Welcome to the European MedDRA Users Group Webinar on ‘Safety Analysis’

The session will be chaired by Ian Slack
Liz Thomas from the MSSO will provide technical support

Asking Questions

Submitting questions during the presentation:
• Pop out the control panel located in the upper right of your screen
• Type your question into the question box
• When finished typing your question click the ‘Send’ button
• Questions will be addressed at the end of the webinar.
• Due to time constraints, we may not be able to answer all questions submitted.

Frequently Asked Questions

• Will I be able to get a copy of these slides?
  
  YES

• Is this Webinar being recorded so that I or others can view it at a later time?
  
  YES
Welcome from the European Industry MedDRA Users Group Steering Committee

Morell David  Barry Hammond  Jane Knight  Martin Menke  Anne Gyllensvaerd

Ian Slack  Hilary Vass  Carol-Ann Wilson  Christina Winter  Claudia Lehmann

Agenda

- Basics of data retrieval
  - Christina Winter, GSK
- Pharmacovigilance - regulatory perspective
  - Kendal Harrison, MHRA
- Clinical Safety and Pharmacovigilance - Industry perspective
  - Dr. David Lewis, Novartis
- Q&A Session
Basics of data retrieval

Christina Winter, GSK

Pharmacovigilance - regulatory perspective

Kendal Harrison, MHRA
Clinical Safety and Pharmacovigilance - Industry perspective

Dr. David J Lewis,
Global Head of Pharmacovigilance
Novartis Global Drug Development

Q&A Session
THANKS
CONTENTS

- Quality of data
- Impact of data conversion, up-versioning techniques, database specific characteristics
- Familiarity with MedDRA
  - Grouping terms (HLGT, HLT)
  - Granularity - variable within MedDRA
  - Primary and Secondary SOCs
- Application of SMQs
- Customised Queries
- Process of conducting a data query
- Signal detection
Many helpful hints in

MedDRA® DATA RETRIEVAL AND PRESENTATION: POINTS TO CONSIDER
ICH-Endorsed Guide for MedDRA Users on Data Output
Release 3.14
Based on MedDRA Version 20.1
1 September 2017

Quality of data

- Reliant on accurate reporting and consistent coding
- Similar verbatims may be coded to different PTs
  - All verbatims below may reflect "headache"
    - Head pressure – PT Head discomfort*
    - Tightening band around head – PT Tension headache*
    - Pressure behind eyes – no term for "behind". Location is in head, so similar to "head pressure".
    - If coder selects LLT Sensation of pressure in eye – PT Ocular discomfort, SOC Eye disorders
    - Throbbing temples – LLT Head throbbing – PT Headache*

*SOC Nervous system disorders
IMPACT OF OTHER FACTORS

- Data conversion – how was this done?
  - Use coded terms - retain granularity of old terminology and coding conventions
  - Recode – consistent with rest of data

- MedDRA versioning
  - Very few organisations recode the entire post marketing database
    - Old reports frozen with archaic terms
  - Clinical trial versioning practices vary

- Database specific characteristics
  - May use tick boxes and MedDRA codes. Examples:
    - Pregnancy Y/N,
    - Overdose Y/N (not coded as reporter did not state 'overdose' but knowledgeable coder has flagged case)

FAMILIARITY WITH MedDRA

- Grouping terms – HLTs, HLGTs
  - May be incomplete if used alone.
    - Remember SOC Investigations, SOC Social circumstances, and SOC Surgical and medical procedures are not multi-axial

- granularity – varies.
  - SOC Neoplasms very granular and single PTs cannot be used for signal detection.
    - 41 PTs in HLT Breast and nipple neoplasms malignant
    - 3 PTs in HLT Breast neoplasms unspecified malignancy

- Multi-axiality
  - Safety databases may not use secondary SOCs
  - Clinical studies – most use primary SOC output and if appropriate, secondary SOC output.
APPLICATION OF STANDARDISED MedDRA QUERIES (SMQs)

Check ‘SMQ Introductory guide’

APPLICATION OF SMQs (2)

- If SMQ available, does SMQ meet requirements?
- If yes,
  - entire SMQ or sub SMQ?
  - ‘Narrow’ or ‘narrow and broad’ PTs?
- SMQ ‘Introductory guide’ may suggest modifications for a complete search
  - e.g. Lack of efficacy/effect SMQ
APPLICATION OF SMQS (3)

