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Annual report of the Pharmacovigilance Inspectors Working Group for 2019 and 2020

Adopted by the PhV IWG on 12 November 2021

The activities outlined in the annual report for 2019 and 2020 have been carried out in line with the Agency's business continuity plan and prioritisation of activities for the preparation of the Agency's relocation and the Covid-19 pandemic, and are therefore substantially reduced in comparison with the activities carried out by the PhV Inspectors Working Group in previous years. These matters have resulted in the delay of the publication of this report.

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1. Introduction

This document is the twelfth 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 for what concerns the 2020 is set out in line with the format and objectives of the 2020 work plan. The 2019 work plan had been deferred.

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 (since March 2020 all of them were conducted remotely due to the Covid-19 pandemic):

- 24 January 2019 (ad-hoc meeting);
- 24-25 October 2019;
- 19 March 2020;
- 12 May 2020 (ad-hoc meeting);
- 25 June 2020;
- 24 September 2020;
- 3 December 2020.

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 these years using teleconference or equivalent:

- For human medicinal products: ad-hoc participation of PhV IWG delegates in PRAC meetings organised to discuss the outcome and follow-up of specific PhV inspections, as necessary.
- For veterinary medicinal products: ad hoc meetings were organised within EMA and the expert group of pharmacovigilance inspectors and assessors in relation to the implementation of the new veterinary pharmacovigilance legislation.

[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 2019 and 2020 pharmacovigilance inspection programmes, respectively, and split by the type of site inspected.

Most of the 2020 pharmacovigilance inspections were conducted remotely due to the Covid-19 pandemic.

[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 2019 and 2020 in the context of the programme for pharmacovigilance inspection of companies with CAPs

2019	QPPV/PSMF (MAH) site	Global PhV site	Subcontractor/ Licensing partner/affiliate site	Total
CHMP requested	3	1	0	4*
National inspection programmes	23	2	0	25
Total	**26**	**3**	**0**	**29****

* Two inspections were requested by the CHMP in 2019 but were conducted in 2020.

2020	QPPV/PSMF (MAH) site	Global PhV site	Subcontractor/ Licensing partner/affiliate site	Total
CHMP requested	6	3	3	12*
National inspection programmes	24	1	5	30
Total	**30**	**4**	**8**	**42*****

* Three inspections were requested by the CHMP in 2020 but were conducted in 2021.

Table 2 - Veterinary pharmacovigilance inspections requested in 2019 and 2020 in the context of the programme for pharmacovigilance inspection of companies with CAPs

2019	QPPV (MAH) site	Global PhV site	Subcontractor/ Licensing partner/affiliate site	Total
CVMP requested	5	0	0	5*
National inspection programmes	0	0	0	0
Total	**5**	**0**	**0**	**5****

* One inspection was requested by the CVMP in 2019 but was conducted in 2020.

2020	QPPV (MAH) site	Global PhV site	Subcontractor/ Licensing partner/affiliate site	Total
CVMP requested	6	1	0	7*
National inspection programmes	0	0	0	0
Total	**6**	**1**	**0**	**7*****

* One inspection was requested by the CVMP in 2020 but was conducted in 2021.

** It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2019 in EU/EEA, which is 223 inspections for human medicinal products and 51 inspections for veterinary medicinal products.

*** It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2020 in EU/EEA, which is 173 inspections for human medicinal products and 44 inspections for veterinary medicinal products.

