Pharmacovigilance Inspections

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What is pharmacovigilance?

- Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medicines, biological products, herbals and traditional medicines with a view to:
  - Identifying information about potential new hazards
  - Preventing harm to patients
- The word is derived from the Greek pharmakon - drug, and the Latin vigilare - to be awake or alert, to keep watch.

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Reasons for Pharmacovigilance Inspections

- To protect public health
- To meet legal obligations and enforce applicable legislation
- Provide an independent measure of compliance with applicable regulations and guidelines
- Detect and take appropriate action in response to non-compliance with pharmacovigilance obligations
- Assist with quality improvements in pharmacovigilance systems

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Legal Basis for Pharmacovigilance Inspections

- Article 19 (1) of Regulation (EC) No 726/2004: "The supervisory authorities shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use or the manufacturer or importer established within the Community satisfies the requirements laid down in Titles IV, **IX** and XI of Directive 2001/83/EC."
- Article 111(d) of Directive 2001/83/EC states that the competent authority of the Member State concerned shall: "inspect the premises, records and documents of marketing authorisation holders or any firms employed by the marketing authorisation holder to perform the activities described in Title IX, and in particular Articles 103 and 104."

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National and CHMP Requested Inspections

Guidance on the conduct of inspections is given in Volume 9A, Part I, Section 2.4

GPvP inspections can be conducted as part of either a national inspection programme or be requested by the CHMP.

A national inspection alone may be sufficient if it covers the scope of that requested by the CHMP to fulfil the need of routine CHMP inspections.

MHRA may also conduct joint inspections with other EU authorities that are not CHMP-requested.

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Who will Carry Out Inspections

- The Competent Authority (CA) for GPvP inspections will be the one in whose territory the MAH's QPPV is located
- If the MAH has an additional facility in an another Member State (MS), then this will be inspected by the CA of the MS where the facility is located.
- For product-specific issues the inspection may involve, or be conducted, by staff from the Rapporteur/Co-Rapporteur or RMS.

Triggers for Inspections

– A list of possible triggers for targeted GPvP inspections is given in Volume 9A, Part I, Section 2.4.3.

– This includes safety and/or compliance related triggers as well as other triggers such as:
  - MAH has placed their first product on the market in EEA
  - MAH has been involved in a merger or takeover
  - MAH has not been inspected before
  - MAH has significantly changed their PV system

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Background to MHRA Pharmacovigilance Inspections

- Voluntary MHRA pharmacovigilance inspections were performed from October 2002 to develop methodology
- Statutory MHRA pharmacovigilance inspections commenced in July 2003: over 300 inspections to date
- Original aim to visit all UK MAHs within three years. A more risk-based approach is now being developed

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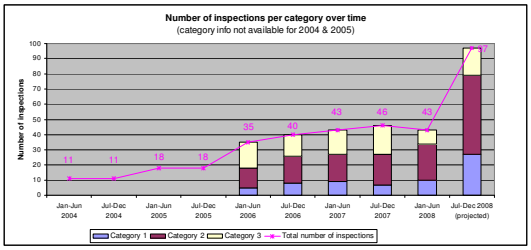
Number of MHRA inspections performed



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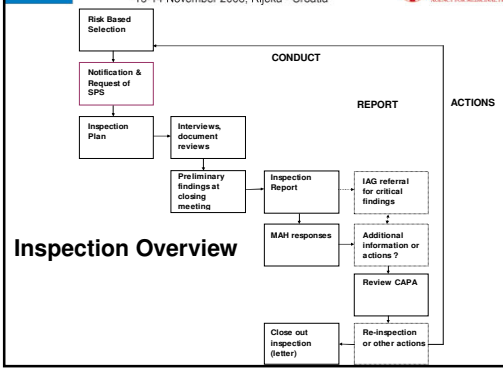
Inspection Overview



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Inspection Preparation

– Announcement of intention to inspect.

– Company requested to complete the Summary of Pharmacovigilance Systems (SPS) document.

– Inspection Plan drafted. Logistical issues addressed;
  - Site(s) to be visited
  - Participants (company divisions/departments, contractors etc.)
  - Tele- or video-conference requirements

– Potential interviewees discussed with company.

– Additional documents (e.g. SOPs, PSURs and contracts) requested prior to inspection.

