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Annual report of the Pharmacovigilance Inspectors Working Group for 2015

Adopted by the PhV IWG on 09 June 2016

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1. Introduction

This document is the eighth annual report of the Pharmacovigilance Inspectors Working Group (PhV IWG). The PhV IWG[1] has been established by the European Medicines Agency (hereinafter "the Agency") 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 Agency's 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 EU (hereinafter also "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 2015 work plan.

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:

- 19-20 March 2015;
- 11-12 June 2015;
- 01-02 October 2015;
- 03-04 December 2015.

Meetings included 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: two subgroup teleconference/meetings (i.e. PhV IWG - PhV WP) were organised to discuss topics of interest and draft related documents.

[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. Pharmacovigilance inspections relating to centrally authorised medicinal products

3.1. General overview

For human medicinal products the CHMP with input from the PRAC and in conjunction with the competent authority of the MS[6] 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 CAPs[7], in accordance with GVP[8] Module III on pharmacovigilance inspections and the Union procedure on the coordination of EU 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 MS in which territory the MAH's QPPV[9] is located and the inspectors' working group, have determined and maintain a programme for inspection in relation to 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[10] has on the EEA[11] 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 EU 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 2015 pharmacovigilance inspection programmes, respectively, and split by the type of site inspected.

[6] Member State
[7] Centrally Authorised Products
[8] Good Vigilance Practice
[9] Qualified Person Responsible for Pharmacovigilance
[10] Marketing Authorisation Holder
[11] European Economic Area

Table 1 - Human pharmacovigilance inspections requested in 2015 in the context of the programme for pharmacovigilance inspection of companies with CAPs

	QPPV / PSMF (MAH) site	Global PhV site	Subcontractor / licensing partner / affiliate site	Total
CHMP requested	4	1	2	7**
National inspection programmes	26	0	10	36
Total	**30**	**1**	**12**	**43***

Table 2 - Veterinary pharmacovigilance inspections requested in 2015 in the context of the programme for pharmacovigilance inspection of companies with CAPs

	QPPV (MAH) site	Global PhV site	Subcontractor / licensing partner / affiliate site	Total
CVMP requested	6	0	1	7**
National inspection programmes	4	0	0	4
Total	**10**	**0**	**1**	**11***

* It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2015 in EU/EEA, which is approximately 127 inspections for human medicinal products and 57 inspections for veterinary medicinal products.

****** One human medicinal product site inspection was requested by the CHMP in 2015 but will be conducted in 2016. One veterinary medicinal product site inspection was requested by the CVMP in 2015 but will be conducted in 2016.

3.2. Categorisation of findings for CHMP requested inspections conducted in 2015

A total of 70 deficiencies, comprising 7 critical (10%), 28 major (40%) and 35 minor (50%) were recorded for the CHMP requested inspections conducted in 2015 (period covered from 01/01/2015 until 31/12/2015).

