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## Union procedure on the coordination of EU pharmacovigilance inspections

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This guideline replaces EMEA/INS/PhV/105504/2008 "Procedure for the preparation of a risk-based programme for routine pharmacovigilance inspections of marketing-authorisation holders (MAHs) connected with human centrally authorised products (CAPs)".



# Union procedure on the coordination of EU pharmacovigilance inspections

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# 1. Introduction

Article 111(1) of Directive 2001/83/EC states that the competent authority of the Member State concerned shall, in cooperation with the European Medicines Agency (hereinafter 'the Agency'), ensure that the legal requirements governing medicinal products are complied with, by means of inspections. Article 111(1) of Directive 2001/83/EC also states that this cooperation shall consist in sharing information with the Agency on both inspections that are planned and that have been conducted. In addition, Member States and the Agency shall cooperate in the coordination of inspections in third countries.

Article 19(1) of Regulation (EC) No 726/2004 provides the specific legal basis for the conduct of pharmacovigilance inspections for centrally authorised products (CAPs) for human use: "the supervisory authorities for pharmacovigilance shall be responsible for verifying on behalf of the Union that the marketing-authorisation holder (MAH) for the medicinal product satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive 2001/83/EC. They may, if this is considered necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the pharmacovigilance system as it has been described by the applicant in support of his application."

In the context of CAPs, Article 57 (1) (i) of Regulation (EC) No 726/2004 provides the Agency with a coordination role, within its committees, for the verification of compliance with pharmacovigilance obligations.

The guideline on good pharmacovigilance practices (GVP) Module III (pharmacovigilance inspections) provides a high level overview of the types of inspections performed by EU pharmacovigilance inspectorates, the factors used to plan inspection programmes, the sites which may be inspected, the scope of inspections and the basic elements of the inspection process. GVP Module III states that pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures consistent with agreed Union pharmacovigilance inspection procedures developed by the European Union (EU) Pharmacovigilance Inspectors Working Group (PhV IWG) to support harmonisation for the mutual recognition of pharmacovigilance inspections within the EU. These Union procedures will be published as annexes to GVP Module III.

This specific procedure supplements GVP Module III by providing additional guidance on the coordination of pharmacovigilance inspections conducted by EU inspectorates on behalf of the Union, and relates to inspection programmes concerning national authorised products (NAPs, i.e. authorised nationally or via the mutual recognition or decentralised procedure) and CAPs. Effective coordination of inspections and inspection programmes is required in order to ensure appropriate inspection coverage, while at the same time minimising duplication and maximising the use of available resources. Effective coordination is also required to enable the flexible use of resource, for example, to respond to requests for triggered inspections. In addition, this procedure outlines the roles of the different parties involved in the coordination of EU inspections and inspection programmes.

In Union procedures on pharmacovigilance inspections, any reference to Regulation (EC) No 726/2004 and Directive 2001/83/EC refers to the Regulation and Directive respectively, always including their latest amendments.

## 2. Scope

The competent authorities of the Member States, in cooperation with the Agency, are responsible for conducting routine and triggered pharmacovigilance inspections to fulfil both national and EU

requirements in order to verify compliance with applicable legislation and guidance. This procedure outlines the processes used for the coordination of EU inspections and inspection programmes, including:

- Processes for the design and maintenance of the **risk-based programme for routine pharmacovigilance inspections**, which relate to the planning and coordination of supervisory authority pharmacovigilance inspections for marketing-authorisation holders (MAHs) with centrally authorised products.
- Factors to consider for the design and co-ordination of **national pharmacovigilance inspection programmes**, which relates to MAHs with product authorisations of all types (i.e. NAPs and CAPs).
- Factors to consider for **“for cause” pharmacovigilance inspections**, including processes to be followed for **“for cause”** requests for inspection from Pharmacovigilance Risk Assessment Committee (PRAC) / Committee for Medicinal Products for Human Use (CHMP).
- Factors to consider for the co-ordination of **inspections in third countries**, whether conducted as part of a national inspection or as part of a supervisory authority inspection.
- Factors to consider for the **inspections of pharmacovigilance contractors**, whether conducted as part of a national inspection or as part of a supervisory authority inspection.
- Processes for the coordination and planning of **pre-authorisation inspections**, which relate to applications made using the centralised procedure.

This procedure describes how different inspection programmes in the EU are integrated in order to provide appropriate inspection coverage while minimising duplication. In addition, this procedure provides guidance in relation to the other Union procedures to be followed for EU pharmacovigilance inspections and provide details of the Agency coordination activities in the context of CHMP requested pharmacovigilance inspections concerning CAPs. Therefore, this procedure should be read in conjunction with the Union procedures referred to in section 5.

