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Annual report of the Pharmacovigilance Inspectors Working Group for 2018

Adopted by the PhV IWG on 08 June 2020

The activities outlined in the annual report for 2018 have been carried out in line with the Agency's business continuity plan and prioritization of activities for the preparation of the Agency's relocation and are therefore reduced in comparison with the activities carried out by the PhV Inspectors Working Group in previous years.
The delay of the publication of this report is also due to the Agency's business continuity plan and prioritization of activities for the preparation of the Agency's relocation in 2019.

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1. Introduction

This document is the tenth annual report of the Pharmacovigilance Inspectors Working Group (PhV IWG). The PhV IWG 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 Committee for Medicinal Products for Human Use (CHMP), Committee for Medicinal Products for Veterinary Use (CVMP), Pharmacovigilance Risk Assessment Committee (human medicinal products) (PRAC H) and Pharmacovigilance Working Party (veterinary medicinal products) (PhV WP V).

This annual report is set out in line with the format and objectives of the 2018 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:

- 15-16 March 2018;
- 07 June 2018;
- 13-14 September 2018.

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:

- Ad-hoc participation of PhV IWG delegates in PRAC meetings (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 Brexit 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.

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 Member States in whose territory the pharmacovigilance system master file (PSMF) 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 good vigilance practice (GVP) 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 Member States in which territory the marketing authorisation holder's (MAH) qualified person responsible for pharmacovigilance (QPPV) 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 has on the European Economic Area (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 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 2018 pharmacovigilance inspection programmes, respectively, and split by the type of site inspected.

Table 1 - Human pharmacovigilance inspections requested in 2018 in the context of supervisory authority inspections of MAHs with CAPs

	QPPV/PSMF (MAH) site	Global PhV site	Subcontractor/ Licensing partner/affiliate site	Total
CHMP requested	4	0	0	4
National inspection programmes	39	0	4	43
Total	43	0	4	47*

Table 2 - Veterinary pharmacovigilance inspections requested in 2018 in the context of the programme for pharmacovigilance inspection of MAHs with CAPs

	QPPV (MAH) site	Global PhV site	Subcontractor / Licensing partner / affiliate site	Total
CVMP requested	15	0	0	15**
National inspection programmes	2	0	0	2
Total	17	0	0	17*

* It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2018 in EU/EEA, which is 255 inspections for human medicinal products and 70 inspections for veterinary medicinal products.

** One veterinary medicinal product site inspection was requested by the CVMP in 2018 but was conducted in 2019.

*3.2. Categorisation of findings for supervisory authority inspections for human medicinal products conducted in 2018****

A total of 175 findings, 18 critical (10,3%) and 157 major (89,7%), were identified during the supervisory authority inspections conducted in 2018 (period covered from 01/01/2018 until 31/12/2018). These numbers include both supervisory authority inspections of MAH with CAPs requested by CHMP and supervisory authority inspections conducted under national inspection programmes.

