Signal Detection from Regulatory Perspective – Postmarketing Surveillance

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Agenda

• Pharmacovigilance at the MHRA
• ADR reporting & the Yellow Card Scheme
• Signal detection tools
• Risk management & communication
• Future Developments
Pharmacovigilance - unmet need...

• Thalidomide and phocomelia in early 60’s

• Around 10,000 fetuses affected in EU countries

• Thalidomide had been widely promoted as safe
Pharmacovigilance at the MHRA

- Medicines and Healthcare products Regulatory Agency
  - UK Government, Licensing Authority, “Medicines Watchdog”

- PV Risk Management Group
  - 35 staff, Medics, Epidemiologists, Assessors

- PV Signal management Group
  - 38 staff, scientists, administrators
  Responsibility for **ALL** 30,000 medicines on the UK market
• Capture and Manage information on suspected adverse drug reactions
• Manage the signal detection process
• Respond to enquiries – over 6,000 per year
• Monitor MAH and MHRA compliance – legal obligations
• Assess emerging risk/benefit issues
• Take necessary regulatory action
• Communicate
The Yellow Card Scheme
Spontaneous reporting systems

- Important role in patient safety
- Allows continual safety monitoring of drugs - old & new
- New drugs - lack of experience on adverse effects
  - Exposure in small numbers of people
  - Short duration
  - Unlikely to detect ADRs
    - Less frequent than 1/1500
    - With long latency
- Lack of experience in special patient groups
  - Elderly, children, pregnancy, multiple disease, polypharmacy
- To detect rare adverse effects
The Yellow Card Scheme

- UK spontaneous reporting scheme collecting suspected Adverse Drug Reactions

- Established in 1964 following the issues over thalidomide

- Vital public health mechanism to:
  - Identify previously unrecognised adverse drug reactions
  - Gain further information about the occurrence of adverse drug reactions in ordinary practice.

- Essential component in MHRA’s pharmacovigilance work

- Scheme is voluntary – relies on goodwill of health professionals and patient reporters

- We ask for reports of suspicions and look for signals
The Evolving Scheme

- Extensions to Scheme:
  - Coroners (1969)
  - Pharmacists (April 1997 & Nov 1999)
  - Nurses, midwives and health visitors (2002)
  - Patient reporting pilot scheme UK-wide (2005)
  - Patient reporting established – Feb 08

- Today, reports can be submitted by:
  - Paper Yellow Card form
  - Electronic Yellow Card form on [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)
  - Telephone
Yellow Card Report

Welcome back. If you would like to fill in a new Yellow Card please click on the button below. You can also update a Yellow Card report you have previously saved by clicking on edit. To edit your details, please change them below and select "save details".

Current Yellow Cards

<table>
<thead>
<tr>
<th>MHRA Number</th>
<th>Reference</th>
<th>Last Update</th>
<th>Edit</th>
<th>PDF</th>
</tr>
</thead>
</table>

There are no currently unfinished yellow cards associated with your account.

Complete a new yellow card.

Edit Details

Fields marked with an * are required

Title *

First Name

Last Name *

Profession

Hospital / Practice Name *

Email Address *

Password *

Confirm Password *

Dr

Sarah

Davis

Other healthcare professional

The Park Surgery

sarah.davis@mhra.gsi.gov.uk

Password

Password

House Number or Name *

Address *

Address Line 2

Address Line 3

Town *

County

Postcode *

Telephone number

I have read and understood the data protection and confidentiality statement.

Save Details
Step 3 - Suspect Reactions

Fields marked with a * are required

As you type in the box, the website will suggesting possible terms from our dictionary and are possible matches for the words you are entering. If one of these terms is an appropriate term for the reaction, then please select this. More than one reaction can be entered if needed, simply click on 'add another Suspect Reaction'.

