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Committees and Inspections

Annual report of the Pharmacovigilance Inspectors Working Group for 2016

Adopted by the PhV IWG on 15 June 2017

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1. Introduction

This document is the ninth 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 2016 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:

- 17-18 March 2016;
- 09-10 June 2016;
- 22-23 September 2016 (including PhV IWG - interested parties meeting);
- 24-25 November 2016.

Meetings included a joint session and two separate sessions, one dedicated to human and one to veterinary medicinal products only. On 22 September 2016 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: 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 pharmacovigilance legislation, and specifically to support the revision of existing procedures and guidance on pharmacovigilance inspections. In the second half of the year interactions between inspectors and pharmacovigilance assessors were strengthened with the establishment of the PhV IWG – PRAC subgroup and two teleconferences were organised on 03 October and 09 December 2016 to initiate the interactions. 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.
- A teleconference call was held within EMA and the Article 57 subgroup of pharmacovigilance inspectors to discuss 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 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 2016 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 2016 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	1	0	1	2**
National inspection programmes	31	0	18	49
Total	**32**	**0**	**19**	**51**

Table 2 - Veterinary pharmacovigilance inspections requested in 2016 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	0	6
National inspection programmes	3	0	0	3
Total	**9**	**0**	**0**	**9***

* It should be noted that these totals are just a subset of the total number of pharmacovigilance inspections conducted in 2016 in EU/EEA, which is 217 inspections for human medicinal products and 80 inspections for veterinary medicinal products.

**One human medicinal product site inspection was requested by the CHMP in 2016 but has been conducted in 2017 .

3.2. Categorisation of findings for CHMP requested inspections conducted in 2016

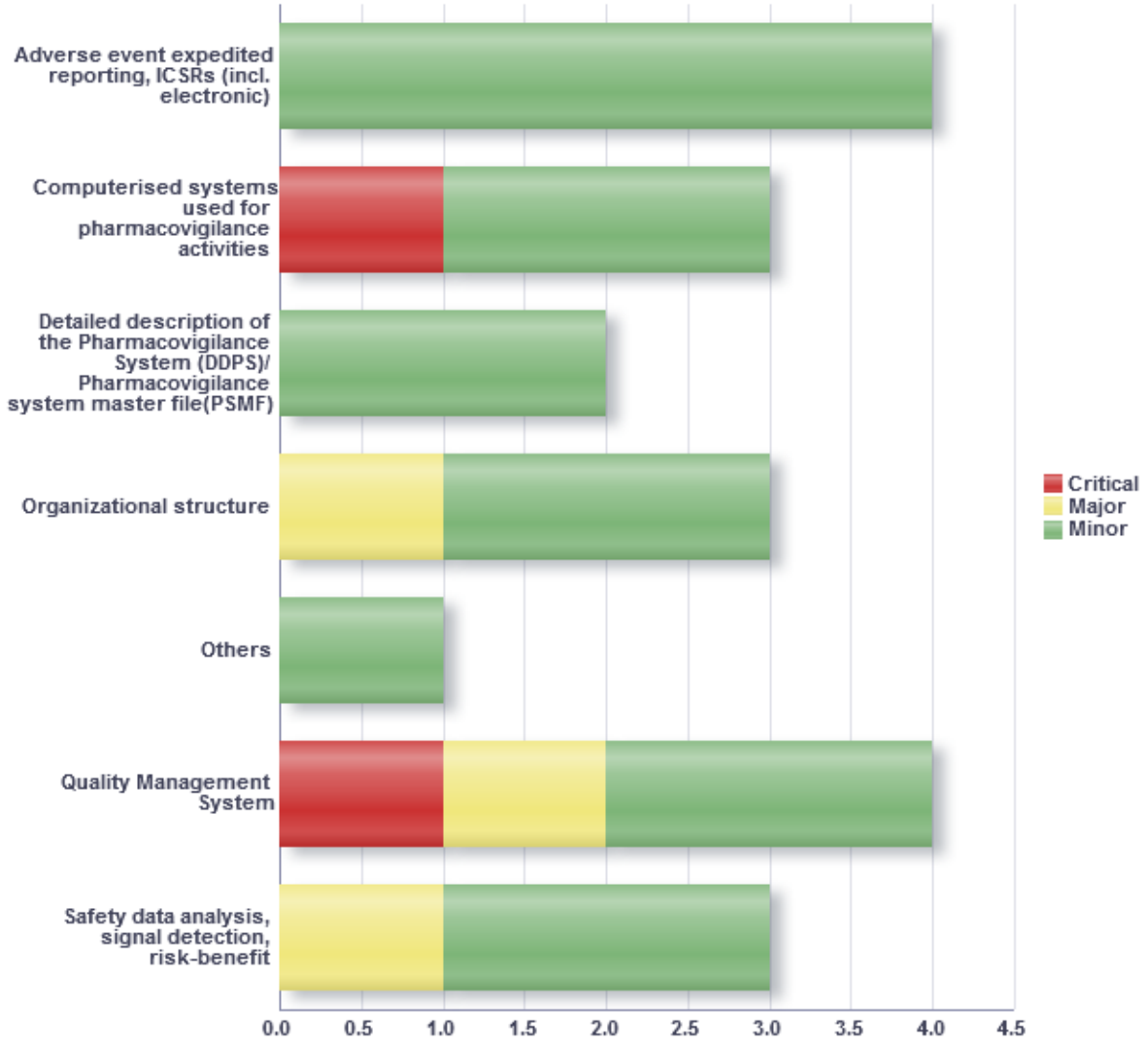
A total of 20 deficiencies, comprising 2 critical (10%), 3 major (15%) and 15 minor (75%) were recorded for the CHMP requested inspections conducted in 2016 (period covered from 01/01/2016 until 31/12/2016).