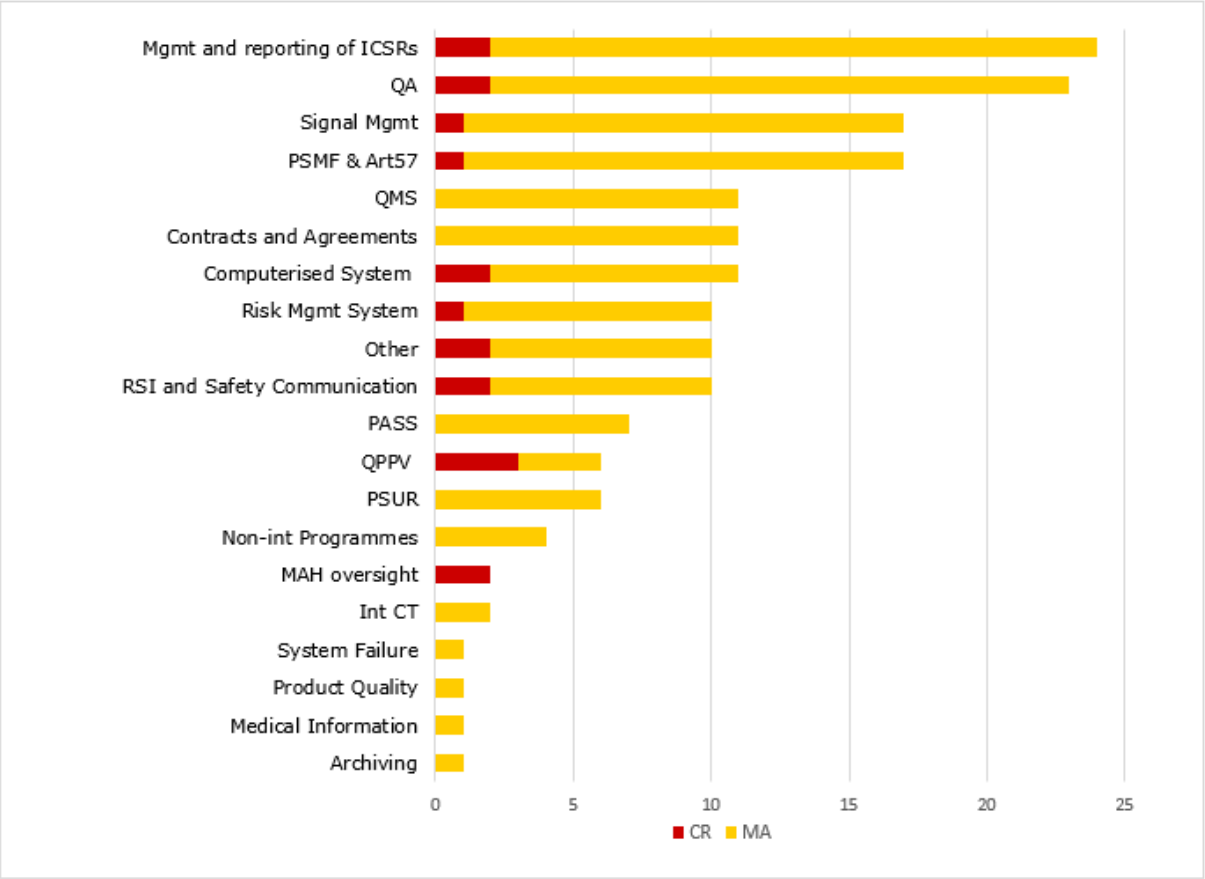
The findings are presented in figure 1 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The categories include: system failure, MAH oversight, contracts and agreements, QPPV, local QPPV, PSMF and Art 57 database, PSUR, risk management system, management and reporting of ICSRs, computerised systems, interventional clinical trials, PASS, non-interventional programmes (PSPs, market research programmes), signal management, product quality, archiving, quality assurance (audits, deviation management, CAPA management), QMS (written procedures, training, record management), reference safety information and safety communication, medical information and others.

As presented in the graph, the three most common areas with findings were:

- Management and reporting of ICSRs;
- Quality assurance;
- Signal management.

There were no critical nor major findings related to local QPPV.

Figure 1 - Number of findings graded as critical and major per category



*** Categorisation of findings for 2018 is the result of the pilot project conducted by the IWG.

3.3. Categorisation of findings for CVMP requested inspections conducted in 2018

A total of 31 findings, comprising 1 critical (3,2%), 5 major (16,1%) and 25 minor (80,6%) findings were identified for the CVMP requested inspections conducted in 2018 (period covered from 01/01/2018 until 31/12/2018).

