Clinical Safety and Pharmacovigilance Inspections

European Approach

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Presentation Content

- European Medicines Agency - Compliance and Inspection Sector Organization
- PhV IWG
- Coordination of PhV Inspections and the centralised procedure
  - Regulatory Framework for PhV inspections
  - Type of Inspection
  - Risk based programme for routine PhV inspections of MAHs connected with CAP products
  - Triggers for inspection
  - Inspection procedure

Clinical Safety and Pharmacovigilance Inspections European Approach
PhV Inspectors Working Group
Pharmacovigilance Inspectors Working Group (PhV IWG)

PhV IWG formed in 2008
Meets Quarterly at the European Medicines Agency
Human and Veterinary medicinal products
Delegates from 30 EU/EEA member states – agencies responsible for inspection H + V
Observers from Croatia, FYRM, Turkey and Switzerland.
Mandate published

PhV Inspectors Working Group

Objectives
- Harmonisation through practice
- Policy/guidelines/SOPs development
- Network of contact between inspectors
- Shared experience, discussion, conclusion
- Joint inspections on most Centralised inspections

Section on the Agency website – mandate, work programme and annual report from the group:
http://www.ema.europa.eu/Inspections/PhVInspmtg.html
Inspections - Pharmacovigilance

Overview

Pharmacovigilance inspections are conducted by the inspectors of the Member States competent authorities in order to provide assurances that Marketing Authorisation Holders are complying with their regulatory obligations and in order to facilitate compliance. The legal requirements for the conduct of PnV inspections are set out for human products in Directive 2001/83/EC as amended and for veterinary products in Directive 2001/82/EC as amended. More detailed guidelines are provided in the Rules Governing Medicinal Products in the European Union (chapter 1.2 of Volume 9A for human products and section 5 of the standalone guideline under Volume 9B for veterinary products).

At the EMEA, part of the Inspections Sector work involves harmonisation and co-ordination of PnV inspection related activity at Community level. It is involved in the preparation of a risk based programme of routine PnV inspections in relation to centrally authorised products (CAPs) and in the co-ordination of PnV inspections requested by the CHMP and CVMP. Through the work of the Ad Hoc PnV Inspectors Working Group made up of inspectors for human and veterinary medicinal products, the sector is involved in the preparation of new and revised guidance on PnV inspection related topics, co-ordination of advice on the interpretation of PnV requirements and related technical issues, and on the development of Community wide guidelines relating to PnV inspections and procedures.

Documents of Interest:

- Annual report for PnV WG. 2008
- Workplan for Ad Hoc PnV WG. 2008, 2009
Inspections - Pharmacovigilance

Inspection procedures and guidance for PhV inspections conducted in the context of the Centralised Procedure.

The Pharmacovigilance inspectors has developed procedures for the coordination, conduct and reporting of PhV inspections carried out in the context of the Centralised Procedure.

A - Human

These inspections are adopted by the CHMP and may be routine or may be triggered by issues arising during the assessment of pharmacovigilance data or by other information such as previous inspection experience.

- Procedure for the preparation of a risk-based programme for routine pharmacovigilance inspections of MAHs connected with human Centrally Authorized Products (CAPs)
- Procedure for coordinating pharmacovigilance inspections requested by the CHMP
- Procedure for conducting pharmacovigilance inspections requested by the CHMP
- Procedure for reporting of pharmacovigilance inspections requested by the CHMP

B - Veterinary

These inspections are adopted by the CVMP and may be routine or may be triggered by issues arising during the assessment of PhV data or by other information such as previous inspection experience.

- Procedure for the preparation of a risk-based programme for routine pharmacovigilance inspections of MAHs connected with veterinary Centrally Authorized Products (CAPs)
- Procedure for coordinating pharmacovigilance inspections requested by the CVMP
- Procedure for conducting pharmacovigilance inspections requested by the CVMP
- Procedure for reporting of pharmacovigilance inspections requested by the CVMP

Coordination of PhV Inspections and the Centralized Procedure
Regulatory Framework

Pharmacovigilance inspection – the Agency Role

Regulation (EC) No 726/2004

- Article 57.1 (c) ...coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation
- Article 57.1 (i) coordinating the verification..... of compliance with pharmacovigilance obligations

Pharmacovigilance inspection
National Competent Authority

Regulation (EC) No 726/2004
• Article 19.1 supervisory authority responsible for verifying that the MAA/MAH or the EU manufacturer or importer..... satisfies the requirements laid down in Titles IV, IX and XI of Directive 2001/83/EC

Regulatory Framework

Directive 2001/83 EC as amended relating to human medical products
• Title IX sets out requirements for pharmacovigilance
• Article 8.3 (ia) requirement for the applicants to provide a detailed PhV system description
• Article 8.3 (n) Proof that the applicant has the services of a qualified person responsible for pharmacovigilance
• Article 111.1: inspections of MAH
Regulatory Framework

**Volume 9** of the Rules Governing Medicinal Products in the European Union

- V 9A (Human)- Part I, Chapter 2: Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm

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**QPPV Qualified Person for Pharmacovigilance of the MAH**

MAH must have at his disposal a QPPV responsible for:

- establishing and maintaining/managing the Marketing Authorisation Holder’s pharmacovigilance system;
- having an overview of the safety profiles and any emerging safety concerns in relation to the medicinal products for which the Marketing Authorisation Holder holds authorisations;
- acting as a single contact point for the Competent Authorities on a 24-hour basis.
Volume 9A Part I Chapter 2.2.3
Elements of the Detailed Description of the Pharmacovigilance System (DDPS)

2.2.3.a) Qualified Person Responsible for Pharmacovigilance (QPPV)
2.2.3.b) Organization
2.2.3.c) Documented Procedures
2.2.3.d) Databases
2.2.3.e) Contractual Arrangements with Other Persons or Organizations Involved in the Fulfillment of Pharmacovigilance Obligations
2.2.3.f) Training
2.2.3.g) Documentation
2.2.3.h) Quality Management System
2.2.3.i) Supporting Documentation

Coordination of PhV Inspections and the centralized procedure
PhV Inspection Policy

- Objectives of the policy:
  - Conduct PhV inspections
  - Inspection resources efficiently allocated/used
  - Increased awareness on inspections and compliance of MAHs
  - Publication of anonymised data on inspections.

