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Annual report of the Pharmacovigilance Inspectors Working Group for 2017

Adopted by the PhV IWG on 7 June 2018

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1. Introduction

This document is the tenth 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 the "Union") level. The group's role and activities are described in more detail in its work plan. 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 2017 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:

- 16-17 March 2017;
- 15-16 June 2017;
- 21-22 September 2017;
- 30 November-01 December 2017 (including PhV IWG - interested parties meeting).

Meetings included a joint session and two separate sessions, one dedicated to human and one to veterinary medicinal products only. On 30 November 2017 part of the plenary meeting was dedicated to a meeting with industry stakeholder representatives.

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

- For human medicinal products: three teleconferences of the PhV IWG – PRAC subgroup, including inspectors and pharmacovigilance assessors were organised on 7 March, 13 July and 20 November 2017. 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.
- Ad hoc meetings were organised within EMA and the Article 57 subgroup of pharmacovigilance inspectors to continue the work on the data available in Article 57 database and their use for pharmacovigilance inspection planning and conduct.

[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 maintained 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 maintained 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 Tables 1 and 2 show the number of inspections requested in relation to the human and veterinary 2017 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 2017 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	5	0	1	6
National inspection programmes	21	0	6	27
Total	26	0	7	33*

Table 2 - Veterinary pharmacovigilance inspections requested in 2017 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	1	8**
National inspection programmes	4	0	0	4
Total	11	0	1	12*

* It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2017 in EU/EEA, which is 229 inspections for human medicinal products and 84 inspections for veterinary medicinal products.

** One veterinary medicinal product site inspection was requested by the CVMP in 2017 but was conducted in 2018.

3.2. Categorisation of findings for CHMP requested inspections conducted in 2017

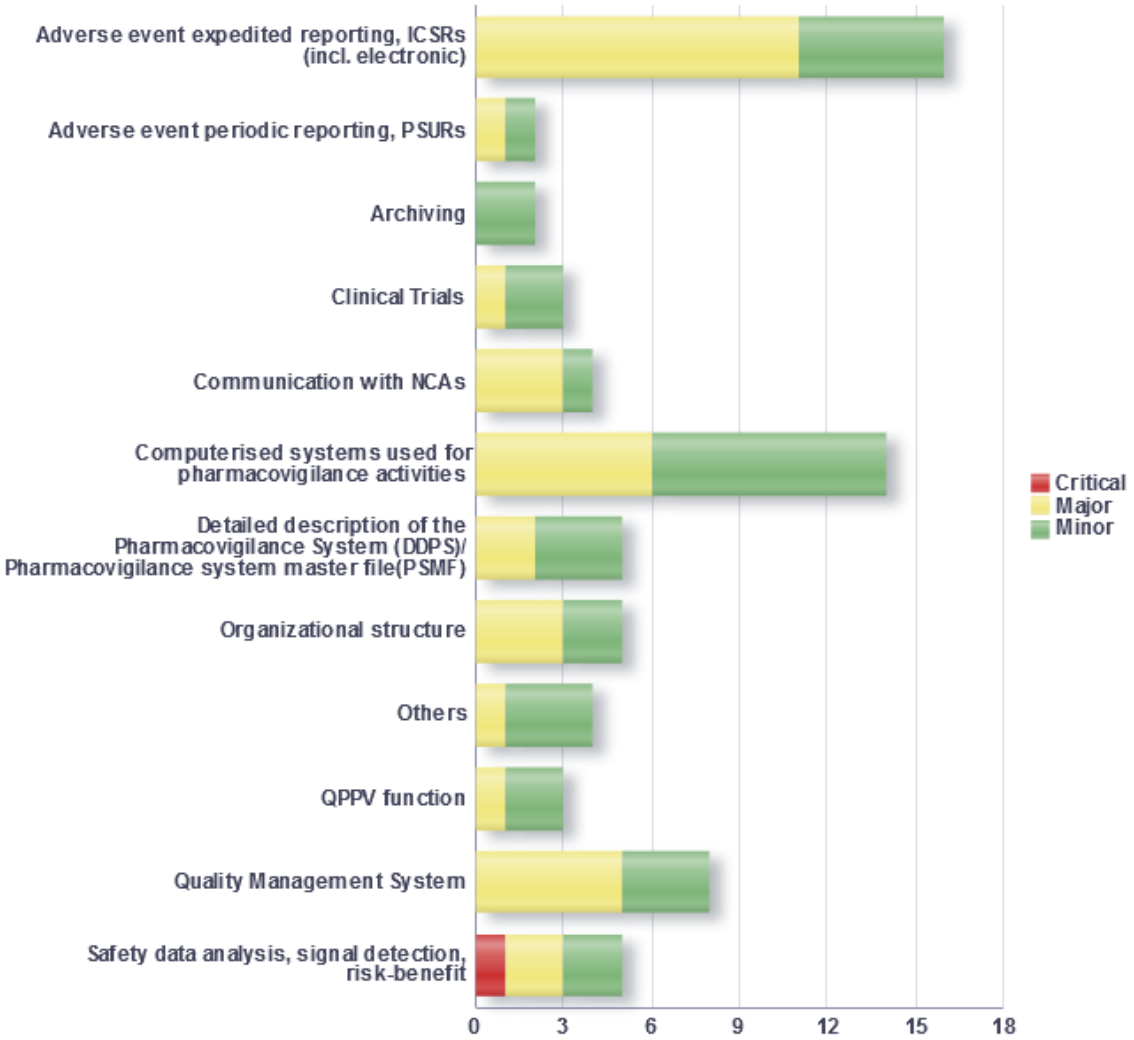
A total of 71 deficiencies, comprising 1 critical (1,4%), 36 major (50,7%) and 34 minor (47,9%) were recorded for the CHMP requested inspections conducted in 2017 (period covered from 01/01/2017 until 31/12/2017).