3.2. Categorisation of findings for CHMP requested inspections conducted in 2019 and 2020

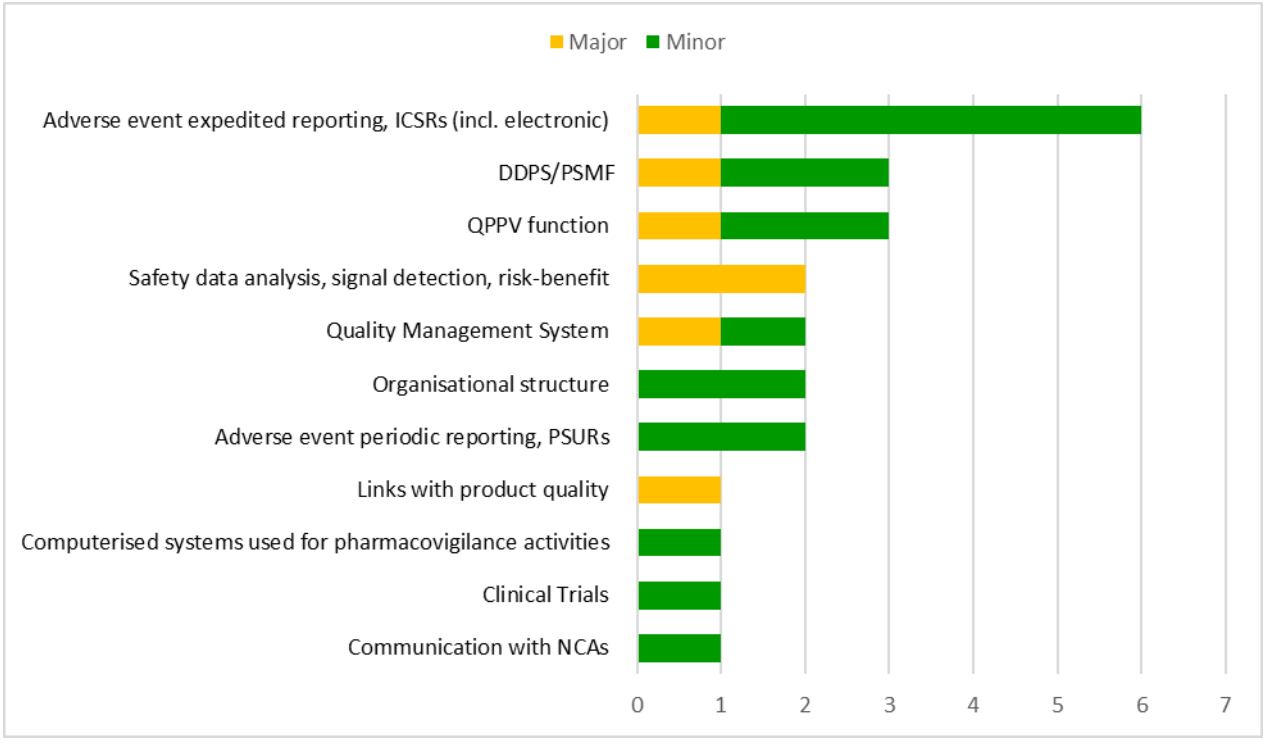
A total of 24 deficiencies, comprising 0 critical, 7 major (29,2%) and 17 minor (70,8%) were recorded for the CHMP requested inspections conducted in 2019 (period covered from 01/01/2019 until 31/12/2019).

A total of 103 deficiencies, comprising 12 critical (11,7%), 47 major (45,6%) and 44 minor (42,7%) were recorded for the CHMP requested inspections conducted in 2020 (period covered from 01/01/2020 until 31/12/2020).

The main findings observed in the 2019 and 2020 inspections are detailed in figure 1 and 2 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings in the 2019 inspections were:

- adverse event expedited reporting, ICSRs;
- pharmacovigilance system master file;
- QPPV function.