Please select an outcome for each suspect:
- Recovered
- Recovering with some lasting effects
- Recovering
- Not recovered
- Caused Death
- Unknown
- Other (Please give details below)

Do you consider the reaction to be serious:
- Yes
- No

You can use this box to describe the reaction if events, any treatment received, or any other factors affected.
Black Triangle Scheme

- Intensive monitoring scheme for new products where knowledge of risk benefit profile is limited
  - *Report all reactions for medicine, including non-serious*

- Black triangle symbol ▼ printed next to product name in BNF, SmPC, advertising material, etc.

- ▼ assigned to:
  - New active substances
  - Established active substances if product:
    - Contains a new combination of active substances
    - Is administered by a novel route or dug delivery system
    - Is for significant new indication which may alter the risk benefit profile of the substance
Seriousness

- Report is defined as serious if one of the following is selected in an ADR:
  - Patient died due to reaction
  - Life threatening
  - Congenital abnormality
  - Involved or prolonged inpatient hospitalisation
  - Involved persistent of significant disability of incapacity
  - Medically significant

- For ADRs with no seriousness assessment – MedDRA serious will be applied – e.g. myocardial infarction.
Industry Reporting

- Legal obligation to report ICSRs
  - Directive 2001/83/EC
  - Regulation (EC) No 726/2004

- UK Reports ~ 50% of total (12,000)

- E2B reporting mandated

- Foreign reports also collected at MHRA – 80,000/year+

- Assessments of company Pharmacovigilance systems also undertaken
How is the ADR data used to improve patient safety?

Regulatory action taken to:

- Update SPC e.g. restriction in use, special warnings and precautions
- Suspension or Revocation of a marketing authorisation
- Changes to product information (PIL) variation of the marketing authorisation (usually voluntarily)
- Change in legal status (POM to P)
What is a signal?

- WHO Definition: ‘reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously….’

- A signal is:
  - previously unrecognised safety issue
  - change in severity
  - change in frequency
  - identification of at risk group
Signal Detection

- Each new report might be a potential signal
- Have to actively look for signals - ‘needle in a haystack’
- Consider each case to decide whether it represents a potential signal
- Use tools to prioritise resources and facilitate decision making
MHRA Signal Detection Tools

Reports entered onto Sentinel ADR database

- Drugs coded to in-house drugs dictionary
- ADRs coded using MedDRA
- Patient demographics, medical history etc.

- Data transferred to Empirica Signal
  - DAPs
  - Data mining runs
  - Drugs dictionary
  - MedDRA – serious terms
  - Identification
  - Alert terms
Signal Detection Process at MHRA

- Spontaneous reports are entered onto the database on daily basis as they are received.

- Signal scores (EBGM and PRR) at PT level upwards are computed every week for reports received in previous week.

- Signals of potential interest are flagged for assessment based on preset criteria.
  - Different criteria apply for black triangle (▼) and non-black triangle drugs (Non-▼).
Signal system workflow

Yellow Cards - Adverse Drug Reaction reports → Sentinel → Nightly ETL → Provision of Information

Weekly Signal Batch → Disproportionality scores
Basic disproportionality

<table>
<thead>
<tr>
<th></th>
<th>Drug of interest</th>
<th>All other drugs</th>
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</thead>
<tbody>
<tr>
<td>Specific reaction</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>All other reactions</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

- PRR = \( \frac{a}{a+c} \) / \( \frac{b}{b+d} \)
## Disproportionality: EBGM v PRR

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TIPRANAVIR</td>
<td>Hepatitis C</td>
<td>1</td>
<td>0.302</td>
<td>1.42</td>
<td>4.96</td>
<td>396.1</td>
<td>182.8</td>
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<tr>
<td>TIPRANAVIR</td>
<td>Fatal (Special PT Group)</td>
<td>3</td>
<td>0.653</td>
<td>1.68</td>
<td>3.72</td>
<td>3.33</td>
<td>5.16</td>
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<tr>
<td>TENOFOVIR</td>
<td>Urinary tract infection</td>
<td>1</td>
<td>0.249</td>
<td>1.07</td>
<td>3.34</td>
<td>4.21</td>
<td>2.44</td>
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<tr>
<td>TENOFOVIR</td>
<td>Blood phosphorus decreased</td>
<td>12</td>
<td>144.5</td>
<td>240.0</td>
<td>379.7</td>
<td>1388.2</td>
<td>5088.4</td>
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<tr>
<td>TENOFOVIR</td>
<td>Blood creatinine increased</td>
<td>21</td>
<td>37.3</td>
<td>54.3</td>
<td>76.9</td>
<td>63.3</td>
<td>1194.3</td>
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<tr>
<td>TENOFOVIR</td>
<td>Bone pain</td>
<td>3</td>
<td>1.14</td>
<td>4.23</td>
<td>31.9</td>
<td>28.8</td>
<td>76.1</td>
</tr>
</tbody>
</table>
Stratification/Subsets

