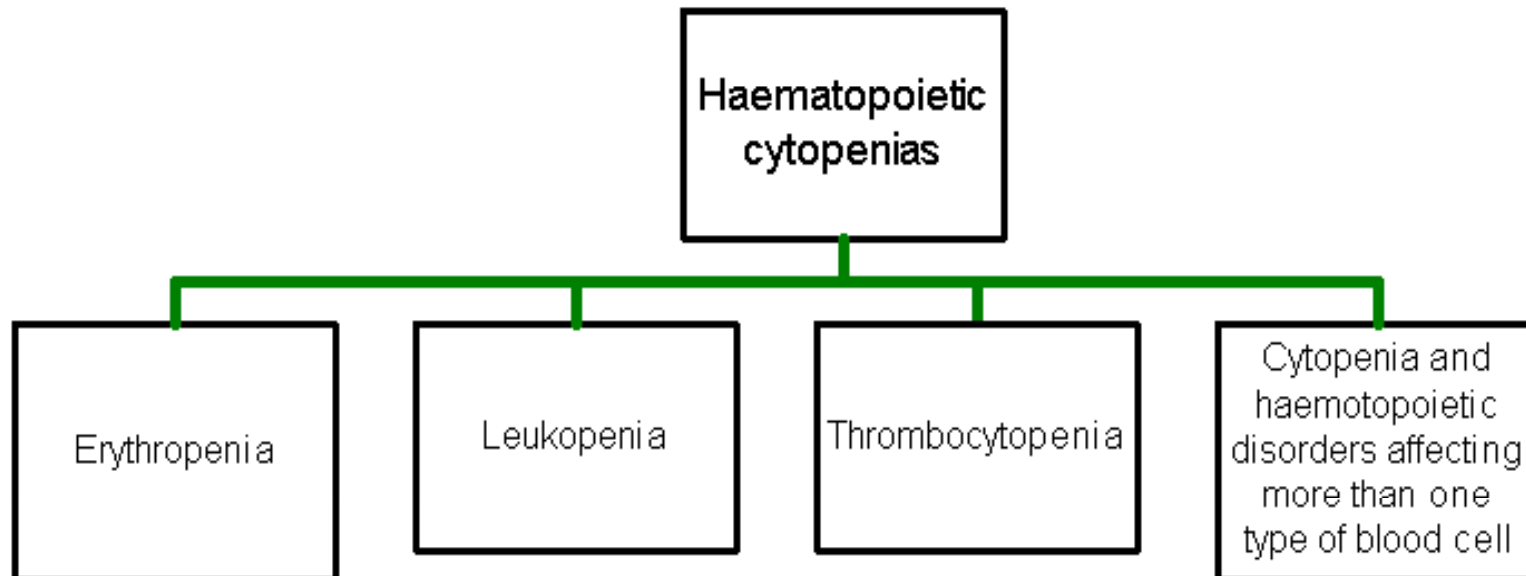
- Case = A (Narrow terms)
- Or Term From Category B and term From Category C
- Or Term From either Category B or Category C plus Term From Category D

Hierarchy Searches



- Hierarchy *SMQs* are a series of queries that have a hierarchical relationship to each other.
- They consist of a series of fairly specific, subordinate *SMQs* that can be combined to create a superordinate, more inclusive *SMQ*.

Hierarchy Example





Why Were SMCs Developed?

- There was a recognized need in the MedDRA user community for standard tools to assist in identification and retrieval of safety data.
- MedDRA Special Search Categories (SSCs) did not adequately address this need.
- The MedDRA MSO had started development of MedDRA Analytical Groupings (MAGs).
- Council For International Organization of Medical Sciences (CIOMS) independently started initiative to develop Standardised Search Queries (SSQs).
- CIOMS and the MedDRA MSO agreed to combine their efforts and develop what are now known as SMCs.

Why Were SMQs Developed ? (continued)

- SMQs cover medical concepts including PTs from different SOCs.
- This ensures consistency in searches at different times or by different parties
- Examples:
 - Torsade de Pointes/QT prolongation
 - Acute pancreatitis

Approximately 55 SMQs are currently in production

How Are SMDs Developed?