The main findings observed in the 2016 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;
- computerised system.

The data in the figure below relates to two inspections conducted in 2016.

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 2016

A total of 33 deficiencies, comprising 3 critical (9,1%), 7 major (21,2%) and 23 minor (69,7%) were recorded for the CVMP requested inspections conducted in 2016 (period covered from 01/01/2016 until 31/12/2016).

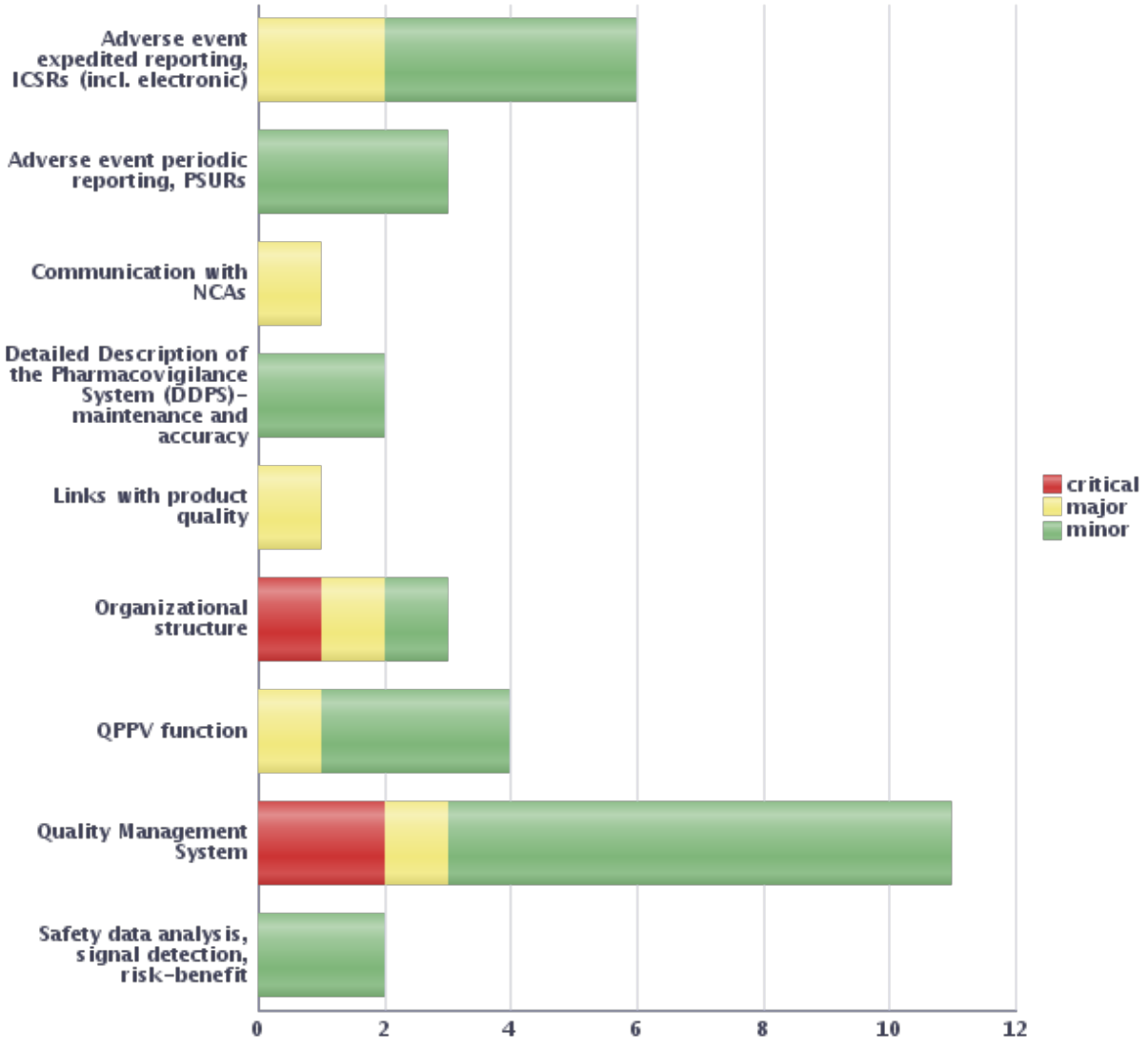
The main findings observed in the 2016 inspections are detailed in Figure 2 below in accordance with the categorisation of pharmacovigilance inspection findings agreed by the PhV IWG. The three most common areas with findings were:

- quality management system;
- adverse reporting;
- qualified person for pharmacovigilance (QPPV) function.