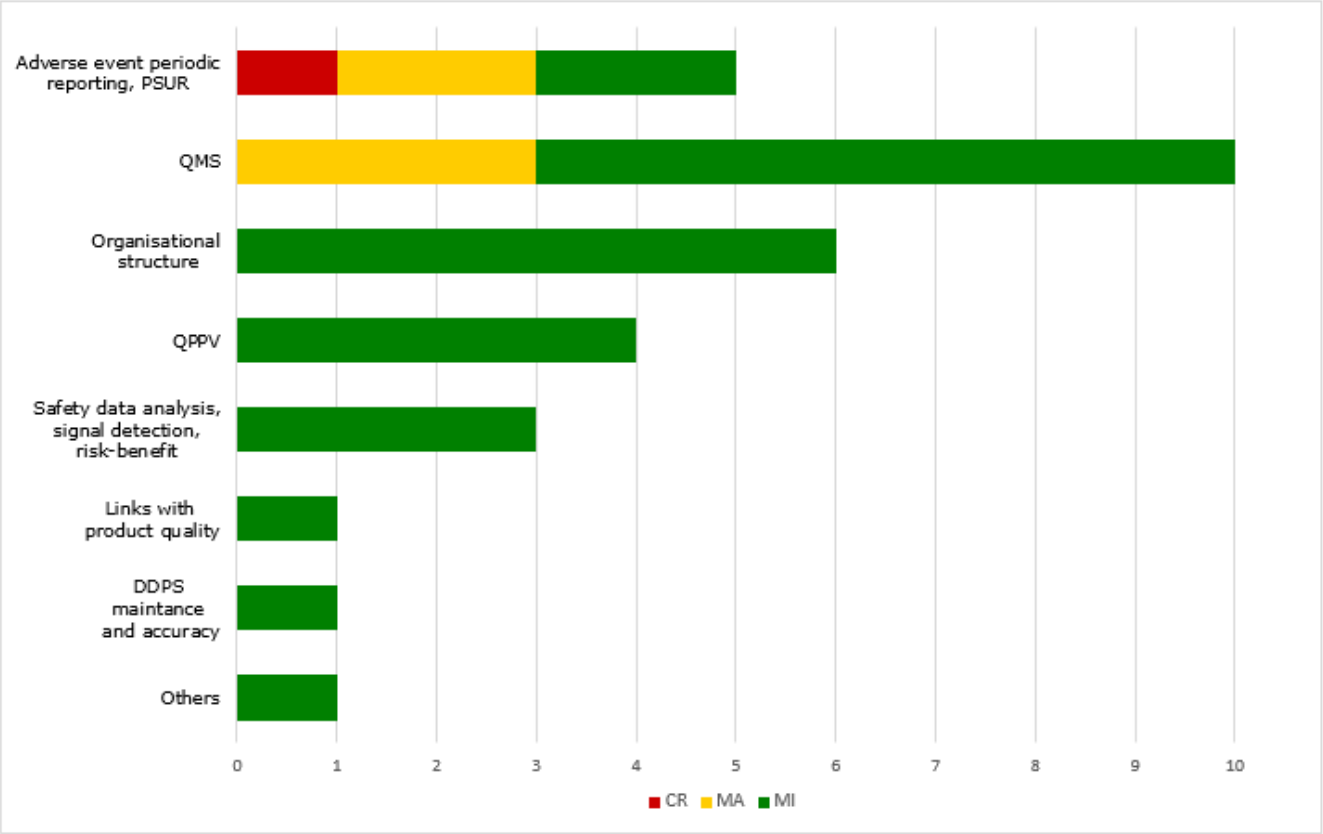
The main findings observed in the 2018 inspections are detailed in Figure 2 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings were:

- Quality management system;
- Organizational structure;
- Adverse event period reporting, PSURs.

The data in Figure 2 below relates to 16 inspections, conducted in 2018.

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 graded as critical, major and minor per category



4. Harmonisation topics

4.1. Procedures and guidance documents

In relation to human medicinal products and in order to support further harmonisation for the mutual recognition of pharmacovigilance inspections within the EU, in 2018 the group continued the work on the preparation of the following guidance document:

- GVP Module I on pharmacovigilance systems and their quality systems (Rev 1).

The following Union procedure has been finalised for publication:

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

The “Union guidance on the follow-up of pharmacovigilance inspections” replaces 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”.

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 pharmacovigilance legislation.

In addition, the group contributed to the preparation of:

- Questions & Answers (Q&As) and other guidance documents,
- Template for PhV assessment information sharing that has been finalized for publication,

- Template for PhV inspections information sharing that has been finalized for publication;

In relation to veterinary medicinal products the following Q&A(s) have been finalised and published:

- Minimum expectations for marketing authorisation holders (MAHs) in implementing pharmacovigilance agreements with other parties involved in fulfilling veterinary pharmacovigilance obligations,
- Minimum expectations for the pharmacovigilance training of staff in veterinary pharmaceutical companies.

4.2. Joint inspections

From the total of 4 CHMP pharmacovigilance site inspections conducted in 2018, 2 CHMP requested have been joint inspections involving more than one MS (see Table 1 in Section 3).

4.3. Training and development

In 2018 the Parmacovigilance Inspectors Working Group training course did not take place due to the Agency's business continuity plan and prioritization of activities for the preparation of the Agency's relocation in 2019.

- during 2018, training and/or information was provided in the following areas:
  - EudraVigilance and EudraVigilance data analysis system/data warehouse (EV and EVDAS/DWH),
  - 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;
- PIC/S[13]activities continued in the field of PhV inspections;
- the group also routinely discussed queries received by EMA, in particular in relation to the pharmacovigilance system master file requirements and the pharmacovigilance legislation.

5. Pharmacovigilance topics

5.1. In relation to medicinal products for human use

- The PhV IWG has prepared and is maintaining the 2018-2021 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 2018, 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;
  - Brexit – Network Preparedness;

- 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 2018-2020 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 2018, discussions on the following topics have taken place:
  - development of peer review of case studies;
  - sharing and discussion of inspection report findings;
  - Brexit – network preparedness;
  - 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 one meeting in 2018 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.

In 2018 one pharmacovigilance inspection outcome was escalated to PRAC for discussion and follow up.

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:

- EMA EudraVigilance and Signal Management Information Day, London, UK (07 December 2018).
- 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.