- Development conducted under the auspices of the CIOMS Working Group For SMDs.
- Working Group composed of senior scientists from:
 - Several drug regulatory agencies,
 - Several international pharmaceutical companies,
 - MedDRA MISO,
 - Japanese Maintenance Organization (JMO),
 - CIOMS secretariat,
 - IFPMA,
 - Others.

How Are SMPs Developed? (Continued)

- Topics For SMPs proposed by the MSO, other Working Group members, and MedDRA users.
- Topics assigned to development teams.
- Development teams then:
 - Prepare a draft SMP,
 - Test the draft SMP generally in one regulatory and one company safety database,
 - Present results to Full Working Group.
- Iterative process.
- Working Group recommends the SMP for production.
- MSO releases SMP for use to MedDRA user community with next reasonable version.
- Process follows ICH procedure.

Are There Limitations to SMDs?

- SMDs may not always be comprehensive, error-free, or universally acceptable.
- Need to use SMD from same version of MedDRA that the database being searched is encoded to.
- SMDs identify relevant cases for further review and assessment. They lead us to the answer, but are not the answer itself!

Why Are SMDs Important?

- If an SMD exists for a topic, there is no need to create a search strategy from scratch since a complete search strategy already exists (although it might be appropriate to "fine tune" some broad searches).
- Some degree of regulatory expectation that SMDs will be used for data retrieval.
 - Volume 9A recommends using SMDs for PSURs and signal detection.
 - ICH-endorsed MedDRA Points to Consider on Data Retrieval and Presentation recommend using SMDs.

EMEA Case Study★



- Although not designed primarily for detection of drug safety issues, is it likely that the SMDs will have advantages over other levels of MedDRA in early signaling of new safety problems?

★ Slattery, J. Standardised MedDRA Queries: A Case Study of the Potential For Signal Detection. March 2007.