The main findings observed in the 2017 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;
- computerised system used for pharmacovigilance activities;
- quality management system.

The data in the figure 1 below relates to 7 inspections conducted in 2017. The number of inspection requested and conducted is not consistent due to the fact that one inspection requested in the last 3 months of the year 2016 was conducted in 2017.

Figure 1 - Number of findings with regard to the main categories graded by critical, major and minor for CHMP inspections requested



3.3. Categorisation of findings for CVMP requested inspections conducted in 2017

A total of 28 deficiencies, comprising 0 critical, 10 major (35,7%) and 18 minor (64,3%) were recorded for the CVMP requested inspections conducted in 2017 (period covered from 01/01/2017 until 31/12/2017).

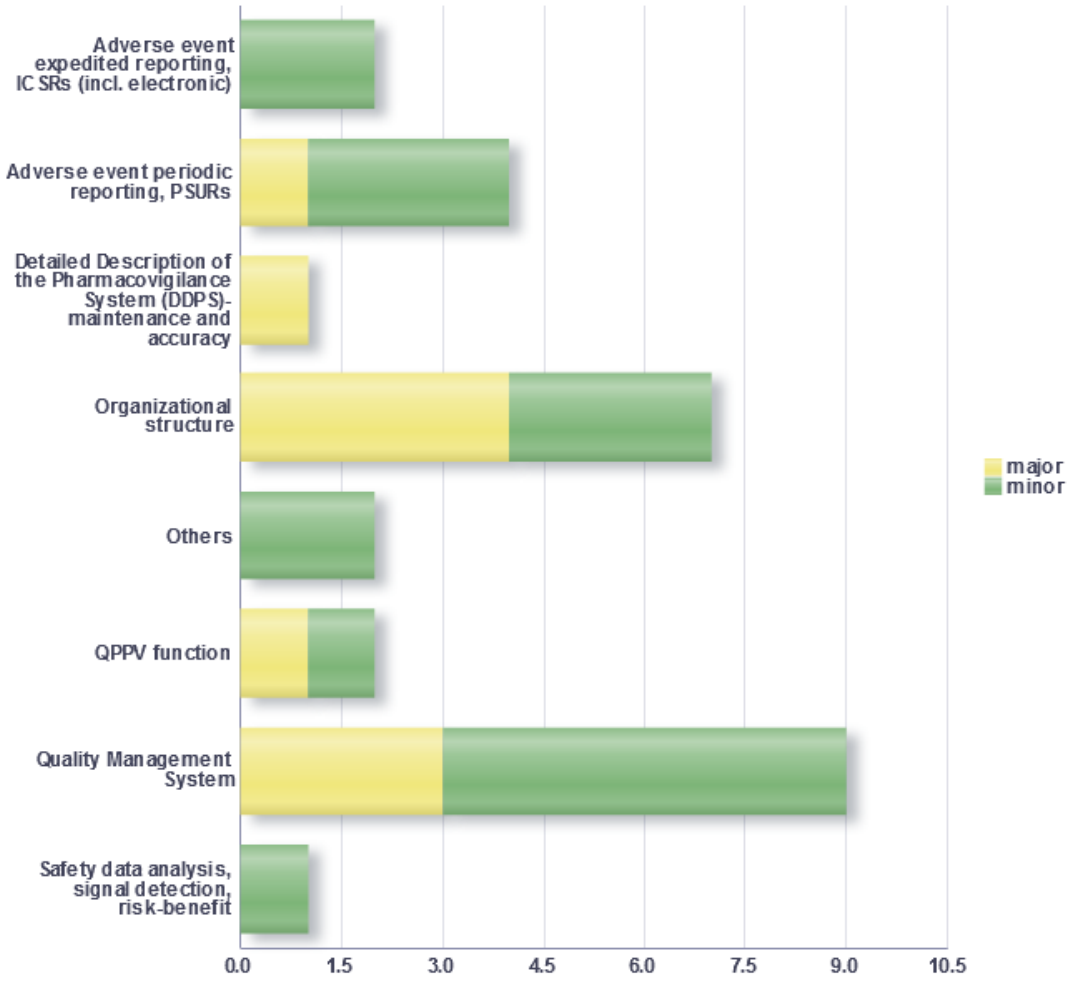
The main findings observed in the 2017 inspections are detailed in Figure 2 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings were:

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

The data in Figure 2 below relates to 7 inspections, conducted in 2017.

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 2017 was conducted in 2018.

Figure 2 - Number of findings with regard to the main categories graded by critical, major and minor for CVMP inspections requested



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, in 2017 the group continued the work on the preparation of the following Union procedures and guidance documents:

- GVP Module II on pharmacovigilance system master file (Rev 3);
- guideline on pre-authorisation pharmacovigilance inspections;
- Union guidance on the follow-up of pharmacovigilance inspections (including corrective and preventive action (CAPA) follow-up);