- Routine data mining runs are subsetted by:
  - Vaccine / Non-vaccine reports
  - UK / Non-UK reports

- Stratified using Mantel-Haenszel approach by:
  - Patient age (0, 1-2, 3-12, 13-18, 19-35, 36-65, 66+, Unknown)
  - Patient gender (male, female, unknown)
  - Time period
UK Reports - Signal Criteria (Non-▼)

• Serious reports where EBGM ≥2.5, EB05 ≥1.8, n ≥3:
  • All unlisted drug-event combinations
  • Listed drug-event combinations – only those where change in frequency detected (proportion of reports received in last quarter ≥ 8%)

• All fatal reports
• All reports involving children (≤16 years)
• All parent/child reports (including spontaneous abortion)
• All reports for ‘Alert’ terms - medical conditions of interest
Foreign Reports - Signal Criteria (Non-▼)

- All serious *unlisted* reports where $\text{EBGM} \geq 2.5$, $\text{EB05} \geq 1.8$, $n \geq 5$

- All fatal reports

- All reports involving children ($\leq 16$ years)

- All parent/child reports (including spontaneous abortion)

- All reports for ‘Alert’ terms - medical conditions of interest
UK and Foreign Signal Criteria (▼)

• Safety profile for newly licensed products not yet established

• Single case report may therefore represent important safety signal

• All serious reports regardless of EBGM score

• EBGM/PRR used for reference rather than to filter signals
What do we do with a signal?

- Next steps: Signal evaluation
  - Impact Analysis
  - Signal prioritisation
  - Regulatory action
Impact Analysis

• This is a statistical tool to prioritise possible signals and decide the next step that should be taken. This takes into consideration the strength of evidence as well as the seriousness of the ADR.

• **Outcome categories are as follows:**
  • A - High priority further evaluation required
  • B - Need to gather more information
  • C - Low priority
  • D - No action at present
RPPS

- Regulatory Pharmacovigilance Prioritisation System. This is further signal prioritisation taking into account public perception of the ADR and Agency obligations.
- The following targets are assigned to each signal
  - Top – 3 months
  - Increased – 6 months
  - Standard – 12 months
Medical Terminology

• MedDRA used as basis for analysis
• Additional Preferred Term included in MedDRA hierarchy:
  ➢ Fatal (Special PT Group)

• Added as extra PT to every fatal report within WebVDME / Empirica

• Acts as an all cause mortality term

• Useful to obtain one signal statistic for all causes of mortality rather than split across many different PTs
Drugs Dictionary

- Sentinel drugs dictionary converted into two drug tables
  - Drug ingredient table
    - based on single active ingredients & returns reports that mention products containing particular ingredient
  - Drug substance table
    - separates single and multi-constituent products and treats them as different drug substances
- Allows flexibility to group reports containing same active ingredient or separate different multi-constituent products
Sentinel Drugs Dictionary