### 3. Coordination overview

The scheduling and conduct of inspections, as required in accordance with Articles 111(1) and 111(1)(d) of Title IX of Directive 2001/83/EC, will be driven by the preparation of inspection programmes based on a systematic and risk-based approach as outlined in III.B.2 and III.C.3.3 of the GVP Module III on inspections.

In the context of CAPs, a risk-based programme for routine inspections of MAHs with CAPs will be determined by the Agency in conjunction with the supervisory authorities of the Member States (the Pharmacovigilance Inspectors Working Group (PhV IWG), the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP)). If the same pharmacovigilance system is used for a variety of authorisation types (centralised/mutual recognition/decentralised/national), then the results of a supervisory authority inspection may be applicable for all products covered by that system. In general, it is anticipated that national inspection programmes will fulfil the need for the routine inspections for the programme related to CAPs and, therefore, it is expected that this programme focused on CAPs will be achieved mainly through the national programmes and inspections may be requested by the CHMP in the situations described in section 4.2.1.

Member States are also responsible for the planning and coordination of pharmacovigilance inspections within their territory in relation to products authorised nationally or via the mutual recognition or decentralised procedures in order to ensure compliance with the legislation within their own Member

States and to verify the effectiveness of the marketing-authorisation holder's pharmacovigilance system at national level.

These programmes will be separate from any for cause inspection, but if a "for cause" inspection has been or will be conducted it may replace the planned routine inspection (see section 4.2.3).

Member States and the Agency shall cooperate in the coordination of inspections in third countries, when a need to inspect sites outside EU is identified (see section 4.2.4).

Where appropriate, inspectors from different Member States may participate in joint inspections of a MAH or pharmacovigilance contractor. The circumstances where this may occur are described in Section 4.2.

In order to make the best use of the European surveillance and enforcement resources whilst maintaining a high level of public health safety, it is important that the information on the planned and conducted inspections of these inspection programmes is shared in a timely manner between the national competent authorities and the Agency. The sharing of this information will help to prevent unnecessary duplication, in some cases by adapting the scope and/or timing of the inspections, which may reduce the inspection-related resource burden for MAHs, improve inspection coverage and ensure better and consistent follow-up of inspections.

The combination of these complementary programmes of routine and for cause national and EU inspections for CAPs and NAPs running in parallel constitute the EU programme of pharmacovigilance inspections.

## **4. EU pharmacovigilance inspection programme**

### **4.1. Risk factors**

A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined according to risk factors. The factors which may be taken into consideration, as appropriate, by the competent authorities when establishing pharmacovigilance inspection programmes are described in section III.B.2 of the GVP Module III on inspections. The list covers a wide, but not exclusive, range of factors which may be inspection related (e.g. inspection history), product related (e.g. requirement for risk-minimization activities), MAH related (mergers, acquisitions, number of products) or related to the pharmacovigilance system (change in the qualified person for pharmacovigilance (QPPV), changes to pharmacovigilance system master file (PSMF) management etc.).

In relation to the programme for routine inspections of MAHs with CAPs mentioned in section 3, the priority list of MAHs to be inspected as part of this programme should be driven by the factors outlined in section III.B.2 of the GVP Module III. In addition to those, the following may be also applied to refine that selection:

- the MAH has multiple licensing partners;
- the need to conduct an inspection early post authorisation for certain MAHs (e.g. MAHs launching first product in EU; risk-minimisation to be implemented for particular products of the MAH);
- introduction of a random element.

A similar risk-based approach may be followed for pharmacovigilance inspection programmes connected with NAPs.

## 4.2. Process

### 4.2.1 Programme for centrally authorised products

The Agency in conjunction with the supervisory authorities of the concerned Member States, the PhV IWG, the PRAC and the CHMP will prepare a programme of routine pharmacovigilance inspections. This programme will relate to CAPs, but as most of these inspections are anticipated to be performed as part of the national programmes, products authorised via the decentralised or mutual recognition procedure may be added to the inspection scope as decided at national level or at the request of the PRAC, whenever the same system is used for these products as well.