- revision of the Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products (revised in conjunction with the drafting of the follow-up of 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:

- GVP Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev. 2);
- GVP Module VIII – Post-authorisation safety studies (Rev. 3);
- GVP Module IX – Signal management (Rev. 1);
- GVP Module XV on Safety communication (Rev 1);
- Q&A(s)[12] and other guidance documents.

4.2. Procedures and guidance documents

The following documents have been finalised and are expected to be published in 2018:

- Union guidance on the follow-up of pharmacovigilance inspections.

4.3. Joint inspections

From the total of 7 CHMP pharmacovigilance site inspections conducted in 2017, 3 CHMP requested have been joint inspections involving more than one MS (see Table 1 in Section 3). From the total of 7 CVMP pharmacovigilance site inspections conducted in 2017, 1 CVMP requested has been joint inspection involving more than one MS (see Table 2 in Section 3).

4.4. Training and development

A Pharmacovigilance Inspectors Working Group training course took place at the European Medicines Agency (EMA), London, United Kingdom, from 16 to 18 October 2017. The training organisation was supported by the programme committee (Germany (BfArM and BVL) (H+V)). Inspectors and assessors of both, veterinary and human units of Member States (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom) as well as inspectors, assessors/experts from EU observer countries (Bosnia and Herzegovina, Montenegro, Serbia, Switzerland, Turkey) and from non-EU countries (Australia, Brazil, Japan, South Africa, 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 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;