PhV Inspection programmes: preparation and implementation of a risk based programme for routine PhV inspections (ongoing since 2007)

Type of inspections: routine (as part of the PhV inspection programme) and targeted (when concerns raised)

Composition of the inspection team

Focus and preparation of the scope of the inspection: depending if it is a routine system inspection, targeted inspection or targeted product-specific inspection

Considerations for the selection of the sites to be inspected
Types of Inspection

Routine inspections
- Focus on systems but products used as examples
- National inspections programmes will fulfil the need for routine inspections/ May be requested by the CHMP if needed
- Inspection outcome available to the CHMP
- Timing:
  - Within 4 years of placing product on the market
  - Re-inspections at intervals
  - Timing of the first and any further inspection to be based on risk assessment
- Programme for inspection (for CAPs) based on risk assessment
- National inspection programmes determined by the NCAs
Types of Inspection

Targeted inspections

- more likely to be CHMP or CVMP requested (product specific or system)
- list of triggers
- Timing: when trigger is recognised and inspection deemed by the CHMP or CVMP and the competent authority where the QPPV is located

Risk based programme for CAP PhV inspections
Volume 9A:

CHMP, in conjunction with the Competent Authority of the Member State (MS) in whose territory the MAH’s QPPV is located and applicable Pharmacovigilance and Inspectors’ Working Parties, ... determine a programme for inspection in relation to centrally authorised products (CAPs).

Inspections prioritised based on the potential risk to public health, the nature of the products, extent of use, number of products that the MAH has on the EEA market and other risk factors.

Risk based PhV Inspection programme

4 yearly, rolling, inspection cycle

Revision takes place bi-annually – addition of new companies and products, review of risk-based priorities

Agency Inspection Sector, PhV Inspectors and the PhV WP are involved in the preparation/revision of the plan which is then submitted for adoption by the CHMP

Inspection usually by NCA of Member State where QPPV is located – other inspectors or experts may perform the inspection (e.g. rapporteur)
Risk based PhV Inspection programme

General Points

Inspections are requested as system/company oriented inspections with one or more specific products selected as examples.

If a triggered inspection is to be conducted in a similar timeframe it may replace the planned routine inspection.

It is anticipated that national inspection programmes will fulfil the need for many of these routine inspections.

Inspections may be in EU at QPPV or other site, and may be outside EU at global pharmacovigilance centres, data processing facilities etc.

Primary prioritisation Factors

- MAH has never been inspected
- MAH has marketed product that received a commission decision at least 3 years ago
- MAH was inspected and critical findings were identified
- MAH has a product with Risk Minimization Activities
- MAH has the QPPV/PhV activity subcontracted or multiple licensing partners
- Re-inspection date recommended by the inspectors as result of a previous inspection
Risk based PhV Inspection programme
Secondary prioritisation factors (examples)

- MAH involved in a merger or takeover process
- MAH has changed their system significantly
- MAH changed the QPPV
- Adverse comments/safety concerns from non-EU agencies/bodies
- Non EU companies PhV system may be focused on third country regulations
- MAH has many products in the market, covering many active ingredients / MAH has only one CAP on the market
- Size of the MAH – resource and experience
- Products with large sale volume/patient exposure
- Absence of the DDPS (e.g. products authorised prior 2005)

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Triggers to be considered for targeted inspections

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Triggers for targeted inspections

Delays / failure to carry out specific obligations or follow-up measures;
Delays in expedited or periodic reporting or incomplete reporting;
Submission of poor quality or incomplete PSURs;
Inconsistencies between reports and other information sources;

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Triggers for targeted inspections

Change in risk-benefit balance;
Failure to communicate change in risk-benefit balance;
Previous inspection experience/Information received from other authorities;
Poor follow-up to requests for information from the authorities;
Communication of information on PhV concerns to the general public without giving prior or simultaneous notification to the Competent Authorities or Agency as applicable;
Product withdrawal with little or no advance notice to the EEA Competent Authorities;

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Inspection Procedure

Steps of the Procedure:

- Preparation of the inspection request
- Designation of the Inspection team
- Inspection announcement
- Inspection Conduct
- Preparation of the Inspection Report
- Circulation of the Inspection Report
- Follow up of the inspection

Circulation of the Inspection Report

- Inspection report sent to Agency inspection sector
- Reports checked against requirements and request
- Reports sent to Rapporteur/Co-Rapporteur and CHMP
- Reports sent to MAH after agreement by CHMP
- Consequences discussed and further actions decided
Statistics on PhV H-CAP Inspections

CHMP requested PhV inspections 2000-2008

Statistics Risk Based Programme Routine Inspections

MAH inspections in the 2009 risk based programme for routine PhV inspections
Thank you