The supervisory authority responsible for performing the inspection will be determined by the location of the PSMF (or, in the transition period, the location where the QPPV resides and works if the master file has not been formally implemented). Once the different supervisory authorities concerned by the programme are identified, they will ensure that the inspection of the PSMF site (or the QPPV site, where applicable) is included in their national programme and, in general, no adoption of a specific inspection request by the CHMP, as outlined in section III.C.2.3 of the GVP Module III on inspections, will be required. However, there are some situations where these inspections might be specifically requested by the CHMP, in particular:

- when global pharmacovigilance sites in third countries are identified for inclusion in the inspection;
- when additional sites within EU are identified for inspection and require joint inspections involving the Member State concerned by that site and the supervisory authority;
- based on a PRAC recommendation (e.g. re-inspection as consequence of a previous negative inspection leading to a more targeted inspection; where PRAC disagrees with the reasons for delaying a supervisory authority inspection proposed by a Member State);
- when a particular Member State supervisory authority prefers to follow this route;
- in the case of a “for cause” inspection (triggers for this type of inspection can be found in section III.B.1.2. of GVP Module III. Frequent changes in the location of the PSMF should also be considered).

Routine inspections will be requested as system inspections as defined in section III.B.1.1 of the GVP Module III on inspections. Product specific examples will be used to demonstrate the operation of the pharmacovigilance system.

The scope of these inspections should be in line with the requirements outlined in section III.B.4.1 of the GVP Module III on inspections. All of the areas listed in this section should be covered in the scope of an initial supervisory authority inspection.

The timing of the first inspection and any re-inspection in the programme will be determined on the basis of the risk factors described in section 4.1. In principle all MAHs with CAPs should be inspected within four years after the Commission decision of the first CAP of the MAH and for this reason a four-year inspection cycle will be used for each MAH, but this may be shortened or lengthened based on on-going risk assessment. The supervisory authorities concerned will inform the Agency prior to or after the inspection if additional sites require to be inspected and the timeframe for those inspections. For additional sites within the EU/EEA, the competent authority where the additional site is located will be informed in a timely manner in order to plan and fit this inspection within its national programme. For additional sites outside the EU/EEA please refer to section 4.2.3.

A supervisory authority inspectorate may request assistance from inspectors from another Member State for the conduct of a supervisory authority inspection, even where there is no site to be inspected

in the other Member State. Acceptance of such requests will be at the discretion of the concerned Member State inspectorate.

In addition, inspectors and/or assessors from a Member State that is not the supervisory authority may request to participate in a supervisory authority inspection e.g.:

- to verify the implementation of national requirements;
- in order to review the implementation of corrective actions and preventive actions for non-compliances identified from a national pharmacovigilance inspection of the same MAH, in situations where the actions can only be fully examined at a main pharmacovigilance processing site;
- due to specific expertise relating to the MAH's pharmacovigilance system and/or to the products to be reviewed during the supervisory authority inspection;
- for training and harmonisation purposes.

For inspections within the EU, acceptance of such requests will be at the discretion of the supervisory authority. For inspections in a third country, the Agency will play a co-ordinating role (see section 4.2.4).

Where non-compliances are identified from national pharmacovigilance inspection(s) of an MAH conducted by non-supervisory authority Member State(s), which relate to the global pharmacovigilance system (and not solely to national issues), it may be advantageous for the concerned Member State inspectorate(s) to discuss with the supervisory authority how production of an integrated corrective and preventive action (CAPA) can be facilitated e.g. in order to avoid multiple CAPAs for the same or similar non-compliances.

Annex 1 provides details and an overview of the different steps in relation to the preparation of this programme.

## **4.2.2 Programme for nationally authorised products**

Each competent authority of the Member States is responsible for preparing a yearly national programme for routine pharmacovigilance inspections which relates to MAHs with product authorisations of all types, which may include third parties.

This programme should be based on a risk-based approach such as that described in the previous paragraph 4.1.

A national standard operating procedure should be available describing the requirements relating to the routine national inspection programme and the set-up of this inspection planning. In drafting the national inspection programme each inspectorate should consider the information already available in-house and, if appropriate, may solicit further information from MAHs.

In the preparation of the scope of these inspections, each inspectorate should take into account all the inspection information (scope and outcome of the inspection) coming from the other Member States and shared in the common repository held by the Agency (Union procedure on sharing of pharmacovigilance inspection information). This is relevant in terms of coordination in order to avoid unnecessary repetition and duplication of inspections or with the aim to improve and complement the coverage of activities to be inspected.

For example, if a supervisory authority (where applicable) plans to conduct an inspection of a particular MAH in their yearly programme, details of which are shared in the common repository, national inspectorates may choose to amend the date for an inspection of the same MAH in order to take into account the findings from the supervisory authority inspection or may propose to the

supervisory authority to cooperate in joint or coordinated inspections of the same MAH or may focus the scope to review of local processes, including but not limited to collection of safety data in that Member State, interface with the QPPV, verification of national implementation of specific risk-minimisation measures, national communications concerning safety, locally conducted safety studies, or issues linked to the national health care systems.