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

  - 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:
  - pharmacovigilance inspection of third parties/contractors and contracts;
  - future signal management process following the release of the EudraVigilance (EV) data for MAHs in Nov 2017 and inspectors' expectations;
  - harmonisation in grading of findings;
  - the electronic submission of data on medicines to the Extended EudraVigilance medicinal product dictionary (XEVMPD);
  - Adverse Drug Reaction (ADR) reporting;
  - EudraVigilance/queries in EudraVigilance Data Analysis System (EVDAS) and the use of medical dictionary for regulatory activities for human medicines (MedDRA).
- The following topics were presented and/or discussed in the veterinary medicinal products related workshops:
  - pharmacovigilance inspection of third parties/contractors and contracts;
  - signal management;
  - harmonisation in grading of findings;
  - harmonisation of detailed description of pharmacovigilance system (DDPS) of veterinary MAHs/management of corrective and preventive actions;
  - Adverse Drug Reaction (ADR) reporting;
  - EudraVigilance-Vet (EV-Vet) queries;
  - the use of medical dictionary for regulatory activities for veterinary medicines (VedDRA).
- PIC/S[13] activities continued in the field of PhV inspections.
- During 2017, training and/or information was also provided in the following areas:
  - EudraVigilance and EudraVigilance data analysis system/data warehouse (EV and EVDAS/DWH) training;
  - veterinary signal detection methodology and practical use of EVVet Datawarehouse;
  - pharmacovigilance inspectors training in good vigilance practice and new processes;
  - Article 57 database (also known as extended EudraVigilance Medicinal Product Dictionary (XEVMPD)) publication dashboard and access to national competent authorities.
- The group also routinely discussed queries received by EMA, in particular in relation to the pharmacovigilance system master file requirements and the pharmacovigilance legislation.

[13] Pharmaceutical Inspection Co-operation Scheme

5. Pharmacovigilance topics

5.1. In relation to medicinal products for human use

- The PhV IWG has prepared and is maintaining the 2017-2020 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 2017, 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;
  - pharmacovigilance database validation;
  - signal detection;
  - sharing of pharmacovigilance inspection information;
  - issues arising in the case of marketing authorisation transfer/transfer of ownership;
  - applicant/MAH queries on the implementation of the pharmacovigilance legislation;
  - international collaboration;
  - Art.57 database;
  - strengthening collaboration between assessors and inspectors.

5.2. In relation to medicinal products for veterinary use

- The PhV IWG has prepared and is maintaining the 2017-2019 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.
- During the PhV IWG meetings held in 2017, 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-based inspection planning;
  - revision of a *pharmacovigilance inspection - aide memoire*;
  - queries on guidance/legislation interpretation.

6. Liaison with other groups

6.1. Interaction with the PRAC

The PhV IWG – PRAC subgroup, established in 2016 with the aim to standardise and strengthen the communication between pharmacovigilance inspectors and assessors, held 3 meetings in 2017 via teleconference. The role of the subgroup is to support the development and updates of guidance documents of common interest and to provide a forum for discussion of topics referred to the subgroup for recommendation and advice, as required. Members of the subgroup were also involved in a session on pharmacovigilance inspections during the PRAC assessor training on 14th of November 2017.

6.2. Interaction with the CVMP Pharmacovigilance Working Party

- The PhV IWG interacted with assessors on topics related to:
  - interaction between assessors and inspectors;
  - updates on inspections planned and conducted;
  - 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/or given presentations on behalf of the group in different European conferences covering different topics of public interest:

- 11th industry stakeholder platform – operation of EU pharmacovigilance at EMA, London, UK (02 June 2017).
- EMA/DIA Signal Management Information Day at EMA, London, UK (27 October 2017).
- EudraVigilance Expert Working Group (EV-EWG) on an *ad hoc* basis as additional domain experts on pharmacovigilance areas of common interest to the PhV IWG and EV-EWG.

A PhV IWG meeting with industry stakeholder representatives took place in 2017. The aim of the meeting was to obtain feedback from stakeholders on the implementation of the pharmacovigilance legislation on a range of topics particularly relevant to stakeholders with focus on pharmacovigilance inspections. For the details of the activities of the PhV IWG see the work plan for 2018.