Pharmacovigilance in the UK - Focus on signal detection and Pv Inspections

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UK MHRA

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Agenda

• Pharmacovigilance in the EU

• UK ADR reporting & the Yellow Card Scheme

• MHRA signal detection tools

• Risk management & communication

• Pharmacovigilance Inspections
Background – Review Of The EU System

Assessment of the European Community System of Pharmacovigilance

Final Report – Final version
25 January 2006

European Commission
Enterprise and Industry Directorate-General, Unit F2, Pharmaceuticals

Reference: Service Contract No: FIF.20040739

Submitted by the
Fraunhofer Institute for Systems and Innovation Research, Karlsruhe, Germany
A lack of clear roles and responsibilities for the key responsible parties and a lack of clear obligations against which they perform their roles (resulting in poor compliance);

Slow EU decision-making on drug safety issues particularly for nationally authorised products and frequent disharmony in action taken by the Member States;

Low levels of transparency relating to pharmacovigilance and relatively limited EU coordination of communication about the safety of medicines, plus complex product information with poor penetration of key warnings; Cumbersome oversight of companies’ pharmacovigilance systems by the authorities;

A lack of proactive and proportionate monitoring including a lack of risk management and structured data collection in the form of post authorisation safety studies and duplicative reporting rules for the industry and authorities relating to both 15-day, literature and periodic (PSUR) reporting of ADRs;

Lack of inclusiveness of stakeholders including a lack of direct patient reporting of ADRs and their virtual absence from decision-making.

At least 591 lives and €237 Million saved
Background - Process

• Positive vote in EU parliament Sept 2010

• Formal adoption and publication 31 December 2010

• Transposition over 18 months
  • Development of guidelines
    – GVP releases
  • Development of systems
  • National regulation changes
  • Implementing measures

• Effective from July 2012
  • Regulation (EU) No 1235/2010
  • Directive 2010/84/EU

• Effective from August 14th 2012
  • National consolidation - UK Human Medicines Regulations 2012
Scope of Changes

- **Authorisation requirements** change (PSMF, key risk management measures in MA)
- **Risk Management Plan**, risk proportionate and for all new products (+justified old)
- **Legal basis for PASS** + legal basis for efficacy studies
- **Effectiveness of risk minimisation**
- **Product information** change – ‘additional monitoring’ + encourages ADR reporting
- **ADR reporting** simplified + patient reporting + medication errors + role of EV + literature monitoring + reporting to WHO
- **Signal detection** has clear roles and responsibilities – **signal management process**
- **PSUR** submission simplified (electronic) and single assessment + benefit: risk
- **Committees** (PRAC/CMD/CHMP) and decision-making
- **Transparency and communication** (webportals, EV access, coordinate MSs, hearings)
- Enhanced coordination of **inspections**
- Regular EMA and MS + MAH **pharmacovigilance audit**
- **Fees** for pharmacovigilance
Governance of the Implementation of the New Pharmacovigilance Legislation

- Project Oversight Committee (ERMS-FG)
- Project Coordination Group (GVP)

Subproject Teams (EMA Task-Force)

Co-chairs EMA/MSs Project Team
- Audit
- Inspections

Co-chairs EMA/MSs Project Team
- PSUR

Co-chairs EMA/MSs Project Team
- ADR report.
- Add. monit.
- Signals

Co-chairs EMA/MSs Project Team
- RMP
- PASS/PAES
- Effect. Risk. Minimisation

Co-chairs EMA/MSs Project Team
- Committees
- Referrals

Co-chairs EMA/MSs Project Team
- Communicat.
- Transpar.
- Web-portals
- Publ. hearing
GUIDANCE ON GOOD PHARMACOVIGILANCE PRACTICES (GVP)

INTRODUCTION Legal Basis and Structure of Pharmacovigilance Guidance

MODULE I Pharmacovigilance Systems and their Quality Systems

MODULE II Pharmacovigilance System Master File

MODULE III Pharmacovigilance Inspections

MODULE IV Audits

MODULE V Risk Management Systems

MODULE VI Data Management of Individual Case Safety Reports

MODULE VII Periodic Safety Update Reports

MODULE VIII Post-Authorisation Safety Studies

MODULE IX Detection and Management of Signals and Information

MODULE X Additional Monitoring

MODULE XV Safety Communications

PRODUCT- AND POPULATION-SPECIFIC CONSIDERATIONS
Various consideration chapters are available for update (e.g. vaccines) or proposed for development (e.g. geriatrics)

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

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

Vigilance Intelligence & Research Group
  • 55 staff, scientists, administrators
  Responsibility for ALL 30,000 medicines on the UK market
- Capture and Manage information on suspected adverse drug reactions
- Look for new ways to encourage ADR reporting and new innovative methods for ADR collection
- Manage the signal detection process
- Respond to enquiries – over 6,000 per year
- Assess emerging risk/benefit issues
- Take necessary regulatory action
- Communicate
The Yellow Card Scheme

Yellow Card

A side effect of your medicine? Report it using Yellow Card

If you think the medicine you are taking may have caused a side effect, you can report it using Yellow Card.