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Summary of Pharmacovigilance Systems (SPS)

– Section 1: Contact Details
– Section 2: Company structure and operating model for pharmacovigilance
– Section 3: Pharmacovigilance System (summary)
– Section 4: Computerised systems used in pharmacovigilance
– Section 5: Quality Management System
– Section 6: Training Records
– Section 7: Archiving
– Section 8: Questions and/or comments relating to information requested by the MHRA and/or presented by the Company
– Appendices: Supporting information

Inspection Conduct

- Opening meeting
  - Introductions
  - Inspection plan review
  - Company background
- Inspection
  - Interview sessions
  - Document request and review
  - Database searches
  - Tour of Pharmacovigilance, Medical Information, archives and computer server rooms
- Closing meeting
  - Inspection findings communicated

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Areas Reviewed During Inspection

- **May include but are not limited to:**
  - Roles and responsibilities of the QPPV
  - Processing of ICSRs from all sources
  - PSUR & ASR production process
  - Validation of computer systems
  - Signal generation and management of safety issues
  - Maintenance of reference safety information (e.g. SmPCs)
  - Risk Management Plans
  - Interactions between PV and Med Info, Reg Affairs, Marketing, Product Quality
  - Quality assurance activities

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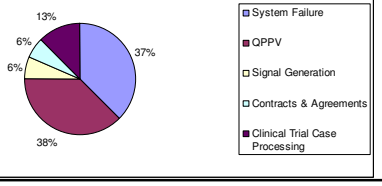
Changing pattern of inspection findings

Between July to December 2006, the MHRA conducted 40 pharmacovigilance inspections (9 were triggered & 50% were of generic manufacturers). 16 critical findings were identified from these inspections.

Number of Critical Findings Identified During Inspections



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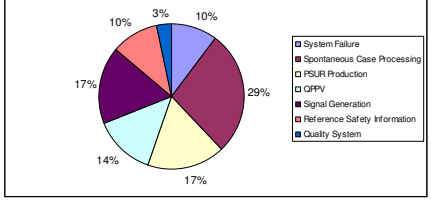
Changing pattern of inspection findings

Between July to December 2007, the MHRA conducted 46 pharmacovigilance inspections (13 were triggered inspections & 37% were of generic manufacturers). 29 critical findings were identified from these inspections.

Types of Critical Findings Identified During Inspections



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Inspection Findings (1)

- **No Pharmacovigilance System**
- **Overall Pharmacovigilance System failure**
  - Multiple serious deficiencies in all areas of PV system, often due to a lack of data exchange/interface issues between departments or partners
- **Qualified Person responsible for pharmacovigilance**
  - Not appointed until notified of inspection/inadequate experience/lack of understanding of the requirements
  - Roles and responsibilities of QPPV not clearly defined
  - Details of QPPV not notified to relevant EU competent authorities
  - Inadequate oversight of the system
  - No authority to make changes to the system

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Inspection Findings (2)

Processing of ADR Reports

- All information about suspected ADRs not accessible from at least one point in the Community
- Non-compliance with expedited reporting timelines
- Lack of understanding of expedited reporting requirements
- Inadequate quality control procedures
- Incorrect decisions made regarding expedited reporting
- Lack of appropriate follow-up of ADR reports
- Lack of reconciliation of safety data when information is exchanged between partners or other departments

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Inspection Findings (3)

Periodic Safety Update Reports

- No formal procedures for PSUR production
- No quality control checks of PSURs
- PSURs not containing all of the required information
- No non-serious unlisted line listings
- Inadequate discussion of lack of efficacy, special populations or pregnancy exposure
- PSURs submitted late to competent authorities or not at all (some licences withdrawn as a result)
- Failure to fully address Assessment Report comments
- Not including follow-up reports
- Inadequate evaluation & discussion of issues of concern

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Inspection Findings (4)

Signal Detection

- No formal procedures for signal detection/trend analysis activities (as appropriate to product type)
- No formal and periodic review of information to identify new safety issues (except at the time of PSUR production)
- Documentation relating to performance of signal detection/trend analysis not retained
- Failure to communicate new safety issues in a prompt manner to competent authorities

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Inspection Findings (5)

Other issues:

- Inadequate or no validation of the safety database or reporting tools
- Inadequate QA auditing of pharmacovigilance activities
- Inadequate agreements concerning safety responsibilities and safety information exchange e.g. with marketing partners
- No policy on retention period or failure to adequately retain ADR records

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Recent issues of concern

1.Delays in reporting significant new safety findings from post authorisation clinical trials and studies:

- Delays in completing final study reports (sometimes 2 years or more since last patient, last visit).
- Failure to adequately discuss trial and study results in PSURs.
- Lack of awareness by drug safety staff/QPPV of trials sponsored by the MAH.
- Failure to discuss in PSURs significant safety findings from academic studies reported in published literature.

