EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 June 2015
EMA/INS/PhV/380702/2015
Compliance and Inspections

Annual report of the Pharmacovigilance Inspectors Working Group for 2014

Adopted by the PhV IWG on 11 June 2015

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

This document is the seventh annual report of the Pharmacovigilance Inspectors Working Group. 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 2014 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:

- 20-21 March 2014;
- 05-06 June 2014;
- 25-26 September 2014;
- 04-05 December 2014.

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: a subgroup teleconference/meeting (i.e. PhV IWG - PhV WP) was 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 2014 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 2014 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	7	3	0	10**
National inspection programmes	32	0	16	48
Total	**39**	**3**	**16**	**58***

Table 2 - Veterinary pharmacovigilance inspections requested in 2014 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	7	0	0	7**
National Inspection Programmes	4	0	0	4
Total	**11**	**0**	**0**	**11***

* It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2014 in EU/EEA, which is approximately 167 inspections for human medicinal products and 35 inspections for veterinary medicinal products.

** One human medicinal product site inspection was requested by the CHMP in 2014 but will be conducted in 2015. It is noted that in addition to the above sites three investigator sites were inspected in 2014 for the conduct of a PASS[12] related to a human medicinal product.

3.2. Categorisation of findings for CHMP requested inspections conducted in 2014

A total of 79 deficiencies, comprising 1 critical (1.3 %), 40 major (50.7%) and 38 minor (48%) were recorded for the CHMP requested inspections conducted in 2014 (period covered from 01/01/2014 until 31/12/2014).

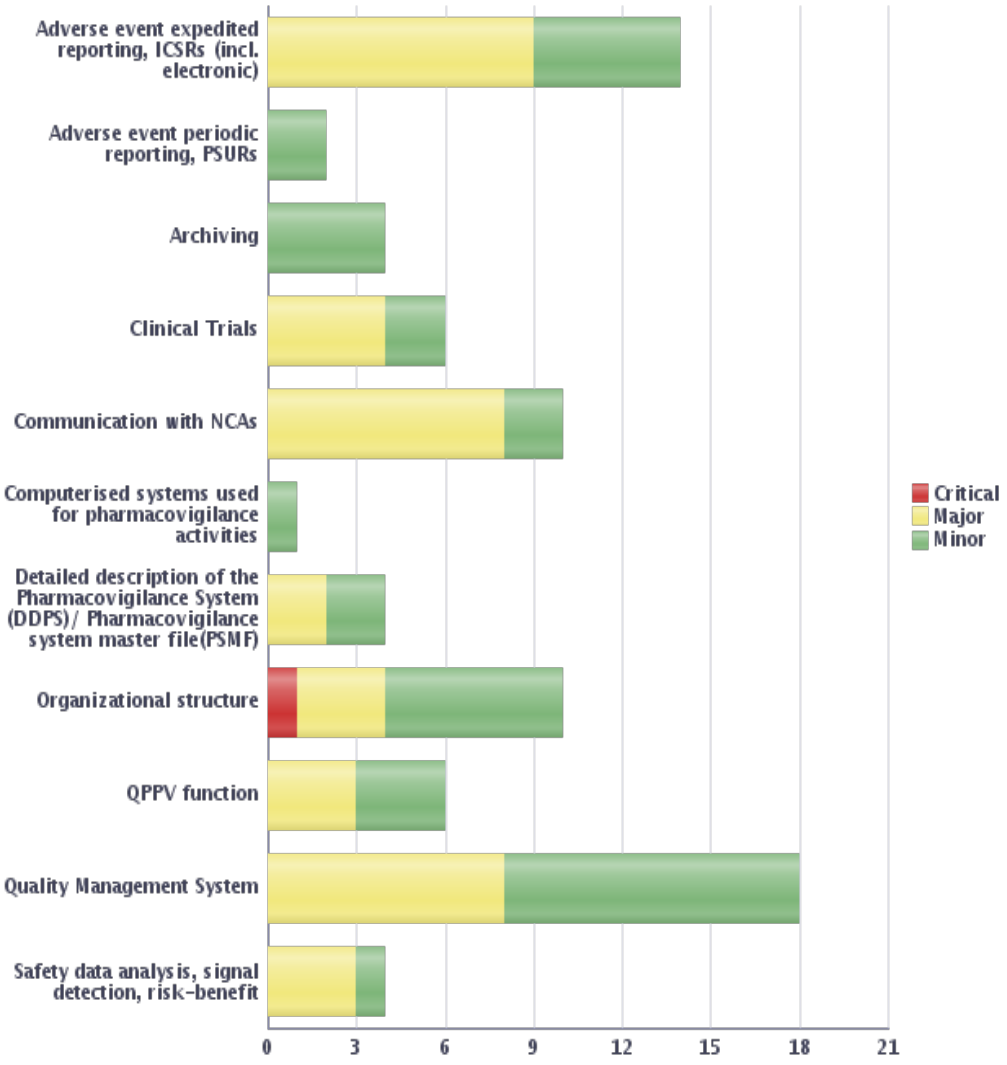
The main findings observed in the 2014 inspections are detailed in figure 1 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings were:

- quality management system;
- adverse event reporting;
- communication with national competent authorities.