Additional relevant information e.g. medical history, test results, other drugs used, other adverse reactions.

[Form for reporting suspected adverse drug reactions]

- Patient Details
- Suspected Drugs
- Suspected Reaction(s)
- Other Drugs
- Reporter Details
- Clinician Details

MHRA

Helping to make medicines safer

The Yellow Card Scheme
Benefits of 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
  - Telephone
ADR reporting 2008-2012

- 3.6% increase in ADR reports from 2011 to 2012
- 4.1% increase in reports from 2008 to 2012
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".

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**: Dr
- **First Name**: Sarah
- **Last Name**: Davis
- **Profession**: Other healthcare professional
- **Hospital/Practice Name**: The Park Surgery
- **Email Address**: sarah.davis@mhra.gsi.gov.uk
- **Password**: ********
- **Confirm Password**: ********
- **House Number or Name**: 1
- **Address**: Lucas Gardens
- **Address Line 1**: 
- **Address Line 2**: 
- **Address Line 3**: 
- **Town**: Luton
- **County**: 
- **Postcode**: LU2 4RW
- **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’.

Suspect Reactions added:

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)

Add another Suspect Reaction

Do you consider the reaction to be serious

- Yes
- No

You can use this box to describe the reaction in events, any treatment received, or any other
Direct Yellow Card reports
2008-2012

- 5% increase in direct reporting from 2011 to 2012
- 52% of all direct ADR reports received in 2012
- In 2012 direct electronic reporting is at its highest level (25% to 68%)
Direct Yellow Card reports 2008-2012

- In 2012 GP reporting increases whilst reports from nurses has decreased since 2009.
- Reports from pharmacists are at its highest with an increase of 37%.
GP reporting

- 26% increase in the proportion of direct reporting.
- Proportion of serious reports at approximately 70%
- Fatal reports at approximately 2%

November 2010:
GPs able to report ADR reports directly to the MHRA using the practice software SystmOne.

In 2012, 63% of all direct GP reports were received via SystmOne
Pharmacovigilance at the MHRA

- Yellow Cards - Adverse Drug Reaction reports
- QA of reports received
- Commit to database
- Assessment
- Signal detection
- Signal Evaluation and Prioritisation
- Risk-benefit evaluation and advice from CHM
- Regulatory action & communication
- Drug and Reaction coding
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 or incapacity
  - Medically significant

- For ADRs with no seriousness assessment – MedDRA serious will be applied – e.g. myocardial infarction.
Additional Monitoring ▼

• 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
Industry Reporting

- Legal obligation to report ICSRs
  - Regulation (EU) No 1235/2010
  - Directive 2010/84/EU
  - GVP Module VI

- UK Reports ~ 45% of total (12,000)

- E2B reporting mandated (R3 from 2017)

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

- Assessments of company compliance also undertaken
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
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>
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<tr>
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<th>Drug of interest</th>
<th>All other drugs</th>
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<tbody>
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<td>Specific reaction</td>
<td>(a)</td>
<td>(b)</td>
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<tr>
<td>All other reactions</td>
<td>(c)</td>
<td>(d)</td>
</tr>
</tbody>
</table>

- \(\text{PRR} = \left( \frac{a}{a+c} \right) \div \left( \frac{b}{b+d} \right)\)
## Disproportionality: EBGM v PRR

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<th>Drug</th>
<th>Event</th>
<th>UK</th>
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<td>Blood phosphorus decreased</td>
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<td>1.14</td>
<td>4.23</td>
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<td>28.8</td>
<td>76.1</td>
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</table>
• 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 $\geq 2.5$, EB05 $\geq 1.8$, n $\geq 3$:
  - All unlisted drug-event combinations
  - Listed drug-event combinations – only those where change in frequency detected (proportion of reports received in last quarter $\geq 8\%$)