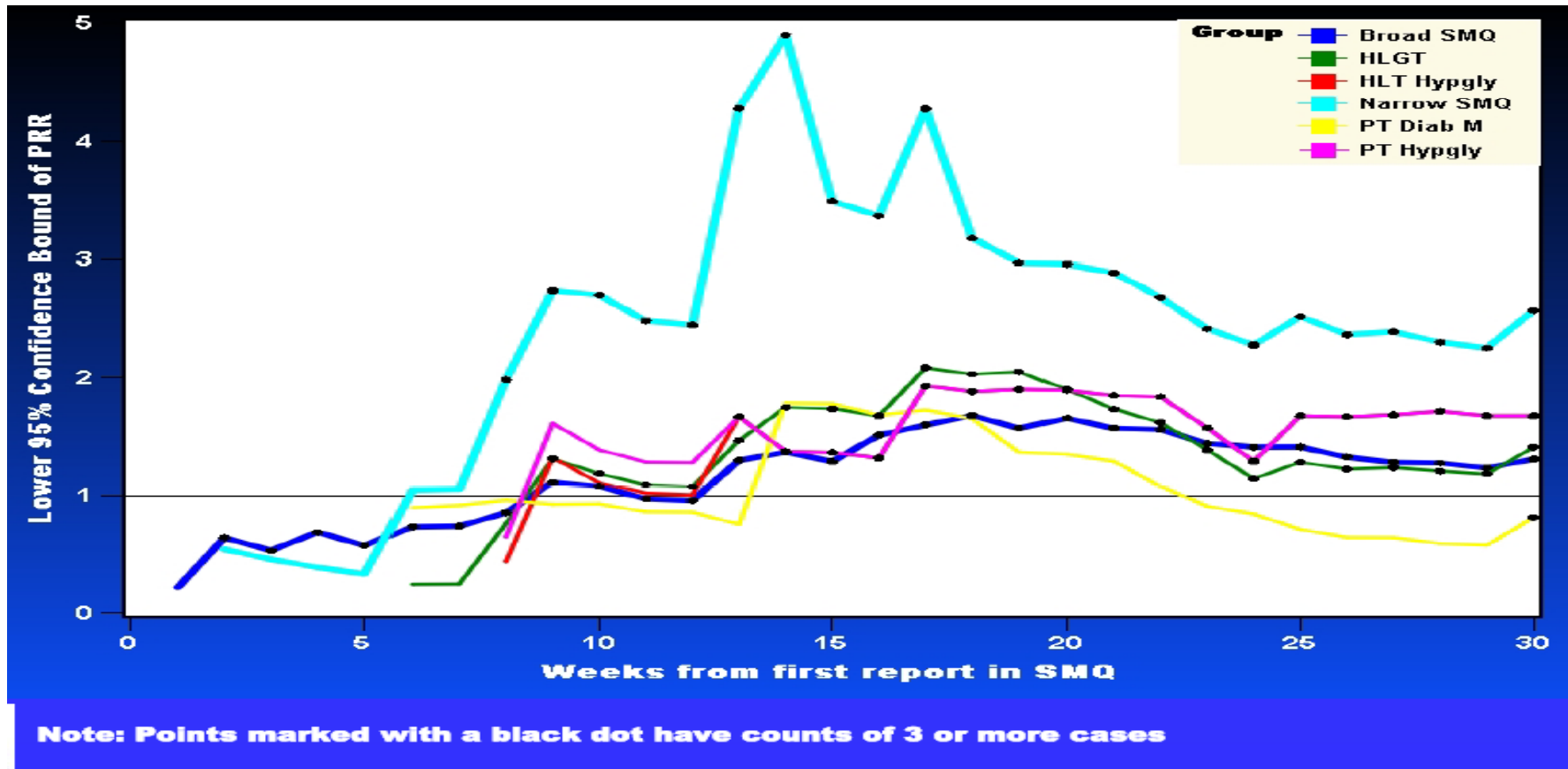


EMEA Case Study* (Continued)

- SMD hyperglycaemia / new onset diabetes mellitus
- An antipsychotic with known association
- Calculate PRR as function of time
- Compare PRR from SMD with PRR from single PTs and other levels of MedDRA hierarchy

* Slattery, J. Standardised MedDRA Queries: A Case Study of the Potential for Signal Detection. March 2007.

EMEA Case Study* (Continued)



*Slattery, J. Standardised MedDRA Queries: A Case Study of the Potential For Signal Detection. March 2007.

Use within Roche



- With each MedDRA version/update received Roche feeds the SMPs automatically into the Query Tool
- For data retrieval the PTs are copied by the data managers to the SAS retrieval tool



How Are SMDs Used At Roche?

- Signal detection in clinical trials
- To identify cases from Roche's post-marketing safety database:
 - For inclusion in PSURs,
 - For inclusion in cumulative case reviews,
 - For answering Regulatory requests.

For Clinical Trial Safety Tables



- Run SAS program containing SMP terms against clinical trial database.
- Prepare such tables on a *regular* basis for specific products and events of interest.
- Prepare such tables on an *ad hoc* basis for specific products and issues.

For Post-marketing Safety Database



- Several SMDs used regularly or semi-regularly include:
 - Lactic acidosis
 - Torsade de pointes/QT prolongation
 - Hepatic Failure, Fibrosis and cirrhosis and other liver damage-related conditions
 - Severe cutaneous adverse reactions
 - Lack of efficacy/effect (For PSURs)

Searching the Post-marketing Safety Database With SMDs



- Searches are conducted against the safety database (ADVENT).
- ADVENT is a customized Oracle application.
- ADVENT was developed before SMDs existed and was not set up to run SMDs as is in MedDRA.
- Users can request analysis using an SMD directly in the query tool.
- Searches for terms for which an SMD exists are endorsed to be searched per SMD criteria, customized changes are accepted

Go to Drug Safety Online Portal and select "MedDRA Browser"



Drug Safety Online Portal - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd

File Edit View Favorites Tools Help

Address <http://drugsafetyquerymanagement.bas.roche.com:18140/dsoportal/> Go Links

drugsafetyonline >>> Login Contact us Query Request Form **MedDRA Browser** Help

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Query Management >
Periodic Reports >
SIGMA

Advent 4.2

welcome

The Drug Safety Online Portal is the place where you can find all the tools you need to do your job in a one-stop-shop...