- Combine SMQs?
  - E.g. For cardiovascular events, consider
    - Cardiac arrhythmias SMQ,
    - Cardiac failure SMQ,
    - Cardiomyopathy SMQ
    - Ischaemic heart disease SMQ.
  - If CV event is secondary to shock, consider sub-SMQs:
    - Shock-associated circulatory or cardiac conditions (excl torsade de pointes) SMQ
    - Torsade de pointes, shock-associated conditions SMQ
    Both sub-SMQs are in Shock SMQ

- SMQs applicable to both post-marketing and clinical study data.

CUSTOMISED QUERIES

- If no suitable SMQ is available
  - Modify SMQ to create Modified MedDRA Query Based on an SMQ
  - Create Customised query de novo.
  - Update / match older Customised queries to the MedDRA version of the dataset

- Tip: Review cumulative list of all PTs reported (for the product) to ensure no vital PTs have been omitted
  - Especially if no SMQ for topic of interest
  - Using newly created Customised Query
PROCESS OF CONDUCTING A DATA QUERY

- What is the purpose of the query?
- Decide how wide the search needs to be
  - Grouping terms (HLT, HLGT)
  - SMQ or sub-SMQ if available
    - Narrow only or Narrow and Broad PTs
  - Customised queries
- Review output
  - Too much noise? Refine query
- Document the search criteria (**including MedDRA version number**)
- Review data retrieved
  - Association is not causation

SIGNAL DETECTION

- MedDRA coded data is only one source
- Disproportionality of drug-event combinations filter events for large data sets
  - Various statistical/datamining methods available for signal detection: e.g. PRR, EBGM (out of scope for this talk)
- May use
  - PT(s), any hierarchical grouping term (HLT, HLGT) or even SOC
  - Customised groups of PTs (terms of interest)
  - SMQs:
    - gather terms for signal score
    - may be too broad (dilute signal)
PLEASE REMEMBER

Thank you
MedDRA and pharmacovigilance: A regulatory perspective

Kendal Harrison 4th October 2017
Pharmacovigilance Information Delivery Manager and Coordinator

Contents

- How the MHRA uses MedDRA
- ICSR submission types
- Patient friendly MedDRA pilot
- Interactive Drug Analysis Profiles (iDAPs)
- Signal Detection
- Standardised MedDRA Queries (SMQs)
How the MHRA uses MedDRA

- MedDRA up versions:
  - Database dictionary updated
  - Web-form for reporting updated
- Historical cases are not recoded
- We code diagnosis as well as symptoms
- MedDRA points to consider used
- Consistency is key

ICSR submissions

- Website, app, paper, phone
- Clinical system integration
  - SNOMED CT mapping to MedDRA
- Marketing Authorisation Holders (MAHs)
- Coding errors (MHRA and MAHs) are reclassified
Patient friendly MedDRA

- Medical review of the data to identify terms frequently used and commonly understood
  - Signs and symptoms
  - Natural word order
- 1,526 patient friendly terms out of >77k MedDRA
- Anonymised YC data will be sent to the researchers for review
  - Are they selecting the terms more often or are they still using the free text?
Spontaneous reports are published as iDAPs.
Signal Detection and MedDRA

• MHRA signal detection
  – Algorithm includes:
    • Disproportionality
    • Alert terms (aligning with Important Medical Events, IME, list)
    • CIOMS seriousness
  – Reviewed by PT and Standardised MedDRA Queries (SMQ) (narrow and broad)
  – Can drill into related terms, SOC etc

SMQs in signal detection

• IMI Protect
  – SMQs had no overall benefit compared to PTs
• Most useful for data retrieval
  – Signal review
  – Publications e.g. Drug Safety Updates
  – Ad hoc queries (Patient, healthcare professional etc)
Thank you for listening!

Kendal Harrison
Pharmacovigilance Information Delivery Manager and Coordinator
Vigilance, Intelligence and Research Group
VRMM, MHRA
Email: kendal.harrison@mhra.gov.uk
Outline of presentation

Current challenges:

1. Investigator Brochure: developing & updating labeling
   - Presentation of data in the Reference Safety Information (RSI)
   - MedDRA term selection
   - Grouping of terms: medical concepts

2. Signal detection and product complaints
   - Use of SOC 27 Product Issues

A new challenge – or an opportunity?