In situations where a MAH has no centrally authorised products, a similar approach as described above should be followed and, when considered appropriate, Member State inspectorates may choose to conduct joint or co-ordinated inspections of an MAH for the same reasons as described in 4.2.1 for the request to join supervisory authority inspections.

In the programme for nationally authorised products the re-inspections considered necessary should be included.

This programme should also include the inspections scheduled in the four-yearly EU programme of routine pharmacovigilance inspections of CAPs, for which the specific Member State acts as supervisory authority.

If the inspectorate should receive an inspection request from the Agency, other NCAs or from departments within the same national competent authority, a “for cause” inspection may substitute for a routine inspection in the EU programme.

The manner and the rationale for the prioritisation in the programme should be documented, where considered appropriate by the Member State in line with their SOPs.

The list of these planned and conducted site inspections will be shared in line with the Union procedure on sharing of pharmacovigilance inspection information.

### **4.2.3 For cause inspections**

If a “for cause” inspection has been or will be conducted it may replace the planned routine inspection and in this case the programme will be revised to reflect the new timeframe. Specific triggers for this type of inspection and some information on the scope of these inspections can be found in sections III.B.1.2. and III.B.4.2 of the GVP Module III on inspections.

In the context of CAPs, “for cause” inspections will be adopted by the CHMP.

### **4.2.4 Third country inspections**

According to Article 111(1) of Directive 2001/83/EC Member States and the Agency shall cooperate in the coordination of inspections in third countries.

As stated in GVP Module III, Member States should liaise with the Agency when the need for an inspection of a third country site is identified in order to ensure productive use of pharmacovigilance inspection resources in the interests of the Union.

Programme for centrally authorised products:

- If CHMP, PRAC or a supervisory authority considers it necessary for a third country site or sites to be inspected in order to obtain a comprehensive overview of an MAH’s pharmacovigilance system, as part of either a routine or “for cause” inspection, the supervisory authority inspectorate is responsible for performing these inspections. These inspections will be included in the risk-based programme for the inspection of MAHs with CAPs and will normally be conducted under a request from the CHMP.



- The supervisory authority may request assistance from other Member State inspectorates in order to perform inspections in third countries e.g. the inspectorate of the rapporteur or co-rapporteur country (see section 5.2 relating to the selection of the inspection team). In addition, assistance may be requested from another Member State inspectorate in order to address linguistic needs.
- When it is not feasible for the supervisory authority inspectorate to conduct a third country inspection, the competent authority of that country may ask, in co-ordination with the Agency, another inspectorate to lead the inspection.
- The Agency will maintain a list of planned and conducted third country site inspections, which will include the name and address of the site; the planned or actual dates of the inspection; details of the Member States involved in the inspection and a summary of the inspection outcome. This list will include both MAH and pharmacovigilance contractor third country sites. This list will be accessible to EU/EEA national competent authority inspectorates.

The Agency will contact local authorities in third countries as appropriate to notify them of the inspection (see section 6.2).

Programmes for nationally authorised products:

- When a national inspectorate plans to inspect a third country site as part of its national inspection programme in relation to NAPs, it should inform the Agency in advance of the inspection. The Agency will check the list of planned and conducted third country inspections in order to avoid duplication of inspection activity.
- The Agency will alert that national inspectorate if the third country site that the inspectorate is planning to inspect has recently been inspected or is due to be inspected by another EU/EEA inspectorate. If after review of findings from an inspection of a third country site recently conducted by another EU/EEA inspectorate, a national inspectorate wishes to proceed with the third country site inspection (e.g. to examine product-specific issues that are specific to that Member State), the national inspectorate should inform the Agency of the reasons for the proposed inspection.
- Inspectorates from different Member States may, in coordination with the Agency, choose to conduct joint inspections of third country sites.
- National inspectorates should provide details of the outcome of these third country inspections in line with the Union procedure on sharing of pharmacovigilance inspection information.

#### **4.2.5 Inspection of pharmacovigilance contractors**

The legal basis for the conduct of the inspection of contractors is provided in Article 111.1g(d) of Directive 2001/83/EC. Contractors may be inspected in the margins of an MAH inspection or as part of a routine programme of system inspections of contractors. In this last case, the processes to be followed in the context of NAPs and CAPs are to be further developed by the PhV IWG.