Select "Basket Directory"



Meddra Browser - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd

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Back Search Favorites

Address <http://beadvp1.kau.roche.com:18140/meddra2/> Go Links

MedDRA brows

MedDRA :: v10.1
Language :: ENGLISH
Current Version
You are not logged in.
[Online User Guide](#)

Search

Options

Browse MedDRA **Basket Directory** Search Results

- ☐ soc Blood and lymphatic system disorders
- ☐ soc Cardiac disorders
- ☐ soc Congenital, familial and genetic disorders
- ☐ soc Ear and labyrinth disorders
- ☐ soc Endocrine disorders
- ☐ soc Eye disorders
- ☐ soc Gastrointestinal disorders
- ☐ soc General disorders and administration site conditions
- ☐ soc Hepatobiliary disorders
- ☐ soc Immune system disorders
- ☐ soc Infections and infestations
- ☐ soc Injury, poisoning and procedural complications
- ☐ soc Investigations
- ☐ soc Metabolism and nutrition disorders
- ☐ soc Musculoskeletal and connective tissue disorders
- ☐ soc Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- ☐ soc Nervous system disorders
- ☐ soc Pregnancy, puerperium and perinatal conditions
- ☐ soc Psychiatric disorders
- ☐ soc Renal and urinary disorders

Basket items

Select "SMQ"



Meddra Browser - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd

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Address <http://beaadvp1.kau.roche.com:18140/meddra2/>

MedDRA browser

Neoplasm Malignant - Heamatological/lymphatic cancers (Tocilizumab)
-08 Aug 2007

MedDRA :: v10.1
Language :: ENGLISH
Current Version
You are not logged in.
[Online User Guide](#)

Browse MedDRA Basket Directory Search Results

Reference No :: 2333
Project Name :: Tocilizumab [more...](#)

All SMQ AEGT

- Neoplasm Malignant - Heamatological/lymphatic cancers (Tocilizumab) -08 Aug 2007
- Pruritus (Tocizumab) -10 Dec 2007
- Rash (Tocilizumab) -10 Dec 2007
- Stroke Tocilizumab (Tocilizumab) -11 Dec 2007
- Urticaria (Tocilizumab) -10 Dec 2007
- Accidents and injuries (SMQ)
- accutane_psychiatric_quarterly_aggression_basket (SRMS_AQP) -29 May 2007
- accutane_psychiatric_quarterly_depression_basket (SRMS_AQP) -29 May 2007
- accutane_psychiatric_quarterly_psych_basket (SRMS_AQP) -29 May 2007
- accutane_psychiatric_quarterly_suicide_basket (SRMS_AQP) -29 May 2007
- Acute central respiratory depression (SMQ)
- Acute pancreatitis (SMQ)
- Acute renal failure (SMQ)
- Adverse pregnancy outcome/reproductive toxicity (incl neonatal disorders) (SMQ)
- AEGT_Atherosclerosis (RA Harmonization) -29 Oct 2007
- AEGT_Autoimmune_Haemolytic_Anaemia_ALL (MabThera) -21 Jan 2008
- AEGT_Cardiac (Revised) (RA Harmonization) -22 Jan 2008

Options

Search

Basket items

Moving the cursor to the SMQ of interest the description will be visible



MedDRA browser
Torsade de pointes/QT prolongation (SMQ)

MedDRA :: v10.1
Language :: ENGLISH
Current Version
You are not logged in.
[Online User Guide](#)

Browse MedDRA Basket Directory Search Results

All SMQ AEGT

Reference No (MedDRA Code) :: 20000001
Description :: [more...](#)