- 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 EBGM ≥2.5, EB05 ≥1.8, n ≥5
- 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
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
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)
Impact Analysis

• This is a methodology 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
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
Eudravigilance – 3419 substances

- 420 CAPs on URD (signals monitored by EMA)
- 2704 on existing signals monitoring list
- 1661 unallocated with no potential (p)-RMS (i.e. 90 unclaimed by existing (p)-RMS)
- 1751 unallocated to a lead member state for signals
- 89 have a PSUR frequency of 5 years or less*

EU - Signal Management
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<th>PTEs</th>
<th>BMJ DIM</th>
<th>Test Fail</th>
<th>Test Pass</th>
<th>New Fail</th>
<th>New Pass</th>
<th>New SSC</th>
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The drugs industry and its watchdog: a relationship too close for comfort?

Drugs licensing flaws exposed

Ministers order action on child medicine safety

Who failed the Seroxat suicide watch?

GSK is accused of withholding damaging data on the antidepressant’s side effects.
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)
Launched in August 2007

Monthly e-bulletin

e-mailed to HCPs across UK

Routinely updated on web

All new and emerging advice

Medicines that are used to treat various infections form 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 dermatophytosis, Microsporum furfur, and chronic candidiasis that cannot be treated topically (p. 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 B (p. 3). Look out for a new package colour coded “new formulation”.

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

Claire Tildesley, Editor
drugssafetyupdate@mhra.gov.uk
No product is ever risk free. Some of the risks are known about when a medicine is first licensed or medical device first used. However, some information only comes to light later as more people use the products. This section includes current and historic alerts, messages and advice and guidance we have issued about products. This section also includes our safety reporting forms for medicines, medical devices and blood.

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**Safety warnings, alerts and recalls**

This section includes current and historic Drug Alerts on defective medicines, Medical Device Alerts and safety warnings and messages about medicines, including letters sent to healthcare professionals.

* Go to the section on safety warnings, alerts and recalls

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**Reporting safety problems**

This section provides information on how to report safety problems in medicines, medical devices and blood.

* Go to the section on reporting safety problems

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**General safety information and advice**

This section contains specific information on products such as hormone replacement therapy, breast implants, the human papillomavirus (HPV) vaccine and testing kits. It also contains advice for consumers, such as the risks of buying medicines over the internet, using herbal medicines and leaving hospital with a medical device.

* Go to the section on general safety information and advice

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**Information for healthcare professional specialties**

As part of our continuing drive to support healthcare professionals, we have set up this section comprising information relevant to different healthcare professional specialties.

* Go to the information for healthcare professional specialties

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**Drug Safety Update (DSU)**

Drug Safety Update is our monthly newsletter for healthcare professionals, with information on the latest recalls.

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**How we monitor the safety of products**

This section describes our processes for monitoring the safety of medicines, medical devices and blood.

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* Download Acrobat Reader for free
* Adobe text conversion tools
The MHRA
Pharmacovigilance Inspection Programme
- MAHs will have to produce and maintain a PSMF, which is a detailed description of the system used by the MAH (guidance will be developed relating to the contents of the PSMF).

- The PSMF may be requested by Competent Authorities and must be provided within 7 days of a request.

- The PSMF will form one of the reference documents for inspections.

- MAHs shall be required to perform a regular audit of their system and must include a note of the main audit findings in the PSMF. Based on the audit findings, an appropriate corrective action plan must be implemented. Once the corrective actions have been fully implemented, the note may be removed.
MHRA Inspection Programme

• Routine MHRA pharmacovigilance (GPvP) inspections have been performed since 2003.
• Approximately 700 inspections have been performed to date.
• MHRA currently performs 80-100 GPvP inspections per year.
• 9 inspectors currently perform GPvP inspections (3 vacancies).
• Pre-July 2012: GPvP inspectors inspect UK MAHs (which occasionally included inspections of contractors, distributors and marketing partners).

