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Annual report of the Pharmacovigilance Inspectors Working Group for 2013

Adopted by the PhV IWG on 20 March 2014

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1. Introduction

This document is the sixth annual report of the Pharmacovigilance Inspectors Working Group (PhV IWG). The PhV IWG[1] has been established by the European Medicines Agency (EMA), within the scope of Article 57(1)(i) of Regulation (EC) No 726/2004. Following a report on the first year of operation, the PhV IWG mandate was endorsed by the Heads of Medicines Agencies on 18-19 May 2009 and by the EMA Management Board on 1 October 2009, thereby formally establishing the PhV IWG.

The PhV IWG focuses on harmonisation and co-ordination of pharmacovigilance related activities at European Union level. The group's role and activities are described in more detail in its workplan. The group supports the co-ordination of the provision of pharmacovigilance inspection related advice and provides a link with other groups such as CHMP[2], CVMP[3], PRAC (H)[4] and PhV WP (V)[5].

This annual report is set out in line with the format and objectives of the 2013 workplan.

2. Meetings

The plenary meetings, involving pharmacovigilance inspectors dealing with human medicinal products and pharmacovigilance inspectors dealing with veterinary medicinal products, were held on the following dates:

- 21-22 March 2013;
- 13-14 June 2013;
- 19-20 September 2013;
- 05-06 December 2013.

Due to the implementation of the new human pharmacovigilance legislation, the meetings were organised to accommodate a joint session and two separate sessions, one dedicated to human and one to veterinary medicinal products only.

In addition, a number of virtual meetings took place this year, using teleconference or equivalent:

For human medicinal products: several *ad-hoc* teleconferences/meetings, including PhV IWG and PRAC delegates, when applicable, were organised (remote access provided) in relation to the implementation of the new pharmacovigilance legislation, and specifically to support the development of the Union procedures on pharmacovigilance inspections. In addition, *ad-hoc* participation of PhV IWG delegates in PRAC meetings (mainly by remote access) was organised to discuss the outcome and follow up of specific PhV inspections, as necessary.

- For veterinary medicinal products: a number of subgroup teleconferences/meetings (e.g. PhV IWG - PhV WP) to discuss topics of interest and draft documents were organised (dates: 05/02/2013, 15/02/2013, 18/03/2013, 24/05/2013, 04/06/2013, 09/09/2013, 25/11/2013)

[1] Pharmacovigilance Inspectors Working Group
[2] Committee for Medicinal Products for Human Use
[3] Committee for Medicinal Products for Veterinary Use
[4] Pharmacovigilance Risk Assessment Committee (Human Medicinal Products)
[5] Pharmacovigilance Working Party (Veterinary Medicinal Products)

3. Development of pharmacovigilance inspections relating to centralised products

For human medicinal products the CHMP with input from the Pharmacovigilance Risk Assessment Committee (PRAC) and in conjunction with the competent authority of the Member State (MS) in whose territory the pharmacovigilance system master file is located (supervisory authority) and the Inspectors' Working Group, have determined and maintain a programme for inspection in relation to centrally authorised products (CAPs), in accordance with GVP Module III on pharmacovigilance inspections.

For veterinary medicinal products, according to Volume 9B, guidelines on pharmacovigilance regulatory obligations and pharmacovigilance inspections of veterinary medicinal products, the CVMP supported by the Pharmacovigilance Working Party, in conjunction with the competent authority of the Member State (MS) in whose territory the MAH's QPPV is located and the Inspectors' Working Group, have determined and maintain a programme for inspection in relation to centrally authorised products (CAPs).

The inspections in those programmes are 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.

The focus of these inspections is to determine whether the MAH has the personnel, systems and facilities in place to meet their regulatory pharmacovigilance obligations for CAPs in the EEA. These inspections are requested as system inspections with one or more specific products selected as examples, for which specific information can be traced and verified through the various processes. This provides a practical evidence for the functioning of the MAH's pharmacovigilance system in the European Union and their compliance with the regulatory requirements.

In general, it is anticipated that national inspection programmes will fulfil the need for the routine inspections of this programme and therefore it is expected that the inspection programme is achieved mainly through the national programmes. However there are situations where these inspections might be specifically requested by the CHMP or CVMP, as applicable, (e.g. global pharmacovigilance sites in third countries). For cause inspections are also reflected in this programme as they may replace the need for a routine inspection.

The results presented in table 1 and 2 show the number of inspections requested in relation to the human and veterinary 2013 pharmacovigilance inspection programmes, respectively, and split by the type of site inspected.