- Severe cutaneous adverse reactions (SMQ)
- Shock (SMQ)
- Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)
- Site unspecified biliary disorders (SMQ)
- Skin premalignant disorders (SMQ)
- Suicide/self-injury (SMQ)
- Supraventricular tachyarrhythmias (SMQ)
- Systemic lupus erythematosus (SMQ)
- Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)
- Taste and smell disorders (SMQ)
- Thrombocytopenia (SMQ)
- Thrombophlebitis (SMQ)
- Torsade de pointes, shock-associated conditions (SMQ)
- Torsade de pointes/QT prolongation (SMQ)**

Reference No (MedDRA Code) :: 20000001
Description ::
Torsade de pointes (TdP) is a form of rapid ventricular tachycardia which can be hereditary or acquired. In some acquired forms, there appear to be genetic predispositions related to sub-clinical potassium channel abnormalities. On electrocardiogram (ECG), TdP is associated with or preceded by polymorphic QRS complexes; other ECG changes include prolonged QT or QTc interval, prominent U waves, T wave alternans or bizarre T wave aberrations, and long-short sequences. TdP can resolve spontaneously, but acquired forms often recur until the underlying cause is corrected, and can progress to ventricular fibrillation. Clinical manifestations include palpitations, dizziness, syncope, and, rarely, sudden death.

Go back Drug Safety Online Portal and select "Query Request Form"



Drug Safety Online Portal - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd

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Advent 4.2

The Drug Safety Online Portal is the place where you can find all the tools you need to do your job in a one-stop-shop...

welcome

After "save" enter criteria for search and output, submit with "next"



Signal Detection/Issue Work Ups/ASIMES - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd

QTT
Query Tracking Tool

Roche

11-Feb-2008 Home | QRF | Query List | Search | Quick Search | Help ASTRID HERPERS

Query Tracking Tool

Signal Detection/Issue Work Ups/ASIMES

Fields marked with a # are mandatory

Description Of Query	
# Your question:	Torsade de Pointes SMQ narrow and broad
Adverse Event(s):	CIOMS report and Excel sheet

Next

Review the search and "submit"



Query Preview - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd
Provisional Query Number: 12002

Requester Details

First Name:	ASTRID
Last Name:	HERPERS
Tel No:	86317
Fax No:	
Email Address:	HERPERSA@EMEA.ROCHE.COM
Country:	SWITZERLAND
Organisation Name:	BASEL
Organisation Type:	Roche Internal

Query Origin

Source Country of Request:	SWITZERLAND
Reporter Type:	Roche Internal

Drug Details

All Drugs:	No
Preferred Drug Name:	5HT2B RECEPTOR ANTAGONIST
Generic Drug Name:	
Route:	
Formulation:	
Indication:	
Dose:	
Other Roche Drugs:	

Response Timelines

Original Due Date:	25-Feb-2008
Urgency:	

Query Details

Query Type:	Signal Detection/Issue Work-Ups/ASIMES
Followup Number:	
Query Title:	

Attachments

Cumulative Details

Cumulative Period:	Yes
Interval:	

Query Description

Nature of question:	PER SMQ TORSADA DES POINTES
Adverse Event(s):	CIOMS

Exclusion of PTs From an SMD Search

- Sometimes you may want to exclude specific PTs from an SMD-based search or add PTs that might have been specifically for your drug.
- Example = α -blockers and *torsade de pointes*:
 - Broad search of Torsade de pointes/QT prolongation SMD includes syncope-related PTs
 - α -blockers are associated with syncope directly related to hemodynamic effect of drug NOT related to *torsade de pointes*
 - Inclusion of syncope-related PTs creates a lot of "noise" that makes interpretation of the case series difficult.
- Sometimes you may want to include specific PTs from an SMD-based search or add PTs that might be specifically relevant for your drug (e.g. due to off label use).

Define this in the query



Signal Detection/Issue Work Ups/ASIMes - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd

QTT
Query Tracking Tool

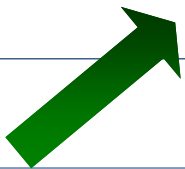
11-Feb-2008 Home | QRF | Query List | Search | Quick Search | Help ASTRID HERPERS

Signal Detection/Issue Work Ups/ASIMes

Fields marked with a # are mandatory

Description Of Query	
# Your question:	<input type="text" value="PER SMQ TORSIDE DES POINTES"/> <input type="text" value="exclude PT syncope"/> <input type="text" value="include PT XYZ"/>
Adverse Event(s):	<input type="text" value="CIOMS reports"/>

Next



Algorithm 1MPS



- Not something that is automatically done.
- Requires some programming and technical support.
- It needs to be announced in the query tool.
- Data management will contact you and discuss the requested output.
- Data delivery might include different outputs.