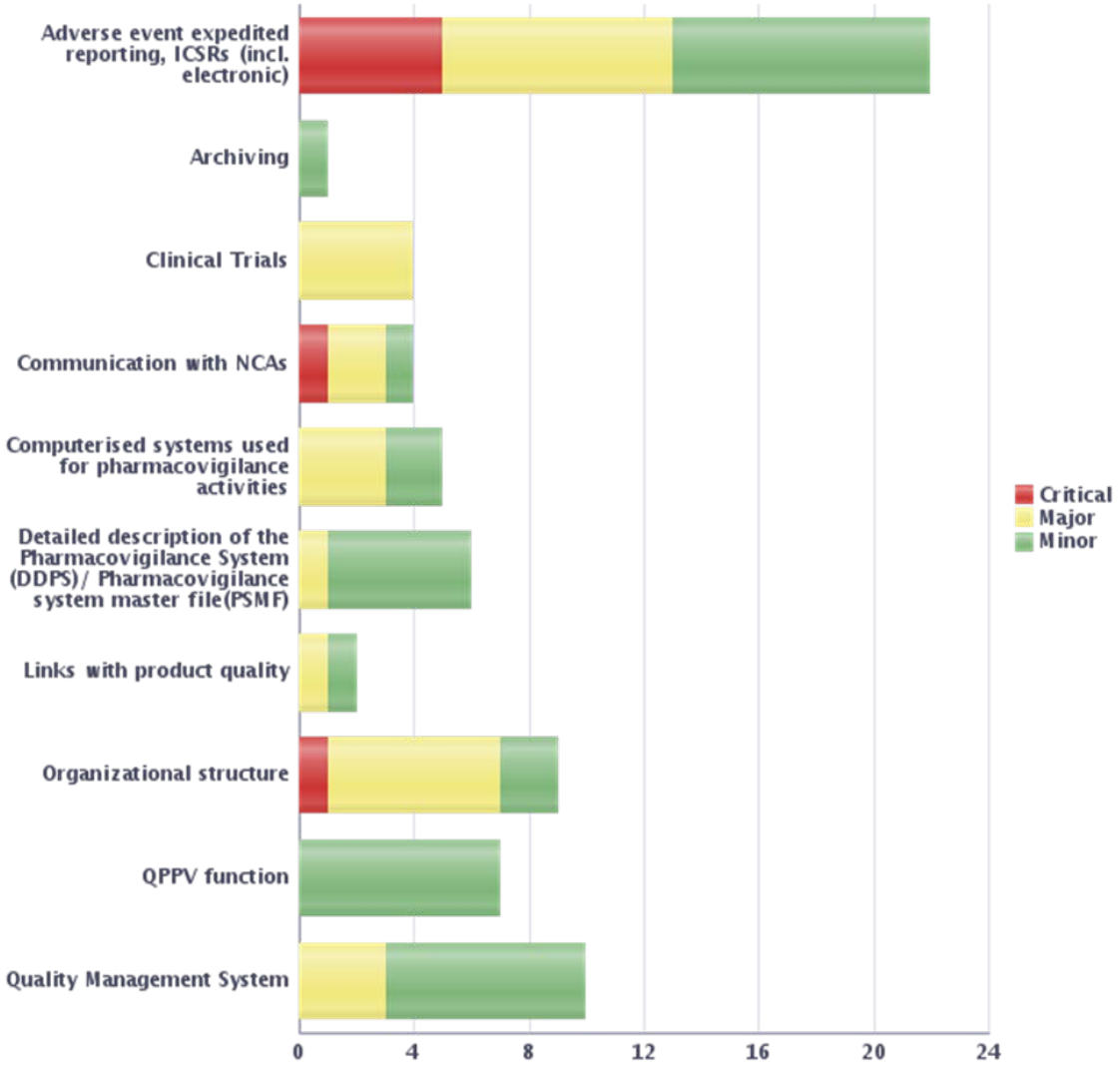
The main findings observed in the 2015 inspections are detailed in figure 1 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings were:

- adverse event reporting;
- quality management system;
- organisational structure.

The data in the figure below relates to inspections conducted in 2015 and therefore it includes deficiencies from the six inspections requested and conducted in 2015 and from one inspection requested in 2014 and conducted in 2015. The number of inspections requested and conducted is not

consistent due to the fact that one inspection requested in the last 3 months of the year 2014 was conducted in 2015 and one inspection requested in the last 3 months of 2015 will be carried out in 2016.

Figure 1. Number of findings with regard to the main categories graded by critical, major and minor



3.3. Categorisation of findings for CVMP requested inspections conducted in 2015

A total of 39 deficiencies, comprising 0 critical, 12 major (30.8%) and 27 minor (69.2%) were recorded for the CVMP requested inspections conducted in 2015 (period covered from 01/01/2015 until 31/12/2015).

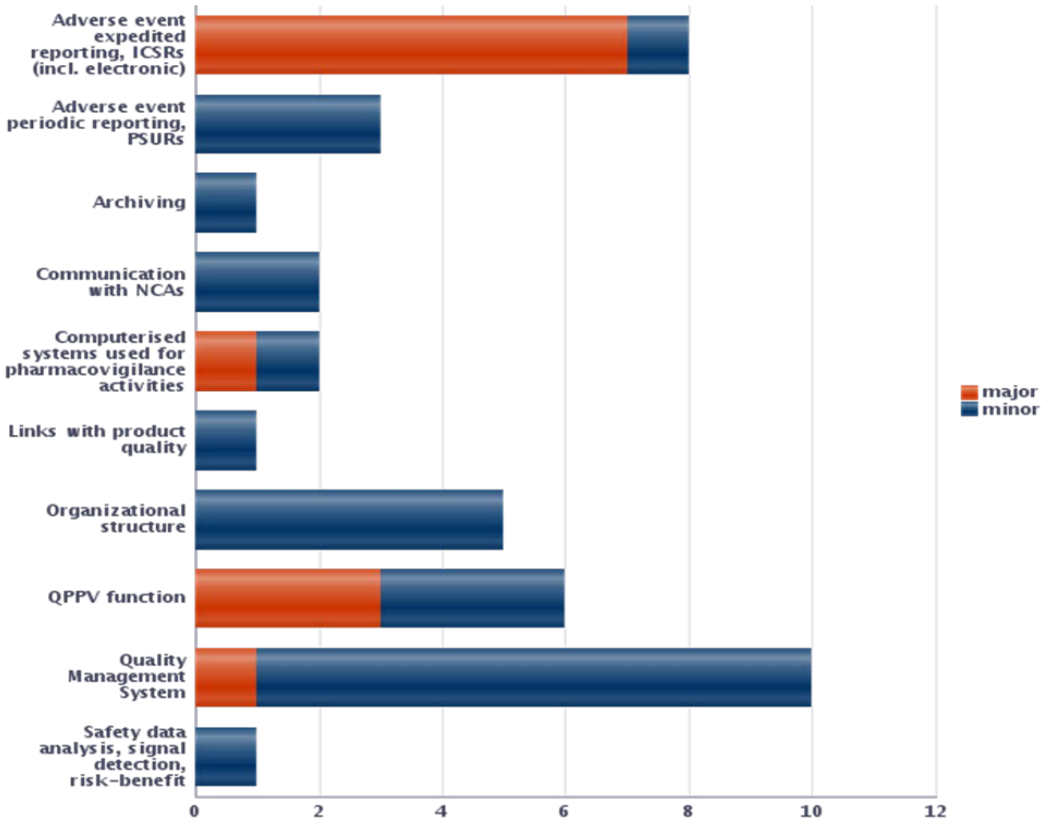
The main findings observed in the 2015 inspections are detailed in figure 2 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings were:

- quality management system;
- adverse event reporting;

- qualified person for pharmacovigilance (QPPV) function.

The data in figure 2 below relates to inspections conducted in 2015 and therefore it includes deficiencies from the six inspections requested and conducted in 2015. The number of inspections requested and conducted is not consistent due to the fact that one inspection requested in 2015 will be carried out in 2016.

Figure 2. Number of findings with regard to the main categories graded by critical, major and minor



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 2015 focused on the preparation of the following Union procedures:

- union guidance on record keeping and archiving of documents obtained or resulting from pharmacovigilance inspections (finalised for publication in 2016).

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

- GVP Module IV on pharmacovigilance audits (Rev.1);
- GVP Module XII on safety-related action on authorised medicinal products;
- good practice guide on recording, coding, reporting and assessment of medication errors;
- good practice guide on risk minimisation and prevention of medication errors;
- Q&A(s)[12] and other guidance documents;
- specific guidance on the use of the Agency 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.

4.2. Procedures and guidance documents

The following documents have been finalised and published in 2015:

- appendix 1 (pharmacovigilance inspection report template) of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections (revision1) (concerning human medicinal products);
- appendix 1 (pharmacovigilance inspection report template) of the procedure for reporting of pharmacovigilance inspections requested by the CVMP (revision1) (concerning veterinary medicinal products).

The following documents have been prepared in 2015 and are expected to be finalised and published in 2016:

- member State requirement for pharmacovigilance contact person at national level.
- union guidance on record keeping and archiving of documents obtained or resulting from pharmacovigilance inspections (concerning human medicinal products).
- revised guidance on inspection programmes and risk-based approach as part of the revised inspection procedures, as appropriate (concerning veterinary medicinal products).

4.3. Joint inspections

From the total of seven CHMP and seven CVMP pharmacovigilance site inspections requested in 2015 and conducted in 2015/2016, five CHMP requested and three 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 the European Medicines Agency, London, United Kingdom, from 9 to 11 of November 2015. The training organisation was supported by the programme committee (France (V), Germany (BfArM, PEI and BVL) (H+V), Italy (H+V), the Netherlands (H+V) and the United Kingdom (H). Inspectors and assessors of both, veterinary and human units of Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia,

[12] Question(s) and Answer(s)

Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom) as well as inspectors, assessors/experts from EU observer countries (former Yugoslav Republic of Macedonia, Montenegro, Kosovo, Switzerland) and from non-EU countries (China, Japan, Mexico, Russia, Singapore, Chinese Taipei, United Republic of Tanzania, USA) and remotely by Adobe connect (Canada, Hungary, Belgium, Estonia, Finland) participated.

Key objectives of the training were:

- to promote awareness and better understanding of legislation and/or guidance, as applicable, with focus on the good pharmacovigilance practices (GVP) and Union procedures on pharmacovigilance inspections and their implementation 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 MS in order to promote further harmonisation of inspection approaches;
- to build an understanding and promote further interaction between assessors and inspectors;
- to share good pharmacovigilance practices competence and promote communication and harmonisation with non-EU countries.