Table 1- Human pharmacovigilance inspections requested in 2013 in the context of the programme for pharmacovigilance inspection of companies with CAPs

	QPPV (MAH) site	Global PhV site	QPPV Subcontractor site	Subcontractor /Licensing partner site	Affiliate site	Total
CHMP Requested	3	2		0	1	6**
National Inspection Programmes	21	1	14	0	1	37
Total	24	3	14	0	2	43*

Table 2- Veterinary pharmacovigilance inspections requested in 2013 in the context of the programme for pharmacovigilance inspection of companies with CAPs

	QPPV (MAH) site	Global PhV site	QPPV Subcontractor site	Subcontractor /Licensing partner site	Affiliate site	Total
CVMP Requested	7	0	0	0	0	7**
National Inspection Programmes	1	0	0	0	0	1
Total	8	0	0	0	0	8*

* It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2013 in EU/EEA, which is approximately 195 inspections for human medicinal products and 49 inspections for veterinary medicinal products.

** One human and two veterinary site inspections were requested by the CHMP and CVMP, respectively in 2013 but will be conducted in 2014.

4. Harmonisation topics

4.1. Implementation of the new human pharmacovigilance legislation

In relation to human medicinal products and in order to support further harmonisation for the mutual recognition of pharmacovigilance inspections within the EU the group in 2013 focused on the preparation of the following Union procedures:

- Union procedure on the coordination of EU pharmacovigilance inspections;
- Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections;
- Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products;
- Union procedure on sharing of pharmacovigilance inspection information;
- Union recommendations on training and experience of inspectors performing pharmacovigilance inspections;
- Union guidance on record keeping and archiving of documents obtained or resulting from pharmacovigilance inspections.

The group also reviewed, as applicable, existing inspection procedures and guidance for pharmacovigilance inspections for medicinal products for human use conducted in the context of the centralised procedure, in particular to support the implementation of the new pharmacovigilance legislation.

In addition, the group contributed to the preparation of Q&A(s) and other guidance documents and specific guidance on the use of EMA databases and IT systems in relation to the pharmacovigilance system master file location, the contact details of the qualified person responsible for

pharmacovigilance and inspection information sharing. The work on the implementation of the new pharmacovigilance legislation is ongoing.

4.2. Procedures and guidance documents

The following documents, concerning human medicinal products, have been prepared in 2013 and are expected to be finalised and published in 2014:

- Union procedures on pharmacovigilance inspections (please see section 4.1 for details).

The following document concerning veterinary medicinal products have been prepared in 2013 and are expected to be finalised and published in 2014:

- Revised classification of inspection findings, as part of the revised procedure for reporting of pharmacovigilance inspections requested by the CVMP.
- Revised guidance on inspection programmes and risk-based approach, as part of the revised inspection procedures, as appropriate.

4.3. Joint inspections

From the total of six CHMP and seven CVMP pharmcovigilance site inspection requested in 2013 and conducted in 2013/2014, one CHMP requested and six CVMP requested have been joint inspections involving more than one MS (see table 1 and table 2 in section 3).

4.4. Training and development

- A Pharmacovigilance Inspectors Working Group (PhV IWG) training course took place at EMA, London, UK from 11th to 13th of November 2013. The training was organised by the European Medicines Agency (human and veterinary), supported by the programme committee (Belgium, France, Germany (BfArM and BVL), Greece, Italy, Poland, and the United Kingdom). Inspectors and assessors of both, veterinary and human units of Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom) as well as inspectors, assessors / experts from EU observer countries (Bosnia and Herzegovina, Kosovo, Former Yugoslav Republic of Macedonia, Montenegro, Serbia, Switzerland) and from third countries (Brazil, Taiwan) participated. Representatives from Canada and Egypt also attended via remote access. Key objectives of the training were:
  - to promote awareness and better understanding of new legislation and/or guidance, as applicable, with focus to the new pharmacovigilance legislation in relation to human medicinal products and to Volume 9B in relation to veterinary medicinal products),
  - to share experiences from inspections (human and veterinary) conducted by individual member states in order to promote further harmonisation of inspection approaches,
  - to build an understanding and promote further interaction between assessors and inspectors;
- The following topics were presented and/or discussed in the workshops:
  - discussion on the current status of PhV inspections in Europe,
  - presentation and discussion on anonymised inspection findings and their classification from different Member States,

- topics on the new EU pharmacovigilance legislation (human medicinal products) – with focus on the main changes, transitional measures and impact on inspection processes (human),
- findings related to the new legislation requirements with focus on the pharmacovigilance system master file (human),
- union procedures on pharmacovigilance inspections (human),
- how do member states organize interactions between inspectors and assessors, with focus on interactions between assessors and inspectors when preparing and/or triggering inspections and in the follow up of pharmacovigilance inspections,
- quality management system in small companies and minimum requirements,
- new reporting requirements; use of EudraVigilance data analysis system (EVDAS) by pharmacovigilance inspectors of MAHs of human medicinal products / EV DAS queries available; data quality checks and what is expected that inspectors check at pharmacovigilance inspection in relation to ICSR quality (human),
- how to check during inspections SmPC updates and alignments of CCDS and SmPc (human),
- analysis of pharmacovigilance data for Inspectors (human),
- signal detection and pharmacovigilance inspection,
- PSUR and pharmacovigilance inspection,
- EudraVigilance-veterinary data warehouse (EV-Vet DWH): queries useful for inspectors/assessors of veterinary medicinal products and practical examples where information from EV-Vet DWH has been used for inspection (vet),
- detailed description of the pharmacovigilance system (DDPS) assessment (vet),
- combined GMP and PhV inspections (vet),
- inspection programmes and risk-based approach (vet);