NPCG → NPCG

PBG

SGP

Formulation

Substance

Variant

Variant Synonym

Synonym
### System Organ Class

<table>
<thead>
<tr>
<th></th>
<th>Single active constituent</th>
<th>Multiple active constituent</th>
<th>Total unique reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Fatal</td>
<td>All</td>
</tr>
<tr>
<td>Blood disorders</td>
<td>140</td>
<td>2</td>
<td>40</td>
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<tr>
<td>Cardiac disorders</td>
<td>100</td>
<td>13</td>
<td>13</td>
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<tr>
<td>Congenital disorders</td>
<td>9</td>
<td>1</td>
<td>15</td>
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<tr>
<td>Ear disorders</td>
<td>8</td>
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<td>Endocrine disorders</td>
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<td>0</td>
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<td>Eye disorders</td>
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<td>General disorders</td>
<td>221</td>
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<td>75</td>
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<tr>
<td>Hepatic disorders</td>
<td>18</td>
<td>7</td>
<td>13</td>
</tr>
</tbody>
</table>

**Legend:**
- Blood disorders
- Cardiac disorders
- Congenital disorders
- Ear disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders
- Hepatic disorders
- Injuries
- Investigations
- Immune system disorders
- Infections
- Metabolic disorders
- Muscle & tissue disorders
- Neoplasms
**Drug name: PARACETAMOL**

| Report run date: 31-Mar-2010 | Report type: Spontaneous |
| Data lock date: 30-Mar-2010 08:00:04 PM | Report origin: UNITED KINGDOM |
| Period covered: 01-Jul-1963 to 30-Mar-2010 | Route of admin: ALL |
| Earliest reaction date: 09-Feb-1964 | Reporter type: ALL |
| MedDRA version: MedDRA 12.1 | Reaction: ALL |
| Age group: ALL |

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<th>Reaction Name</th>
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<th>Multiple active constituent</th>
<th>Total unique reports*</th>
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<td>Fatal</td>
<td>All</td>
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<td>HLT</td>
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<tr>
<td>PT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
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<td></td>
<td></td>
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<tr>
<td>Cardiac conduction disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrioventricular block first degree</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sinoatrial block</td>
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<td>Cardiac signs and symptoms NEC</td>
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<td>6</td>
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<td>4</td>
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<td>Palpitations</td>
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<td>1</td>
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<tr>
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<td>3</td>
<td>1</td>
<td>5</td>
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<tr>
<td>Myocardial ischaemia</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Left ventricular failures</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</table>
The drugs industry and its watchdog: a relationship too close for comfort?

The Guardian

Drugs licensing flaws exposed

Ministers order action on child medicine safety

HRT warning

Who failed the Seroxat suicide watch?

GSK is accused of withholding damaging data on the antidepressant's side effects.
Medicines that are used to treat various infectious forms the theme of our articles in Drug Safety Update this month.

Ketoconazole, an antifungal agent, has recently had a review of its risks and benefits. Because of the risk of serious hepatotoxicity, ketoconazole should be used only for dermatophytes, Malassezia furfur and chronic candidiasis that cannot be treated topically (pp 2).

Tazocin, which contains the active ingredients piperacillin and tazobactam, has been reformulated, improving its physical compatibility. Tazocin is now compatible with lactated Ringer’s (Hartmann’s) solution and, in some circumstances, amphotericin (p 9). Look out for a new package colour marked “new formulation”.

Tabovir is a new nucleoside analogue for adults with chronic hepatitis B. Our advice to healthcare professionals is that the combination of tabovir and interferon cannot be recommended because of a risk of peripheral neuropathy. Find out more on page 4.

Claire Tittell, Editor
drugssafetyupdate@mhra.gsi.gov.uk

• Launched in August 2007
• Monthly e-bulletin
• emailed to HCPs across UK
• Routinely updated on web
• All new and emerging advice
Communication of regulatory actions

- **Urgent**
  - Issue of ‘Dear Healthcare professional’ letters
  - Publication on MHRA website
  - Targeted information for patients/press releases

- **Less urgent**
  - Publication of
    - update of SPC and Patient information leaflet
    - Non urgent information cascade/rapid alert (EU member states)
  - Drug Analysis Prints (DAPs)
Future Developments

- New EU pharmacovigilance legislation
- Increased use of the EHR
- E2B (R3)
- Common Product Dictionary
- Terminology mapping
Thank you