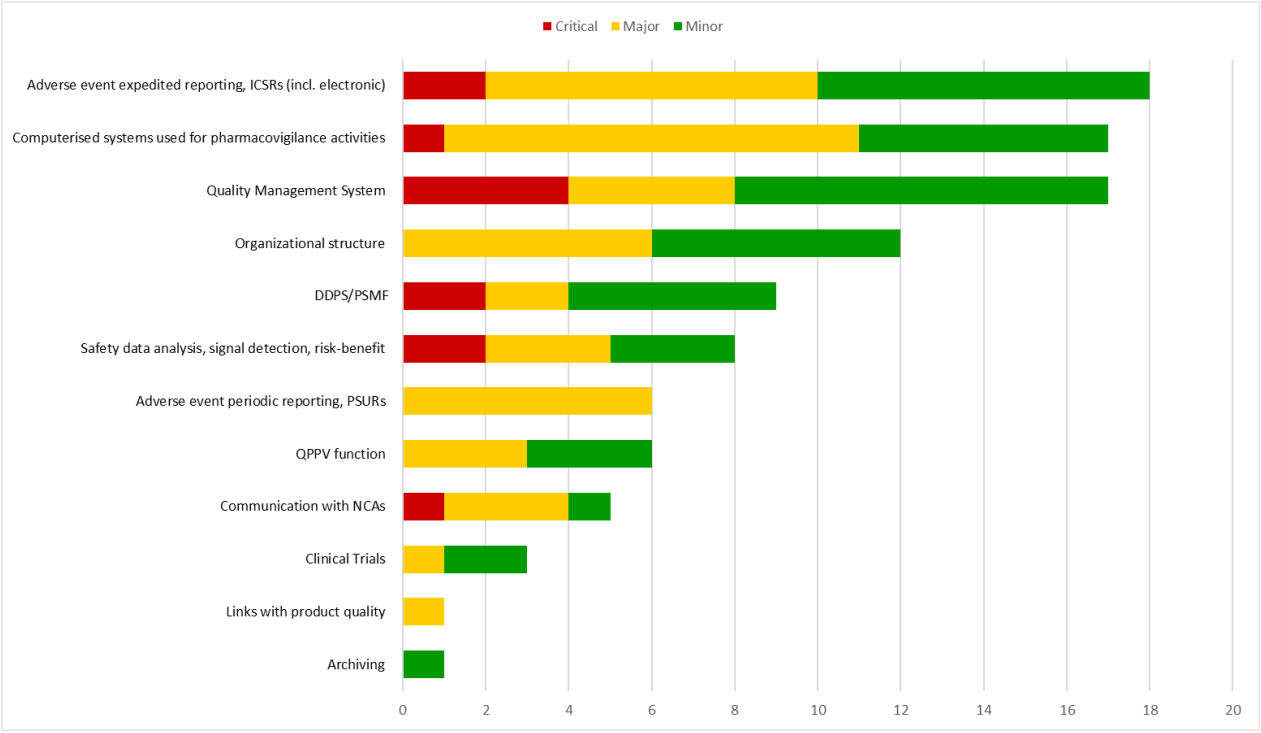
Figure 1 - Number of findings with regard to the main categories graded by critical, major and minor for CHMP inspections conducted in 2019



The three most common areas with findings in the 2020 inspections were:

- adverse event expedited reporting, ICSRs;
- computerised system used for pharmacovigilance activities;
- quality management system.

Figure 2 - Number of findings with regard to the main categories graded by critical, major and minor for CHMP inspections conducted in 2020



3.3. Categorisation of findings for CVMP requested inspections conducted in 2019 and 2020

A total of 23 deficiencies, comprising 0 critical, 8 major (35%) and 15 minor (65%) were recorded for the CVMP requested inspections conducted in 2019 (period covered from 01/01/2019 until 31/12/2019).

A total of 46 deficiencies, comprising 0 critical, 18 major (39%) and 28 minor (61%) were recorded for the CVMP requested inspections conducted in 2020 (period covered from 01/01/2020 until 31/12/2020).

The main findings observed in the 2019 and 2020 inspections are detailed in Figure 3 and 4 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings in both 2019 and 2020 inspections were:

- quality management system;
- QPPV function;
- adverse event expedited reporting, ICSRs (incl. electronic).