3. MedDRA and social media (after Web-RADR)
Label in the Investigator Brochure: Questions raised to regulators

1. What is the fundamental concern that needs to be addressed?
   - **Reference Safety Information (RSI) serves three purposes:**
     1. Basis for expectedness determination impacting expedited reporting
     2. Basis for expectedness in the DSUR impacting data presentation
     3. Information for investigator (table with seriousness, frequency etc.)

2. What is the aim of the guidance provided in the draft Q&As?
   [Objective is to] simplify methods for generation and presentation of RSI by Sponsors [&] to remove inconsistencies which limit value of expedited reports [&] improve supervision of safety of patients & subjects in trials.

3. How does the added complexity/additional guidance contribute to optimising the safety of study subjects?

Guidance for Sponsors of trials

**CT-3 (2011) Section 7.2.3.2 Reference Safety Information**

- “...IB should contain a clearly-identified [RSI] section..."

- Sponsor should present adverse reactions based on facts (evidence) or arguments suggesting a causal relationship

- Novartis, as Sponsor, must make clear:
  - **Seriousness** of the adverse reactions (serious or non-serious)
  - **Frequency** of occurrence (numeric value as well as category)
  - **Nature** of the reaction e.g. ‘rash’ if serious should be qualified
    - Generalised or localised? Add descriptive term ‘vasculitic’, ‘pustular’, etc.
    - Diarrhoea, usually non-serious, but up-graded if >3 days, dehydration, etc.
  - **Severity** or grade of the **serious** reactions
# How does this look in the Investigator Brochure?

## Section 6.2 Adverse Reactions

[Adopted from CTFG 2013_12 Q&A]

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Nature</th>
<th>Serious (Grade 3)</th>
<th>Severity (Grade 4 / 5)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>nn (%)</td>
<td>nn (%)</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>Count rarely falls &lt;1000/mm³</td>
<td>X</td>
<td>nn (%)</td>
<td>nn (%)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Rapid recovery to normal range after stopping study drug.</td>
<td>X</td>
<td>nn (%)</td>
<td>nn (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia</td>
<td>nn (%)</td>
<td>nn (%)</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>nn (%)</td>
<td>nn (%)</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>nn (%)</td>
<td>nn (%)</td>
<td>Common</td>
<td></td>
</tr>
</tbody>
</table>

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### And RSI for authorized products?

**CT-3 (2011) Section 7.2.3.2 Reference Safety Information**

- Sponsor must present reactions based on evidence of causality
- Table of reactions: "events to be presented by PT"
- Straightforward at first glance, but significant complications
- RSI includes a description of nature, seriousness, severity & frequency of ARs including list of all observed cumulative adverse reactions.
- Novartis presented ARs in RSI as they appear in SmPC (often by an ‘umbrella term’ representing a medical condition)... ...examples:
  - “Treatment-emergent diabetes” umbrella term for multiple PTs related to the medical condition (clinically or as lab findings)
  - Immunosuppressants include references to increased risk of ‘Infections’
  - Chemotherapeutic agents refer to ‘Myelosuppression’ and ‘Blood dyscrasias’
  - Known teratogens refer to ‘Congenital anomalies’
- Novartis as MAH has an approved label – rejected in the RSI table!!
**Real world example [response to an Assessor]**

Table 6-1: AEs which are considered to be expected for reporting purposes

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Nature¹</th>
<th>Serious² (Grade3)</th>
<th>Severity³ (Grades 4/5)</th>
<th>Frequency⁴</th>
<th>GGE (N=151)</th>
<th>Category (based on IMP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reactions (such as injection site erythema, injection site pain, injection site pruritus, injection site swelling, injection site warmth)</td>
<td></td>
<td></td>
<td>Life Threatening</td>
<td>Fatal</td>
<td>(N) (%)</td>
<td>Very common</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction</td>
<td>Two cases required epinephrine</td>
<td>X</td>
<td></td>
<td></td>
<td>3 (1.6%)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria, Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angioedema, Pruritus, Erythema</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Medically relevant description of serious terms (if available).
² For the purpose of individual case safety reporting in the clinical trial, serious terms of adverse reactions indicated as non-serious in this table will always be considered unexpected.
³ Life-threatening or fatal.
⁴ The frequency of above listed events is based on the limited safety database (GGE01, N=151). The category is based on the following convention: very common (≥1/10), common (1/1000 < ≤1/100), uncommon (1/10,000 < ≤1/1000), rare (<1/10,000), very rare (<1/100,000).