#### **4.2.6 Pre-authorisation inspections (only for CAPs)**

Pre-authorisation pharmacovigilance inspections are inspections intended to examine an existing or new pharmacovigilance system before a marketing authorisation is granted. The legal basis for this type of inspection is provided in Article 19 of Regulation (EC) No 726/2004 and only concerns centrally authorised products. These inspections may be recommended by PRAC and will be conducted under a CHMP request.

Although pre-authorisation inspections will not be requested on a routine basis, a risk assessment based on a combination of product-specific safety issues (e.g. product with risk-minimisation activities etc.) and system-related issues (e.g. first time introduction of a pharmacovigilance system or negative inspection history etc.) should be performed as outlined in section III.B.1.3 of GVP Module III before deciding on the need for this type of inspection.

The timelines for the conduct and reporting of pre-authorisation inspections will be subject to the timelines of the assessment of the marketing authorisation application under evaluation and therefore will normally be shorter than those in the post-authorisation setting (see section 6 and appendix 2).

The outcome of this type of inspection should be considered to determine the estimation date for the first (if the applicant is a new MAH in the EU) or next (if the applicant is an existing EU MAH previously inspected) post-authorisation pharmacovigilance inspection in the four-yearly programme of MAHs connected with CAPs described in section 4.2.1.

## **5. Implementation of EU pharmacovigilance inspections**

Member States should provide sufficient resources and appoint at least one adequately qualified inspector to ensure effective determination of compliance with good pharmacovigilance practice. The following Union procedures should be taken into account for the implementation of EU pharmacovigilance inspections:

- Union procedure on sharing of pharmacovigilance inspection information;
- Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections;
- Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products;
- Union recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

## **6. The Agency's coordination activities for CHMP requested inspections**

The agency plays a key role in the coordination of pharmacovigilance inspections requested by the CHMP. This section describes the activities in which the Agency is involved as part of the coordination role, however for the details about the preparation, conduct, reporting and follow-up of these inspections please also refer to the Union procedure listed in section 5.

An overview of the timelines for the different steps in the CHMP requested inspections is provided in Annex 2.

### ***6.1 Preparation of an inspection request***

For each inspection, an inspection request should be prepared which indicates the MAH concerned and site(s) to be inspected, the product(s) to be examined during the inspection, and, if applicable, a list of specific questions to be addressed during the inspection (system and /or product related) based on concerns from the pharmacovigilance assessors/PRAC, any other issues relevant to the inspection and the target date for the availability of the inspection report(s). Interaction between inspectors and PRAC/CHMP assessors is encouraged during the inspection request preparation and, in particular in the case of "for cause" inspections, to ensure that the reasons for the request and any link between the

request and a particular procedure that may be on-going or anticipated (e.g. PSUR review, renewal of the marketing authorisation etc.) are taken into account.

The concerned service head or designated delegate at the Agency will sign the request. The inspection request will be circulated to PRAC for agreement and for recommendation to the CHMP for its adoption. After the adoption by the CHMP, the Agency's Compliance and Inspections Department will initiate the co-ordination of this inspection.

## **6.2 Inspection team**

The Agency's Compliance and Inspections Department checks the availability of the inspectorate(s) in EU/EEA, which will be invited to conduct the requested inspection. A contact point for the purpose of deciding on the availability of the inspectorate to perform an inspection is appointed by each Member State inspectorate(s) and notified to the Agency. The CHMP adopted inspection request is sent to this contact person for information and indication of potential availability to participate in the inspection as reporting inspector or as team member when applicable. The Agency will also provide the adopted inspection request to the reporting inspectorate and lead inspectorate once the final team is decided.

In principle, the reporting inspectorate should be from the competent authority of the Member State in whose territory the PSMF is located (or, in the transition period, of the Member State where the QPPV resides and operates, if the PSMF has not been formally implemented). However, if for any reason, this competent authority cannot fulfil this task or it is more appropriate for another Member State to take this responsibility, the Agency's Compliance and Inspections Department should determine the availability of other inspectorates and designate another reporting inspectorate. The Agency designates the reporting inspectorate according to the following sequence, subject to the availability of inspector(s):

- competent authority of the Member State in whose territory the PSMF is located i.e. the supervisory authority (or, in the transition period, of the Member State where the QPPV resides and operates, if the PSMF has not been formally implemented);
- the Member State where the site to be inspected is located when this site is not located in the Member State where the PSMF is located or in a third country;
- competent authority of the Member State of the rapporteur concerned by one or more products or that express an interest to participate;
- competent authority of the Member State of the co-rapporteur concerned by one or more products or that express an interest to participate;
- other Member States who agree to participate.