[12] Post-Authorisation Safety Study

The data in the figure below relates to inspections conducted in 2014 and therefore it includes deficiencies from the nine inspections requested and conducted in 2014 and from one inspection requested in 2013 and conducted in 2014. In addition, the data include findings reported during the inspection of the three investigator sites inspected in 2014 for the conduct of a PASS. 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 2013 was conducted in 2014 and one inspection requested in the last 3 months of 2014 will be carried out in 2015.

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 2014

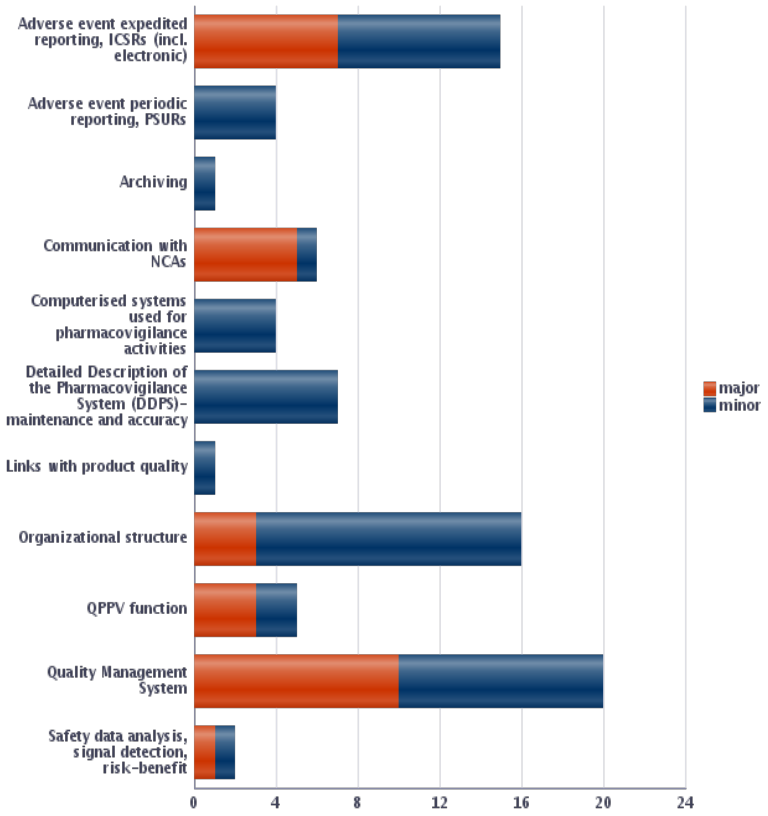
A total of 81 deficiencies, comprising 0 critical, 29 major (35.8%) and 52 minor (64.2%) were recorded for the CVMP requested inspections conducted in 2014 (period covered from 01/01/2014 until 31/12/2014).

The main findings observed in the 2014 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;
- organisational structure;
- adverse event reporting.

The data in figure 2 below relates to inspections conducted in 2014 and therefore it includes deficiencies from the seven inspections requested and conducted in 2014 and from two inspections requested in 2013 and conducted in 2014. The number of inspections requested and conducted is not consistent due to the fact that several inspections requested in the last 3 months of the year 2013 were conducted in 2014 and some inspections requested in the last 3 months of 2014 will be carried out in 2015.

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 2014 focused on the preparation of the following Union procedures:

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

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)[13] and other guidance documents and 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. 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 2014 and are expected to be finalised and published in 2015:

- 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.

The following documents concerning veterinary medicinal products have been 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.
- Procedure for reporting of pharmacovigilance inspections requested by the CVMP (revision1)

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

The following document concerning veterinary medicinal products has been prepared in 2014 and is expected to be finalised and published in 2015:

- 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 10 CHMP and seven CVMP pharmacovigilance site inspections requested in 2014 and conducted in 2014/2015, one CHMP requested and five CVMP requested have been joint inspections involving more than one MS (see table 1 and table 2 in section 3). One of the three investigator site inspections requested in 2014 in relation to the conduct of a PASS was also joint inspection.