• Post- July 2012: GPvP inspectors continue to inspect UK MAHs. MHRA is also proposing to implement a specific voluntary inspection programme of pharmacovigilance contractors.
National inspections of MAHs without centrally authorised products (CAPs)

• Risk-based inspection programme.
  – RBI Compliance report used to collect risk information
• Generally systems-based and announced
  – initial inspections and re-inspections,
  – routine and “for cause” following critical inspection findings.
• Unannounced, triggered and virtual inspections (where there is no site in the UK) can be performed, but are rare.
Inspection Types

Inspections to fulfill the EMA routine plan for holders of centrally authorised products (CAPs)

- Pre-July 2012: Member State performing the inspection has been the country where QPPV is located.
- Post-July 2012: the Supervisory Authority is the Member State where the master file (PSMF) is located (which will often be the same).
- Pre-authorisation inspections are a possibility for CAP applications.
Inspection Types

CHMP requested inspections

- Not always systems based (examining specific product concerns)
- Performed at the primary site where pharmacovigilance activities are undertaken (allows easier access to relevant people and data) which may include sites outside of the EU
- Approximately 12 inspections led by the MHRA to date
- Can involve inspectors from other Member States
The Inspection Process
Risk-based selection process


- Data is collected in the form of questionnaires and analysed to determine a risk score.
  - Data collection has/will occur in 2009, 2011 and 2013 (November).
  - Process improvements at each time.

- Approximately 400 questionnaires returned to the MHRA in 2011.
Risk-based selection process

• Questionnaire examines a number of areas of potential risk:
  – products, resource, staff turnover, compliance (expedited and periodic reporting), QMS, licensing agreements, product related safety issues.

• A MHRA risk-based intelligence database/application has been developed, which will more efficiently collate risk information and which will be used to aid inspection planning in future.
Inspection overview (1)

PLAN

Risk-based selection

Notification & request SPS/DDPS/PSMF

Inspection plan

CONDUCT

Interviews, document & computer system reviews

Closing meeting: preliminary findings

Next slide…
Inspection overview (2)

...previous slide

REPORT

Inspection report

MAH responses

IAG referral

Dashed box: Additional information or actions

Review CAPA

Reinspection or other actions

Inspection close-out
Post inspection actions
Post-inspection actions

- Dependent upon the nature and severity of the non-compliances identified

- The ultimate aim is to bring organisations into compliance by using the most appropriate method (or combination of methods) available in the inspectors toolkit
Sanctions

- Article 102 (f), “Member States shall… take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in this Title is subject to effective, proportionate and dissuasive penalties”.

- At MHRA, critical inspection findings are referred to a cross-agency, multi-disciplinary Inspection Action Group (IAG). IAG make recommendations for actions to be taken.
Potential actions

Tiered approach followed

Desired approach

Frequency

High

Low

Most

Least

Education and interaction with Industry

Inspection

Re-inspection

Company meeting and/or Warning letter

Company-agreed action

Regulatory Action

Criminal prosecution
Infringement Notice (IN)

- Introduced by MHRA for pharmacovigilance non-compliance

- INs are statutory notices that will specify steps the MAH must take and in what timeframe, in order to:
  - rectify the non-compliance and
  - prevent a further case of non-compliance

- Where the legislation is unclear, the IN may add clarity by documenting the expectations of the MHRA (i.e. how MHRA interprets the legal requirements).

- INs will be circulated to EMA (to be made available to other Member States) and the Commission, in order to ensure that other EU regulators are aware of the issues.

- MHRA intend to publish INs in at least some cases (“name and shame”). The use of an IN will not prevent MHRA from making a referral for criminal prosecution, where considered appropriate.
Criminal Prosecution

- In UK law, most of the pharmacovigilance requirements are associated with a criminal offence for a breach of the requirement.

- However, referral for criminal prosecution is only considered in rare cases e.g.
  - where a serious breach of legislation occurs that results in significant harm to patients or patient death(s), and;
  - where evidence exists to confirm the occurrence of the serious breach, and;
  - where it is considered to be in the public interest.

- If the MAH is found guilty, the following penalties apply:
  - on summary conviction (in a Magistrate’s Court), to a limited fine
  - on conviction on indictment (in a Crown Court), to an unlimited fine and/or to imprisonment for a term not exceeding two years.
The Regulation was implemented in order to ensure the enforcement of certain obligations connected with MAHs granted in accordance with Regulation 726/2004.

The Regulation states that as a result of the system of parallel powers in relation to supervision and enforcement by the Community and the Member States, Regulation 658/2007 can only be effectively enforced in a framework of close cooperation between the Member States, EMA and the Commission.

The Regulation allows financial penalties to be levied on an MAH by the Commission. It does not prevent Member States also taking action at national level. The Regulation has not been used since its implementation.
Conclusions

• The EU legislation covers all aspects of pharmacovigilance
• Impact is on member states, manufacturers, health professionals and patients
• Member States have a responsibility to carry out ADR collection & promotion in order to support signal detection
• PV inspections are carried out to ensure compliance with legal requirements and therefore strengthen Pv and patient safety
спасибо

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