When it is not feasible for the selected inspectorate to carry out the requested parts of the inspection, the competent authority of that country may ask, in co-ordination with the Agency, another inspectorate to conduct the inspection. For the purpose of promoting harmonisation, consideration should be given to involving more than one Member State inspectorate in the conduct of CHMP requested inspections. If more than one EU/EEA inspectorate needs to be involved in the inspection, one will be designated as the "reporting inspectorate" in accordance to the set of rules mentioned above.

Where relevant or on request, and in particular for product specific issues, the reporting inspector may be assisted, or the inspection (in a third country) may be conducted, by an inspector and/or expert from the rapporteur and co-rapporteur Member State. If an inspectorate wishes to request the

assistance of another inspectorate they should indicate this to the Agency within 5 working days from the notification of the inspection.

Member States may send trainees to the inspection, subject to considerations of the size of the inspection team. Such trainee participation will not give rise to a share of the inspection fee, or claim of expenses from the applicant.

The Member State inspectorate undertaking the reporting inspectorate role should ensure effective communication with the rapporteur, co-rapporteur and the relevant assessors.

For each site to be inspected, one lead inspector should be designated (this may be the same or different people when more than one site is selected for inspection). For the selection of the lead inspector the following rules should be considered:

- Pharmacovigilance inspections in EU/EEA countries: the lead inspector will be from the inspectorate in the country where the site(s) to be inspected is/are located. This does not prevent a lead inspector of one site to be involved, as an inspection team member, in the inspection of another related site located in a different EU/EEA country.
  - When it is not feasible for the inspectorate of the country where the inspection site is located to carry out the requested parts of the inspection, the competent authority of that country may ask, in co-ordination with the Agency, another inspectorate to lead the inspection.
- Pharmacovigilance inspections in third countries: the reporting inspector, and/or (co)-rapporteur Member State/other inspectors from EU/EEA States may act as lead inspector.

The Agency will contact local authorities in third countries as appropriate to notify them of the inspection. Inspectors are responsible for all visas, permission and arrangements.

The CHMP will be informed in case there are no inspection resources available.

The inspection request is communicated to the reporting inspectorate and lead inspectorates by the Agency.

### ***6.3 Announcement and preparation of the inspection***

The pharmacovigilance inspections will be announced to the MAH and/or the inspected entity (e.g. service provider) using the Agency standard letter, unless unannounced inspection is required. The Agency product leaders/procedure managers, rapporteurs and inspectors are copied in this correspondence.

In this announcement letter the MAH and/or the inspected entity is requested to ensure cooperation of all inspected parties and to confirm in writing that the sites accept to be inspected and that they will make all required documents available, for direct access by the inspectors. The MAH/inspected entity is also requested to provide copies of an initial set of documents (including the current version of the PSMF) for the preparation of the inspection to the inspection team indicated in this letter within a given deadline. The inspectors can then supplement this list with additional requests to the MAH/inspected entity.

The inspection should be announced within [10]\* days from the date of adoption of the inspection request by the CHMP and the inspection should be prepared within [20]\* days after the delivery of the documents requested from the MAH/inspected entity. Concerned inspectorates should participate in the discussion about the feasibility of the inspection as requested and the time schedule. Any change in the sites selected for inspection should be adopted by the CHMP.

For general considerations about the inspection preparation refer to section 4.4. of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.

#### **6.4 Conduct of the inspection**

The CHMP requested inspections should be conducted within [30]\* days after the preparation of the inspection.

For general considerations about the conduct of the inspections refer to section 5 of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.

#### **6.5 Reporting of the inspection**

In the case of CHMP requested inspections, for each site inspected, the lead inspector prepares an inspection report (IR) and forwards it to the reporting inspector within [70]\* days after the completion of the inspection. When more than one site is inspected and, where applicable, more than one inspection report is produced, the reporting inspector will also be responsible for the preparation of the inspection overview (IO). The IO, which will include the individual reports as attachments, should be forwarded to the Agency within [80]\* days after the completion of the inspection.

For general considerations about reporting inspections refer to section 5 of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.

#### **6.6 Inspection follow-up**

The Agency Compliance and Inspections Department will inform the PRAC and the CHMP rapporteur/co-rapporteur of the outcome of the inspection and further follow-up actions will be undertaken, as applicable, in accordance with 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.

## **Definitions**

The following definitions refer to the use of the specific terms for CHMP requested inspections. For inspections conducted under the Member State national programme the terms will be defined within the national procedures and the definitions below will only be used as guidance.