The data in Figure 2 below relates to seven inspections, conducted in 2016.

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 2015 was conducted in 2016.

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 2016 the group focused on the preparation of the following Union procedures and guidance documents:

- GVP Module II on pharmacovigilance system master file (Rev 2, administrative);
- guideline on pre-authorisation pharmacovigilance inspections;

- Union guidance on routine pharmacovigilance inspection follow-up (including corrective and preventive action (CAPA) follow-up).

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 - Management and reporting of adverse reactions to medicinal products (Rev 2);
- GVP M V on risk management system (Rev 2);
- 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 are expected to be published in 2017:

- GVP Module II on pharmacovigilance system master file (Rev 2, administrative);
- 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).

4.3. Joint inspections

From the total of two CHMP and seven CVMP pharmacovigilance site inspections conducted in 2016, one CHMP requested and four 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 training course took place at the Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany, from 5 to 7 October 2016. The training organisation was supported by the programme committee (Belgium (H+V), France (V), Germany (BfArM, PEI and BVL) (H+V), Croatia (H) 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, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden, United Kingdom) as well as inspectors, assessors/experts from EU observer countries (former Yugoslav Republic of Macedonia, Montenegro, Switzerland) and from non-EU countries (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

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

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:
  - interaction between PhV and GMP and pharmacovigilance inspection of biologicals;
  - pharmacovigilance inspection of biologicals;
  - ADR reporting;
  - EudraVigilance/queries in EVDAS;
  - presentation on CAPA management and inspections follow-up;
  - interaction between inspectors and PRAC on post inspection CAPA activities, current situation and proposals for improvement in the future;
  - post-authorization safety studies and PhV inspections;
  - contracts/agreements/statements of work.
- The following topics were presented and/or discussed in the veterinary medicinal products related workshops:
  - interaction between PhV and GMP and pharmacovigilance inspection of biologicals;
  - pharmacovigilance inspection of biologicals;
  - ADR reporting;
  - EudraVigilance-Vet queries;
  - presentation on CAPA management and inspections follow-up;
  - interaction between inspectors and assessors on post inspection CAPA activities, current situation and proposals for improvement in the future;
  - inspection of post-authorisation clinical studies;
  - external audits;
  - harmonisation in grading of findings;
  - contracts/agreements/statements of work.
- The activities of the PIC/S[13] have been expanded to include training in the field of PhV inspections.
- During 2016, training and/or information was also provided in the following areas:
  - EV and EVDAS/DWH training;
  - veterinary signal detection methodology and practical use of EVVet Datawarehouse;

[13] Pharmaceutical Inspection Co-operation Scheme

- medication errors;
- collecting and reporting information on off-label use;
- pharmacovigilance inspectors training in good vigilance practice and new processes;
- PSUR repository (human);
- 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.

5. Pharmacovigilance topics

5.1. In relation to medicinal products for human use

- The PhV IWG has prepared and is maintaining the 2016-2019 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 2016, 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[14], delays in the implementation or inappropriate corrective and preventive actions;
  - 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 for operating pharmacovigilance in Europe (SCOPE) work package 7 on quality management systems;
  - strengthening collaboration between assessors and inspectors and the establishment of the PhV IWG and PRAC/assessors subgroup.

5.2. In relation to medicinal products for veterinary use

- The PhV IWG has prepared and is maintaining the 2016-2018 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.

[14] Pharmacovigilance System Master File

- During the PhV IWG meetings held in 2016, 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;
  - finalisation 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).

A PhV IWG – PRAC subgroup was established in 2016 with the aim to standardise and strengthen the communication between pharmacovigilance inspectors and assessors. 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.

6.2. Interaction with the CVMP Pharmacovigilance Working Party

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

- SCOPE work package 7 - Topic 7.3: interaction with pharmacovigilance inspectors, pilot training, in Budapest (22-23 June 2016).
- 7th industry stakeholder platform - operation of EU pharmacovigilance legislation at EMA, London, UK (4 April 2016).
- 8th industry stakeholder platform - operation of EU pharmacovigilance legislation at EMA, London, UK (1 July 2016).

- 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 2016. 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 2017.