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**SOC 27: Interface between GMP & GPVP**

- Focus on quality issues in manufacturing & interface with pharmacovigilance

  **GMP (quality issues)**
  - Quality defects (technical complaints)
  - (S)AEs with complaints

  **GPVP (patient safety)**
  - ICSRs (pharmacovigilance data)

- Examples of how to use SOC 27 within existing processes
- Suggestions for adoption of SOC 27 into GxP processes
Use case #1: Augmented batch reviews

- Current process involves case counts & filtering

<table>
<thead>
<tr>
<th>Count of Record ID</th>
<th>Classified</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>AQWA</td>
<td>Action</td>
</tr>
<tr>
<td>Argentina</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Australia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bahrain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Belgium</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>China</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Additional screening conducted applying SOC 27
  - Review trend reports to identify relevant MedDRA terms

Use #2: Medical impact of quality defects

- Current process involves:
  - Trend analyses and disproportionality statistic for signal generation
  - Define specific terms from within SOC 27 plus lack of efficacy
  - Run Novartis MedDRA query [with apologies to the MedDRA MSSO]
  - Complete medical review & impact assessment based on tailored outputs

  - **Example:**
    - Failure of childproof container = quality defect [reports in QA & Safety databases]
    - PT 10066374 Failure of child resistant mechanism for pharmaceutical product
    - Coincident & correlated with ICSRs of accidental overdose in children
    - Facilitated prevention of serious outcomes by early detection of defective (non-childproof) container
Sub-standard medicines (SSM)
Definition of poor quality or sub-standard medicines

- SSMs are manufactured to quality standards which are substantially below those of authorized, GMP-approved medicines.
- There is published evidence that the use of SSMs can result in treatment failure or even death.
- Public confidence in local, regional or national healthcare systems may be eroded following use of SSMs.
- WHO has confirmed that both branded and generic products are also subject to SSM substitution.
- SSMs have been used for the treatment of life-threatening conditions to minor ailments (e.g. headache, pruritus).

Sub-standard medicines (SSM)
Definition of poor quality or sub-standard medicines

- Sub-standard medicines include products:
  - With the correct active ingredient(s), but contaminated with other substances;
  - With the wrong active ingredient(s);
  - Without any active ingredients;
  - With insufficient or too much active ingredient; or
  - With fake packaging, including incorrect instructions for use or the wrong pack insert
Use #3: Review for SSFFC medicines

<table>
<thead>
<tr>
<th>Preferred Terms (NMQ - Narrow - Sub-standard medicines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug ineffective</td>
</tr>
<tr>
<td>Therapeutic product ineffective</td>
</tr>
<tr>
<td>Unintended pregnancy</td>
</tr>
<tr>
<td>Drug effect decreased</td>
</tr>
<tr>
<td>Drug effect delayed</td>
</tr>
<tr>
<td>Drug effect increased</td>
</tr>
<tr>
<td>No therapeutic response</td>
</tr>
<tr>
<td>Therapeutic response decreased</td>
</tr>
<tr>
<td>Therapeutic response delayed</td>
</tr>
<tr>
<td>Therapeutic response prolonged</td>
</tr>
<tr>
<td>Therapeutic response increased</td>
</tr>
<tr>
<td>Drug effect prolonged</td>
</tr>
</tbody>
</table>

Data mining for sub-standard medicines

- **Goal**: To conduct data mining for sub-standard generic medicines on pharmacovigilance datasets.