- The following topics were presented and/or discussed in the human medicinal products related workshops:
  - inspection of RMPs, signal detection, PSUR and interaction with PRAC/assessors;
  - regulatory procedures and product information updates;
  - computer validation;
  - WEB-RADR: recognising adverse drug reactions - project;
  - topics on the human medicinal products EU pharmacovigilance legislation with focus on the Union procedures on pharmacovigilance inspections, main changes and impact on inspection processes;
  - PSUR[13] repository (human);
  - medical literature monitoring and impact on MAHs;
  - PSMF & third party inspections;
  - analysis of pharmacovigilance data for inspectors;
  - clinical trials and safety reporting;
  - interactions between assessors and inspectors when preparing and/or triggering inspections and in the follow-up of pharmacovigilance inspections;
  - EV[14] and EVDAS[15] / DWH[16] training;
  - presentation and discussion on anonymised inspection findings and their classification from different Member States;
  - international collaboration / PICs activities.

[14] EudraVigilance
[14] EudraVigilance
[15] EudraVigilance data analysis system
[16] Data Warehouse

- The following topics were presented and/or discussed in the veterinary medicinal products related workshops:
  - quality management systems – what are the minimum criteria;
  - inspection follow up - how to handle CAPA;
  - multiple MAH entities and fulfilment of requirements (DDPS, PSURs, SOPs);
  - risk-based inspection planning/ inspection of affiliates/third parties;
  - computer validation;
  - EV-Vet DWH[17]: queries useful for inspectors/assessors of veterinary medicinal products and practical examples where information from EV-Vet DWH may be used for inspection (vet);
  - interactions between assessors and inspectors when preparing and/or triggering inspections and in the follow-up of pharmacovigilance inspections;
  - presentation and discussion on anonymised inspection findings and their classification from different Member States;
  - international collaboration / PICs activities.
- The PhV IWG was updated regarding the initiative of the PIC/S[18] to expand its activities to include training in the field of PhV inspections. Initially the aim will be to facilitate joint visits, develop guidance and promote harmonisation in the field of pharmacovigilance inspections.
- During 2015, training was also provided in the following areas:
  - EV and EVDAS / DWH training;
  - pharmacovigilance inspectors training in good vigilance practice and new processes, within the scheduled PhV IWG meetings for 2015. The topics covered in 2015 were GVP Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1), risk management systems, signal management (GVP Module IX)/ signal detection. The group initiated the planning for training on the management and reporting of adverse reactions to medicinal products;
  - updates and training was also provided for the following topics:
    - PSUR[19] repository (human);
    - Article 57 database (also known as extended EudraVigilance Medicinal Product Dictionary (XEVMPD)) publication dashboard and access to national competent authorities.
    - launch of medical literature monitoring service by the Agency.
- The group also routinely discussed queries received by EMA, in particular in relation to the pharmacovigilance system master file requirements.

[17] EudraVigilance-veterinary data warehouse
[18] Pharmaceutical Inspection Co-operation Scheme
[19] Periodic Safety Update Report

5. Pharmacovigilance topics

5.1. In relation to medicinal products for human use

- The PhV IWG has prepared and is maintaining the 2015-2018 risk-based programme for routine pharmacovigilance inspections of MAHs connected with human 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 2015, discussions on the following topics have taken place:
  - development of peer review of case studies;
  - sharing and discussion of inspection report findings;
  - EV and EVDAS/ DWH updates;
  - literature monitoring;
  - management of deviations and associated corrective and preventive actions listed in the PSMF[20], delays in the implementation or inappropriate corrective and preventive actions;
  - responsibility for safety data exchange and pharmacovigilance activities for DCP/MRP products and different local MAHs;
  - risk management plans and inspection findings;
  - issues arising in the case of marketing authorisation transfer/transfer of ownership;
  - applicant/ MAH queries on the implementation of the new pharmacovigilance legislation;
  - international collaboration.

5.2. In relation to medicinal products for veterinary use

- The PhV IWG has prepared and is maintaining the 2015-2017 risk-based programme for routine pharmacovigilance inspections of MAHs connected with veterinary CAPs. These programmes (human and veterinary) are not publicly available as they contain confidential information.

[20] Pharmacovigilance System Master File

- During the PhV IWG meetings held in 2015, discussions on the following topics have taken place:
  - development of peer review of case studies;
  - sharing and discussion of inspection report findings;
  - EV-Vet and DWH demonstration of queries available to pharmacovigilance inspectors of veterinary medicinal products to facilitate the preparation of inspections (vet);
  - risk management plans;
  - risk-based inspection planning;
  - preparation of a pharmacovigilance inspection - aide memoire;
  - queries on guidance/legislation interpretation;

6. Liaison with other groups

6.1. Interaction with the PRAC

- 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 (see also section 2 and section 4.1).

6.2. Interaction with the CVMP Pharmacovigilance Working Party

- The PhV IWG interacted with assessors on topics related to:
  - interaction between assessors and inspectors;
  - preparation of a pharmacovigilance inspection - aide memoire;
  - 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 CAPs.

6.3. 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.

For the details of the activities of the PhV IWG see the work plan for 2016.