The system will send you the requested dataset



Pharmaceuticals

Query Answer - Microsoft Internet Explorer provided by F. Hoffmann-La Roche Ltd

Address: http://beaadvp1.kau.roche.com:18140/qtt/QueryResponse.do?qno=12718&key=3e44a55042057e75e1ed5595bc0fe3f1

QTT Query Tracking Tool

11-Feb-2008 Home | QRF | Query List | Search | Quick Search | Help ASTRID HERPERS

Query Answer

Query Answer Information

Query No. QTT012718

Drug Name: ROFERON-A
Query Type: Signal Detection/Issue Work-Ups/ASIMES

Response Document Name	Date Deposited	Deposited By	
EMAIL WITH DATA	30-Jan-2008	SCHWARR1	

QRF

Requester Details


First Name: ASTRID
Last Name: HERPERS
Tel No: 86317
Fax No:
Email Address: HERPERSA@EMEA.ROCHE.COM
Country: SWITZERLAND
Organisation Name: BASEL
Organisation Type: Roche Internal

Query Origin

Source Country of Request: SWITZERLAND
Reporter Type: Roche Internal

Drug Details

All Drugs: No
Preferred Drug Name: ROFERON-A
Generic Drug Name:
Route:
Formulation:
Indication:
Dose:



How Do You Proceed From Here?



- The system will send you the requested dataset within the requested timelines and agreed output (CIOMS reports, line listing, data sheets, PSUR tables)
- Case analysis will be recorded in a safety report

After Excluding Syncope-Related PTs From SMQ



DRUG SAFETY REPORT N°1023704.

Date: 27 November 2007

Author(s)	Astrid Herpers
Reviewer(s)	Martin Wermelinger, Malte Schutz, Miklos Salgo, Lucille Donatucci
Department	Pharma Development Medical Science, Safety Risk Management F. Hoffmann-La Roche Ltd, 4070 Basel, Switzerland
Theme(s)	2008
Roche-number(s)/ Drug Preferred name	RO0318959 / Invirase / Fortovase
SOC(s)/ADR(s): (preferred term)	QT- prolongation as per MedDRA SMQ Torsade de pointes; QT prolongation (wide search)
Cut-off date /Requester	October 1, 2006 - October 31, 2007 / Continued Monitoring

When should SMDs be Used?

- Any cumulative case series review.
 - To respond to a regulatory request.
 - For inclusion in a CTD post-marketing safety summary.
 - For use as part of an internal review (after signal detection).
 - To support CDS/labeling revisions.
- For use in PSURs.

How Should SMD Terms Be Included?

- For "narrow" searches, include ALL PTs that are part of the narrow portion of the SMD.
- For "broad" searches, should include all PTs that are part of the broad search if feasible.
 - It may be appropriate to modify the broad search if it is considered appropriate to do so, such as if the broad search includes particularly non-specific PTs or other PTs that might be expected to identify a large number of irrelevant cases.
 - If the broad search is modified, a written justification should be provided as part of the methodology of the case review.
- For algorithm searches, include ALL PTs that are part of the algorithm.

Summary of Presentation

- **SMQs are groupings of MedDRA terms used for data retrieval and analysis.**
- **SMQs cover medical concepts including PTs from different SOCs.**
- **"Types" of SMQs include Narrow and Broad, Algorithm, and Hierarchy.**
- **SMQs are used at Roche to generate safety tables from clinical study databases and to identify cases from the post-marketing safety database.**

Acknowledgements

- Greg Gribko, Pfizer
- Patty Mozzicato, M/SO



Thank you!



Pharmaceuticals