- Supervisory authority (SA): in the context of centrally approved products, the supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is located [Article 18 (3) of Regulation (EC) No 726/2004]. In the transition period, before the MAH formally implements a PSMF, the supervisory authority remains the competent authority of the Member State in which the QPPV resides and operates.
- Reporting inspectorate: the inspectorate from an EU/EEA State requested and accepting to be designated as the reporting inspector.
- Reporting inspector: the inspector designated by the reporting inspectorate to co-ordinate the preparation of the inspection, the conduct of the inspection and the activities of the inspectors. The reporting inspector has the following general duties:
  - Co-ordinating the preparation of the inspection.
  - Practicalities of the inspection (with the inspectors and the MAH).

- Conduct of the inspection.
- Preparation of the reports by the inspectors involved.
- Checking that the timelines for the inspection are kept.
- Writing and co-signing the inspection overview when applicable i.e. for multi-site inspections with one inspection report per site inspected.
- Acting as the main communication point between the inspection team and the Agency's Compliance and Inspections Department.
- Responsible, in conjunction with the Agency's Compliance and Inspections Department, for communication between the inspectorates and inspectors involved, the rapporteur/co-rapporteur and the CHMP (the system of communication should, however, be flexible and there can be direct communication between the involved parties, including the assessors, where this is more practical).
- Management of the live central archive related to the pharmacovigilance inspection.
- The reporting inspector may also be the lead inspector (see below) for one or more sites.
- Lead inspector: the inspector who has the following duties for the pharmacovigilance inspection of at least one inspection site:
  - Evaluation of the feasibility of the inspection as requested and discussion with the reporting inspector.
  - Organisation of the practicalities of the inspection with the inspected entity.
  - Leading the conduct of the inspection on site.
  - Communication between the inspected entity and the reporting inspector/Agency's Compliance and Inspections Department, as applicable (the system of communication should be flexible and there can be direct communication between the involved parties where this is more practical. In any case, the reporting inspector shall be kept informed about this communication outcome).
  - Writing and signing the inspection report.
  - Reviewing and co-signing the inspection overview, when applicable.

The reporting inspector and lead inspector will be the same person when only one site is concerned by the inspection.

- Inspection report (IR): details about the definition, availability, signatures, language and content of the IR can be found in the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.
- Inspection overview (IO): details about the definition, availability, signatures can be found in the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.
- Joint inspection: an inspection at which two or more Member State inspectorates participate in the same inspection at the same inspection site(s).
- Coordinated inspections: inspections of the same MAH conducted by different Member State inspectorates as part of a coordinated programme of review. Co-ordinated inspections may, for example, be used to examine the implementation of a corrective and preventative action plan at

both a main MAH pharmacovigilance processing site and at an affiliate site in a different Member State.

## References

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended.
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Union code relating to medicinal products for human use, as amended.
- Commission Implementing Regulation (EU) No 520/2012, on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.
- Guideline on good pharmacovigilance practices (GVP) - Module III – pharmacovigilance inspections.
- Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.
- Union procedure on sharing of pharmacovigilance inspection information.
- Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products.
- Union recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

# Annex 1

## Preparation of the risk-based programme of pharmacovigilance inspections of MAHs with centrally authorised products

### Gathering information

At least twice per year (1Q and 3Q), the Agency will gather information regarding changes to the information currently available in the four-yearly programme (e.g. changes in the location of the PSMF) and also information on any new MAHs with CAP authorisations to be included in the programme with the aim of revising the programme as indicated in the following sub-section. However, as soon as the Agency becomes aware of a change in the supervisory authority e.g. change in location of the PSMF or the QPPV (where the PSMF has not yet been formally implemented), the Agency will communicate this information to the previous and new supervisory authority concerned due to the impact on the national authority responsible for conducting the inspection.

In addition, previous information available on CAP inspections or inspections conducted/planned at national level will also be taken into consideration (e.g. the re-inspection dates proposed by the inspectors after the conduct of the inspections proposed in this programme) in order to ensure that the scheduled year for an inspection of a particular MAH in this programme is appropriate in light of changes in risk.

### Revision of the programme

The programme will be a dynamic rolling four-year cycle which will be revised at least twice per year to reflect the inspections already performed, the revised risk factors and the new MAHs/CAP products joining the system.