2. Inadequacies in the construction of, or process used for, literature searching (sources used, adequacy of scope of search with respect to search objective, local literature scanning, language restrictions, lack of QC).

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Recent issues of concern

3. A variety of concerns have been identified relating to the control and updating of reference safety information (CCDS, SPC, IB):

- Following identification of a new safety signal & MAH decision to update the CCDS, delays in submitting variation(s) to update the SPC(s). Delays of over a year have been observed.
- Delays in implementing SPC and PIL changes following approval of safety variations.
- Poor processes for ensuring that the minimum core safety information contained in the CCDS is consistently represented, as appropriate, in local product information.
- Unwarranted inconsistencies in safety information between reference documents e.g. CCDS, SPC(s) and IB.
- Use of inappropriate reference safety document for the determination of expectedness.
- Wrong version of the SPC made available to health care professionals e.g. on the eMC web site.

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Harmonising EU Inspection Processes

- First formal meeting of EU Pharmacovigilance Inspectors Working Party held in June 2008:
  - Four meetings a year
  - Meetings will aid harmonisation, facilitate the exchange of inspection-related information and assist with the development of inspection EU procedures & guidance
- Joint inspections are occurring with other Member State Inspectorates and assessors in the EU and in third countries
- MHRA has hosted two EU Pharmacovigilance Inspection Training Courses. A third course is due to take place in 2009
- A database is being developed to aid collation of inspection information (which may help to reduce duplication of activity)

Good Pharmacovigilance Practice Guide Purple Guide

- Complements currently available legislation and guidance (does not add to or replace it)
- Provides practical advice to key stakeholders
- Aimed primarily at UK Marketing Authorisation Holders
- Reference to EU legislation/guidance
- UK-specific issues addressed
- Due to be published this month

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MHRA Pharmacovigilance and GCP Inspectorates Webpages

– http://www.mhra.gov.uk

- How we regulate > Medicines > Inspection and Standards > Good Clinical Practice
- How we regulate > Medicines > Inspection and Standards > Good Pharmacovigilance Practice

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And Finally

Any questions?

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Legislation and guidance for your information

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European Medicines Legislation

- **Regulations**
  - Centralised legislation
  - Create laws that take immediate effect in all Member States (MSs) in the same way as national legislation, without any further action on the part of the national authorities.
  - Only one version
- **Directives**
  - Decentralised legislation
  - Binding on the MSs as to the results to be achieved, but leaves them the choice of the form and method they adopt to realise the objectives of the Directive within the framework of their national legal system.
  - Transposition into national law leads to differences between Member States
  - In UK Medicine Act Statutory Instruments are used to implement medicinal product Directives

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EU Pharmacovigilance & Clinical Trial Legislation

- **Regulation 726/2004:** contains pharmacovigilance requirements for centrally authorised products.
- **Directive 2001/83/EC as amended by Directive 2004/27/EC:** requirements for products approved nationally/by mutual recognition in the EEA. Directive 2004/27/EC should have been implemented in all Member States by 30 October 2005.
- **Directive 2001/83/EC as amended by Directive 2004/24/EC:** For herbal medicinal products, which were already on the EU market on the entry into force of the Directive, a seven-year transition period exists.
- **Directive 2001/20/EC & Commission Directive 2005/28/EC:** state the requirements for Clinical Trials and should by now have been implemented in all Member States.

Volume 9A

- Volume 9A contains the guidelines referred to in Article 106(1) of Directive 2001/83/EC (as amended).
- Article 106(2) of 2001/83/EC states:
  - "the marketing authorisation holder and the competent authorities shall follow the guidelines referred to in paragraph 1."
- The "guidelines" in Volume 9A are therefore binding and enforceable.

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PV for Clinical Trials – Legislation & Guidance

- Clinical Trials Directive 2001/20/EC (contains safety reporting requirements for clinical trials).
- EudraLex Volume 10:
  - Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006, Revision 2.
  - Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance : Clinical Trial Module), April 2004.

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Guidelines: 1

- CPMP/ICH/377/95: (E2A) "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/135/95: (E6) "Note for Guidance on Good Clinical Practice".
- CPMP/ICH/288/95: (E2C) "Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs" plus E2CA (Addendum).

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Guidelines: 2

- CPMP/ICH/3945/03: (E2D) "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting".
- CPMP/ICH/5716/03: (E2E) "Pharmacovigilance Planning".
- EMEA/CHMP/PhVWP/235910/2005: "Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population.
- Regulation (EC) No 1901/2006
- Volume 10 of The Rules Governing Medicinal Products in the European Union – Clinical Trials.