Figure 3 - Number of findings with regard to the main categories graded by critical, major and minor for CVMP inspections conducted in 2019

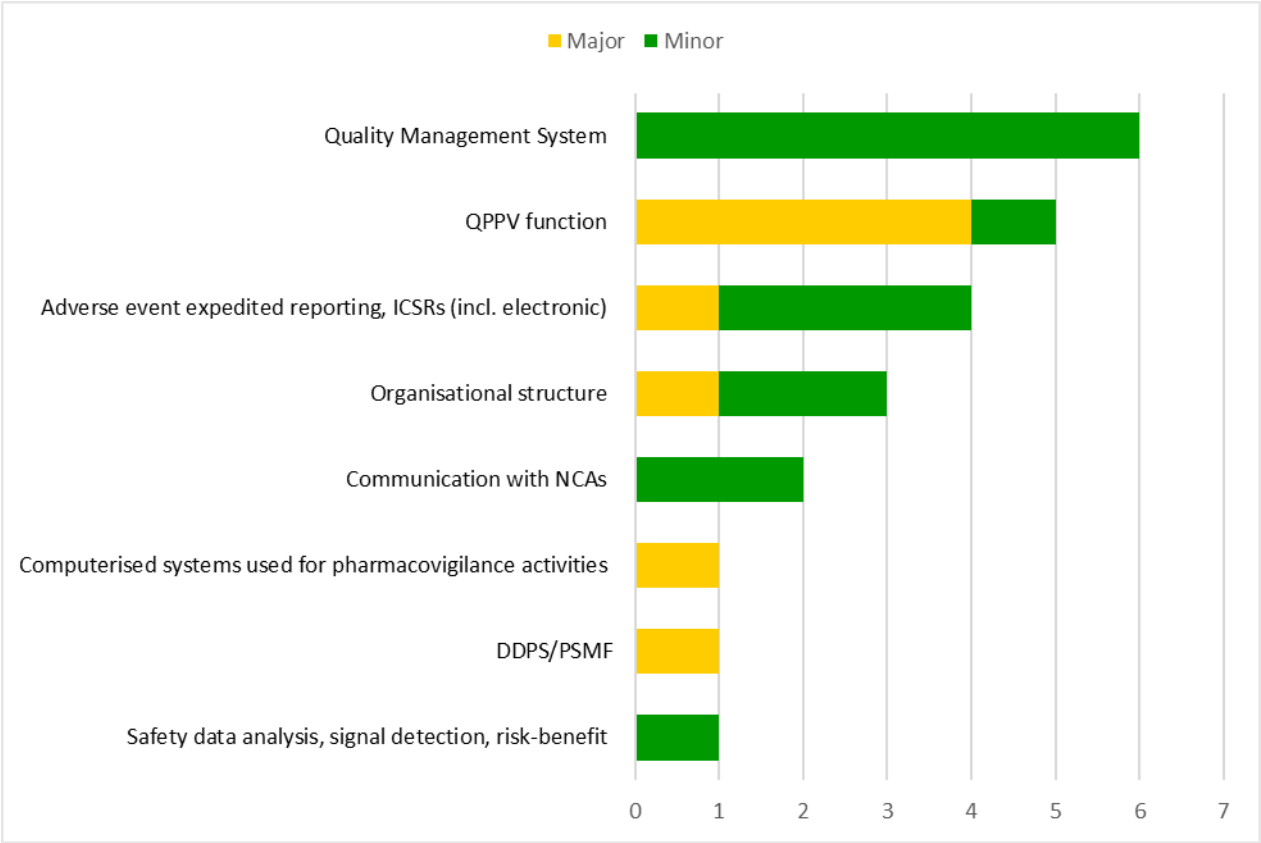
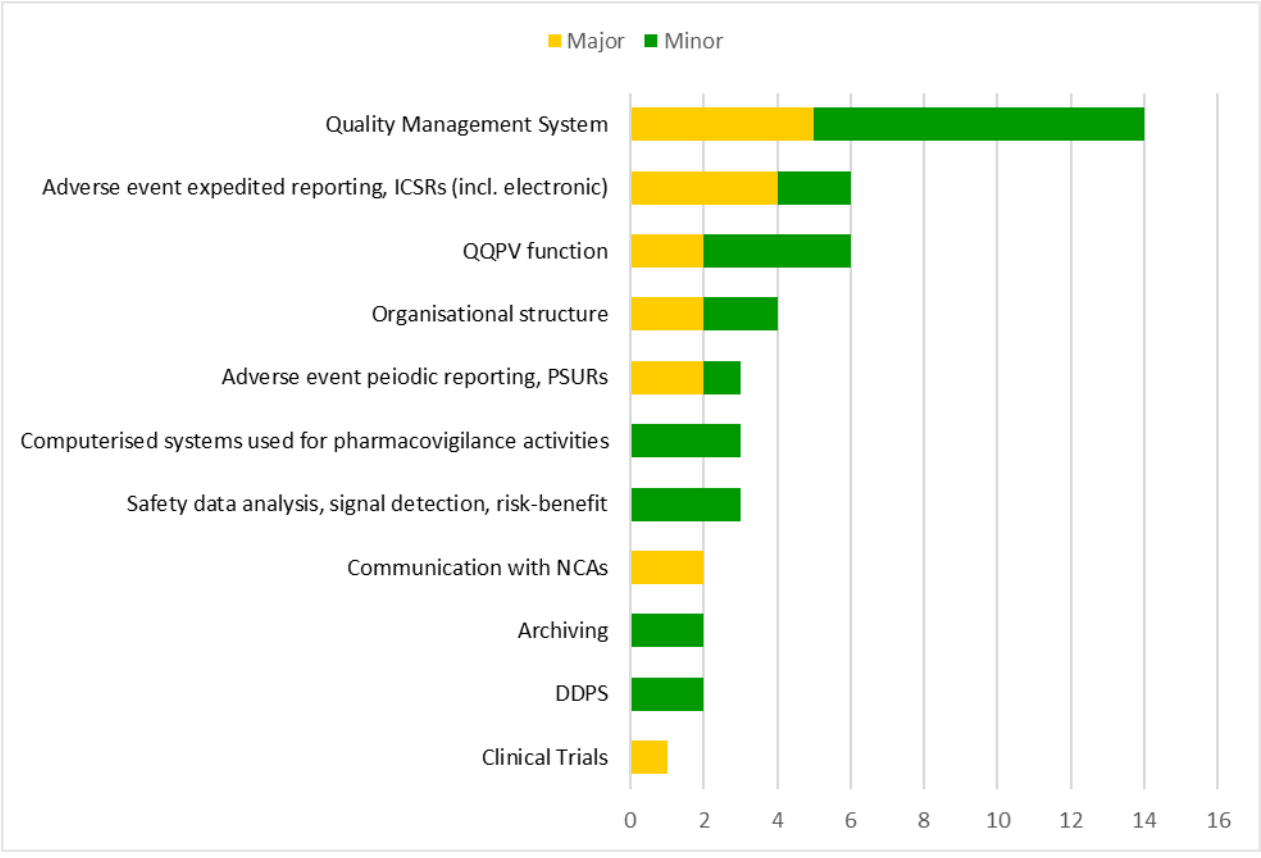