4.4. Training and development

- A Pharmacovigilance Inspectors Working Group (PhV IWG) training course took place in Rome, Italy, from 13 to 15 of October 2014. The training was organised by the Italian Medicines Agency, 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, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom) as well as inspectors, assessors/experts from EU observer countries (Montenegro, Switzerland) and from non-EU countries (Canada, Egypt, Ghana, Japan, Saudi Arabia, USA) participated. Key objectives of the training were:
  - to promote awareness and better understanding of legislation and/or guidance, as applicable, with focus on the implementation of the 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 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 workshops:
  - non-technical aspects of inspection;
  - sharing of pharmacovigilance inspection information and implementation of the common repository;
  - computer validation;
  - the role of PRAC;
  - 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 (human);
  - PSUR[14] cycle (human);

[14] Periodic Safety Update Report

- Quality of PSURs (veterinary);
- EPITT[15] and how inspectors may use the information available;
- XEVMPD[16];
- analysis of pharmacovigilance data for inspectors (human);
- non-interventional studies that involve database research and quality assurance of databases (human);
- inspection of post-authorisation (safety) studies (human);
- interactions between assessors and inspectors when preparing and/or triggering inspections and in the follow-up of pharmacovigilance inspections;
- approaches to pharmacovigilance inspections of different types of sites (supervisory authority headquarters), national affiliates, third parties/contractors);
- expectations on contractual arrangements and communication between MAH headquarters, affiliates and distributors;
- surveillance of veterinary medicinal products;
- VedDRA[17]: best practice and exercises;
- EV-Vet DWH[18]: queries useful for inspectors/assessors of veterinary medicinal products and practical examples where information from EV-Vet DWH may be used for inspection (vet);
- presentation and discussion on anonymised inspection findings and their classification from different Member States;
- harmonisation and global pharmacovigilance including presentations from non-EU countries;

- The PhV IWG was updated regarding the initiative of the PIC/S[19] 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 2014, training was also provided in the following areas:
  - EV[20] and EVDAS[21] / DWH[22] training of pharmacovigilance inspectors of human medicinal products took place on 1 October 2014 and 21 October 2014,
  - pharmacovigilance inspectors training in good vigilance practice and new processes, within the scheduled PhV IWG meetings for 2014. The topics covered in 2014 were 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,
  - the group also routinely discussed queries received by EMA, in particular in relation to the pharmacovigilance system master file requirements.

[15] European Pharmacovigilance Issues Tracking Tool
[16] Extended EudraVigilance Medicinal Product Dictionary
[17] Veterinary Dictionary for Drug related Affairs
[18] EudraVigilance-veterinary data warehouse
[19] Pharmaceutical Inspection Co-operation Scheme
[20] EudraVigilance
[21] EudraVigilance data analysis system
[22] Data Warehouse

5. Pharmacovigilance topics

5.1. In relation to medicinal products for human use

- The PhV IWG has prepared and is maintaining the 2014-2017 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 2014, 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 and draft "Best practice guide for coding Individual Case Safety Reports";
  - literature monitoring;
  - off-label use;
  - management of deviations and associated corrective and preventive actions listed in the PSMF[23], delays in the implementation or inappropriate corrective and preventive actions;
  - inspectors' expectations with regards to recording audits performed by MAH and business partners in the PSMF;
  - responsibility for safety data exchange and pharmacovigilance activities for DCP/MRP products and different local MAHs;
  - argus database limitations;
  - risk management plans and inspection findings;
  - updates on the proposals for the mandate of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme Working Group(s) ("WG") on GCP[24] and GVP;
  - updates on the work of the PAFG[25];
  - applicant/ MAH queries on the implementation of the new pharmacovigilance legislation.

5.2. In relation to medicinal products for veterinary use

- The PhV IWG has prepared and is maintaining the 2014-2016 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.

[23] Pharmacovigilance System Master File
[24] Good Clinical Practice
[25] Pharmacovigilance Audit facilitation Group

- During the PhV IWG meetings held in 2014, 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 demonstration of queries available to pharmacovigilance inspectors of veterinary medicinal products to facilitate the preparation of inspections (vet);
  - PSUR and DDPS assessment;
  - risk management plans;
  - joint pharmacovigilance inspections;
  - request for MAH/inspectee feedback on the process of pharmacovigilance inspections;
  - queries on guidance/legislation interpretation;
  - proposal for revision of the veterinary legislation.

6. Liaison with other groups

6.1. Interaction with the PRAC

- Sessions for PhV IWG – assessors interaction were organised during the plenary meetings of PRAC on 04 December 2014 and during the PhV IWG training on 13 to 15 October 2014 to discuss the Union procedure on the management of pharmacovigilance inspection findings which may significantly impact the benefit/risk profile of the concerned medicinal products, risk management plans related issues identified as part of pharmacovigilance inspections and topics related to the implementation of the new human pharmacovigilance legislation and the interaction and sharing of information between inspectors and assessors.
- 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:
  - harmonisation of the assessment of the DDPS[26] document;
  - interaction between assessors and inspectors;
  - 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.

[26] Detailed Description of the Pharmacovigilance System

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 workplan for 2015.