- During 2013, training was also provided in the following areas:
  - EudraVigilance (EV) and data analysis system (EVDAS) / data warehouse (DWH) training of pharmacovigilance inspectors of human medicinal products took place on 11 December 2013 and 12 December 2013,
  - data analysis (data in Excel®) for pharmacovigilance inspectors of MAHs of human medicinal products workshops took place on 7 May 2013 and 22 May 2013 (via remote access) and on 5 December 2013,
  - pharmacovigilance inspectors training in good vigilance practice and new processes, within the scheduled PhV IWG meetings for 2013. The topics covered in 2013 were PSUR and referrals. The group also routinely discussed queries received by EMA, in particular in relation to the pharmacovigilance system master file requirements.

5. Pharmacovigilance topics

A) In relation to medicinal products for human use

- The PhV IWG has prepared and is maintaining the 2013-2016 risk-based programme for routine pharmacovigilance inspections of MAHs connected with human centrally authorised products (CAPs).
- Pharmacovigilance inspectors have also provided recommendation(s) to the PRAC in relation to pharmacovigilance inspections or related assessment issues.
- During the PhV IWG meetings held in 2013, discussions on the following topics have taken place:
  - development of peer review of case studies;
  - sharing and discussion of inspection report findings;
  - EudraVigilance (EV) and data analysis system (EVDAS) / data warehouse (DWH) updates and draft “Best practice guide for coding Individual Case Safety Reports (ICSRs)”;
  - handling of non-serious cases from non-interventional studies;
  - off-label use;
  - management of deviations and associated corrective and preventive actions listed in the pharmacovigilance system master file (PSMF), delays in the implementation or inappropriate corrective and preventive actions;
  - patient support programmes and market research programmes workshop follow up;
  - EU Incident Management Plan for human medicines;
  - MHRA Press Release: Medicines regulator implements innovative software to analyse risk data and target inspection activity;
  - updates on the proposals for the mandate of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Working Group(s) (“WG”) on GCP & Pharmacovigilance (“GVP”);
  - haemovigilance and inspections;
  - applicant / MAH queries on the implementation of the new pharmacovigilance legislation.

B) In relation to medicinal products for veterinary use

- The PhV IWG has prepared and is maintaining the 2013-2015 risk-based programme for routine pharmacovigilance inspections of MAHs connected with veterinary centrally authorised products (CAPs). These programmes (human and veterinary) are not publicly available as they contain confidential information.
- During the PhV IWG meetings held in 2013, discussions on the following topics have taken place:
  - development of peer review of case studies;
  - sharing and discussion of inspection report findings;
  - EudraVigilance and EudraVigilance data analysis system demonstration of queries available to pharmacovigilance inspectors of veterinary medicinal products to facilitate the preparation of inspections (vet);

- PSUR and DDPS assessment;
- joint pharmacovigilance inspections;
- request for MAH/inspectee feedback on the process of pharmacovigilance inspections;
- queries on guidance / legislation interpretation.

6. Liaison with other groups

Interaction with the Pharmacovigilance Risk Assessment Committee (PRAC)

- Sessions for PhV IWG – assessors interaction were organised during the plenary meetings of PRAC (04 December 2013) and PhV IWG (12 November – PhV IWG training) to discuss topics related to the implementation of the new human pharmacovigilance legislation and specifically the Union procedure on the management of pharmacovigilance inspection findings which may significantly impact the benefit/risk profile of the concerned medicinal products (see section 2 and section 4.1).
- *Ad-hoc* participation of PhV IWG delegates in PRAC meetings (mainly by remote access) was organised to discuss the outcome and follow up of specific PhV inspections, as necessary.

Interaction with the CVMP Pharmacovigilance Working Party

- The PhV IWG interacted with assessors on topics related to:
  - Harmonisation of the assessment of the detailed description of the pharmacovigilance system (DDPS) document;
  - follow up of pharmacovigilance inspections;
  - training of assessors and inspectors;
  - preparation and maintenance of the risk-based programme for routine pharmacovigilance inspections of MAHs connected with veterinary centrally authorised products (CAPs).

Communication with the public and external bodies

- Delegates from the PhV IWG have participated and given presentations on behalf of the group in different European conferences, covering different topics of public interest.
  - 14th EudraVigilance information day (23 May 2013), in relation to pharmacovigilance inspections and the first experiences with the pharmacovigilance system master file.
  - Workshop on patient support programmes and market research programmes: understanding the diversity of such programmes and the management of safety information (7 June 2013).
- Interaction with human and veterinary medicinal product industry representatives took place during a dedicated session on 13 November 2013 as part of the Pharmacovigilance Inspectors Working Group training course at EMA, London, UK (see section 4.4).
  - For the details of the activities of the PhV IWG see the workplan for 2014.