Figure 4 - Number of findings with regard to the main categories graded by critical, major and minor for CVMP inspections conducted in 2020



4. Harmonisation topics

4.1. Implementation of the 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 2019 and 2020 the group continued the work on the preparation of the following Union procedures and guidance documents:

- GVP Module I on pharmacovigilance system and quality systems (Rev 1);
- GVP Module II on pharmacovigilance system master file (Rev 3);
- 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 pharmacovigilance legislation.

In addition, the group contributed to the preparation of:

- GVP Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 3);
- GVP Module XVI on risk minimisation measures (Rev 3) and its new Addendum II on methods for evaluating the effectiveness of these measures;
- Q&A(s) on expectations regarding qualification documentation;
- Other guidance documents and templates for pharmacovigilance inspection and assessment information sharing.

4.2. Implementation of the new veterinary pharmacovigilance legislation

In relation to the implementation of the new veterinary pharmacovigilance legislation the group contributed to the preparation and finalisation of the following:

- Scientific recommendations for implementing measures under Article 77(6) of Regulation (EU) 2019/6 on veterinary medicinal products regarding good pharmacovigilance practice;
- Scientific recommendation for implementing measures under Article 77(6) of Regulation (EU) 2019/6 on veterinary medicinal products regarding the pharmacovigilance system master file.

The work on the implementation of the new pharmacovigilance legislation is ongoing.

4.3. Procedures and guidance documents

The following documents have been finalised and published in 2020:

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

- Guidance on Remote pharmacovigilance inspections of MAHs during a crisis situation – Points to consider (Rev 1);
- Veterinary pharmacovigilance inspections Q&As on:
  - 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.

4.4. Joint inspections

From the total of 2 CHMP pharmacovigilance site inspections requested and conducted in 2019, both inspections have been joint inspections involving more than one MS (see Table 1 in Section 3). From the total of 9 CHMP pharmacovigilance site inspections requested and conducted in 2020, 2 inspections have been joint inspections involving more than one MS (see Table 1 in Section 3).

From the total of 4 CVMP pharmacovigilance site inspections requested and conducted in 2019, 1 inspection has been joint inspections involving more than one MS (see Table 2 in Section 3). From the total of 6 CVMP pharmacovigilance site inspections requested and conducted in 2020, 1 inspection has been joint inspections involving more than one MS (see Table 2 in Section 3).

4.5. Training and development

No Pharmacovigilance Inspectors Working Group training courses took place during 2019 and 2020 due to the Agency's business continuity plan and prioritisation of activities for the preparation of the Agency's relocation and the Covid-19 pandemic.

4.6. In relation to medicinal products for human use

- The PhV IWG has prepared and is maintaining the 2019-2022 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 2019 and 2020, discussions on the following topics have taken place:
  - Brexit transition period and network preparedness;
  - Coronavirus pandemic impact on PhV Inspections;
  - development of peer review of case studies;
  - sharing and discussion of inspection report findings;
  - EudraVigilance (EV)V and EudraVigilance Data Analysis System
  - (EVDAS) /Data Warehouse (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.

4.7. In relation to medicinal products for veterinary use

- The PhV IWG has prepared and is maintaining the 2019-2021 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 2019 and 2020, discussions on the following topics have taken place:
  - Brexit transition period and network preparedness;
  - Coronavirus pandemic impact on PhV Inspections;
  - Regulation (EU) 2019/6 on veterinary medicinal products and corresponding implementing and delegated acts;
  - development of peer review of case studies;
  - sharing and discussion of inspection report findings;
  - EudraVigilance -Veterinary (EV-Vet) and Data Warehouse (DWH) demonstration of queries available to pharmacovigilance inspectors of veterinary medicinal products to facilitate the preparation of inspections (vet);
  - risk-based inspection planning;
  - queries on guidance/legislation interpretation.

5. Liaison with other groups

5.1. 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, didn't hold any meeting during 2019 and 2020 due to the Agency's business continuity plan and the Covid-19 pandemic. 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.

5.2. Interaction with the CVMP Pharmacovigilance Working Party

- The PhV IWG interacted with assessors on topics related to:
  - Regulation (EU) 2019/6 on veterinary medicinal products and corresponding implementing and delegated acts;

- interaction between assessors and inspectors;
- updates on inspections planned and conducted;
- follow-up of pharmacovigilance inspections;
- preparation and maintenance of the risk-based programme for routine pharmacovigilance inspections of MAHs connected with veterinary CAPs.