- To evaluate the results and seek correlations (if any) with investigation results initiated in parallel by GMP & QA labs

- Pilot focused on Novartis products as proof of concept

- Preliminary findings confirmed need for further research

*Trippe A, Lewis D et al*  
*Identification of substandard medicines via disproportionality analysis of ICSRs*  
Basis for the Novartis method (mining for SSMs)
Early findings published by WHO UMC & collaborators

Disproportional reporting by Country & Year

**Netherlands 2013**

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Generic</th>
<th>Novartis princeps</th>
<th>Event</th>
<th>N</th>
<th>EBGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permento®</td>
<td>Rivastigmine</td>
<td>Exelon®</td>
<td>Product quality issue</td>
<td>24</td>
<td>15.3</td>
</tr>
<tr>
<td>Permento®</td>
<td>Rivastigmine</td>
<td>Exelon®</td>
<td>Therapeutic response unexpected with drug substitution</td>
<td>25</td>
<td>10</td>
</tr>
</tbody>
</table>

**Netherlands 2014**

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Generic</th>
<th>Novartis princeps</th>
<th>Event</th>
<th>N</th>
<th>EBGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permento®</td>
<td>Rivastigmine</td>
<td>Exelon®</td>
<td>Product quality issue</td>
<td>6</td>
<td>52</td>
</tr>
<tr>
<td>Permento®</td>
<td>Rivastigmine</td>
<td>Exelon®</td>
<td>Therapeutic response unexpected with drug substitution</td>
<td>7</td>
<td>19.6</td>
</tr>
</tbody>
</table>
Lareb letters on [rivastigmine] patch

Warnings issued to pharmacists

<table>
<thead>
<tr>
<th>Patient, Number, Sex, Age, Source</th>
<th>Drug, daily dose, Indication for use</th>
<th>Concomitant Medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, Action with drug outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 166037 F, 70 years and older Genetritian</td>
<td>permethan patch transdermal Alzheimer's disease</td>
<td>furosemide, calcium carbonate, tiolazoled, perindopril</td>
<td>erythema, pruritis, therapeutic response unexpected with drug substitution</td>
<td>1 day discontinued recovering</td>
</tr>
<tr>
<td>B 164924 F, 70 years and older Genetritian</td>
<td>permethan patch transdermal Alzheimer's disease</td>
<td>pantoprazole, paracetamol, isosorbide mononitrate, isosorbide dinitrate, carbasalate calcium, aliskiren, bisoprolol</td>
<td>itching rash, therapeutic response unexpected with drug substitution</td>
<td>days discontinued recovered</td>
</tr>
<tr>
<td>C 164113 F, 70 years and older Genetritian</td>
<td>permethan patch transdermal Alzheimer's disease</td>
<td>olmesartan, fluvastatin, pantoprazole, enalapril, metformin, cilostazol</td>
<td>rash, therapeutic response unexpected with drug substitution</td>
<td>2 day discontinued not recovered</td>
</tr>
</tbody>
</table>

Discussion of experiment and findings

Combination of signal detection and field-based quality assays for SSMs

- Evidence provided of an effective method for detecting signals of potential SSMs
- Independent corroboration of SSM in the Netherlands
- Further refinement of method ongoing:
  - Geographic heat maps
  - Review sensitivity and selectivity of the standard Novartis method
  - Assess threshold for signal, type 1 and type 2 errors
- Augment detection of clusters and potential signals by conducting field-based sampling
- Determine potential for joint actions with regulators
Conclusions on SOC 27: safety & quality

SOC 27 constitutes an important addition to MedDRA
- Provides the potential to extend and improve current processes
  - Review of ICSRs (especially biologicals & vaccines)
  - Aggregate reporting (APR, PQR and DSUR, PSUR, RMP)
  - Signal detection can be strengthened by combining SOC 27 with selected terms e.g.:
    - Overdose-related (child-proof container example)
    - Sterility-related (post-injection bacterial infections, abscesses etc.)

Have you considered how & where to apply SOC 27?
- Focus on the interface between GMP and GPVP
- Consider areas of risk and the potential for competitive advantage

WEB-RADR Innovative research - consortium

- MedDRA mapping to other terminologies
  - 2.5k-3k PTs in social media cover ~95% of all adverse reactions
  - Mapping supports links to other apps & healthcare systems
  - SNOMED (IHTSDO) for US-based systems
  - ICD 10 for WHO-aligned healthcare systems
  - And other coding systems e.g. Reed codes

- Utility for Pharma companies is mapping in support of:
  - Pharmacovigilance
  - Pharmacoepidemiology
  - Non-interventional studies
  - Electronic health records & Big data

Expertise being sought

- MedDRA coding
- Digital media
- IT (apps and APIs)
Thank you