The preparation/revision of the four-yearly programme will take into consideration the following rules:

- for new MAHs to be included in the programme, the feedback from the inspectorates on when they plan to inspect these MAHs according to their national programmes will be considered. This proposal may need to change based on risk factors and other considerations as outlined in 4.1;
- for the MAHs already included in the programme, the inspectorates will be asked to confirm whether or not a change is needed based on new risk factors identified and a justification for these changes should be provided, in particular, when the changes relate to delaying the inspection by one or more years;
- re-inspections will be prioritised based on risk factors and will be focused on addressing critical/major findings observed in previous inspections, changes in the system and/or any product-specific issues of concern to the assessors.

The preparation/revision of the four-yearly programme will take place at least twice per year i.e. 1Q and 3Q of each year.

The programme schedule should at least include the details below:

- MAH;
- brand name;
- international non-proprietary name (INN);
- PSMF country;



- PSMF number assigned by the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPPD), when available;
- QPPV country;
- rapporteur country;
- co-rapporteur country;
- Member State inspectorate proposed to lead the inspection (e.g. where the PSMF is located or where the QPPV resides and works, if a PSMF has not yet been formally implemented);
- requestor of the inspection, i.e. Member State or CHMP;
- scheduled year of the inspection;
- comment field (e.g. for justifications on changes).

Additional details concerning the inspections (e.g. inspected sites, dates of inspection, inspection findings etc.) will be tracked in other documents shared in line with the Union procedure on sharing of pharmacovigilance inspection information.

### Adoption of the programme

This four-yearly programme should be agreed by the PhV IWG and PRAC and adopted by the CHMP the year before its implementation. As the programme schedule will be a live document requiring periodic revision through the year, it is expected to be circulated for adoption at least twice, in the 2Q and 4Q of the year.

The PhV IWG will be provided with each adopted revised programme schedule to ensure its implementation by the supervisory authorities concerned.

### Re-inspections

The calculation of the next inspection date for the programme should result from the last inspection date and the risk assessment process. In principle, a four-year inspection cycle will be used, but this may be shortened or lengthened based on risk assessment.

### Overview of the steps for the preparation of the 200X-200(X+3) programme

Steps	Sources	Responsibility	Timelines
1- Gathering information	SIAMED Member State Inspectorates Other: e.g. XEVMPPD	Agency- Compliance and Inspections Department	At least 1Q and 3Q 200(X-1)
2- Preparation and revision of the programme 200X-200(X+3)	SIAMED Member State Inspectorates Other	Agency- Compliance and Inspections Department  PhV IWG PRAC	At least 1Q and 3Q 200(X-1)
3- Adoption of the programme 200X-200(X+3)		PhV IWG PRAC	At least 2Q and 4Q

		CHMP	200(X-1)
4- Implementation of the programme 200X-200(X+3)		Member State Inspectorates	200X-200(X+3)
5- Re-inspections		Member State Inspectorates	Four-year cycle unless considered to be performed later/earlier

## Annex 2

### Activities related to pharmacovigilance inspections requested by CHMP: indicative time schedule \*

Steps of the procedure	Time allowed	
<p><b>1. Early activities of the Agency / CHMP</b></p> <p>Request for a pharmacovigilance inspection.</p> <p>Initial selection of sites.</p> <p>Set up of overall time schedule.</p> <p>Designation of the reporting inspectorates.</p> <p>First contacts Agency / inspectorates concerned.</p> <p>Notification of the inspection to MAH.</p>	<p>To be determined by the Agency/CHMP.</p> <p>Notify MAH within [10] days of CHMP meeting.</p> <p>Notify reporting inspectorate and other concerned inspectorate(s) within [10] days of CHMP meeting.</p> <p>Forwarding of required documents, (within [10] days of CHMP meeting).</p>	
<p><b>2. Inspection preparation</b></p> <p>Notification / announcement of site inspections.</p> <p>Preparation of the inspection plan.</p> <p>Obtaining and reviewing required documents.</p> <p>Finalisation of travel arrangements with the MAH.</p>	<p>[20] days * after the delivery of the documents requested from the MAH to the inspectorates.</p>	
<p><b>3. Site inspection</b></p>	<p>[30] days *</p>	
<p><b>4. Writing and circulation of the reports</b></p> <p>Writing of the inspection report.</p> <p>Reply from the inspected entity /party(ies) responsible (include this as an attachment to the IR).</p> <p>Comments from the inspectors to the inspected entity's response (include this as an attachment to the IR) and submission of the IR to the reporting inspectorate.</p> <p>Where applicable, writing the inspection overview.</p>	<p>[30/15<sup>1</sup>] days *</p> <p>[30/15<sup>1</sup>] days *</p> <p>[10] days *</p> <p>[10] days *</p>	<p>Total: [80/50<sup>1</sup>] days<sup>2</sup> *</p>

<b>5. Review of the reports by the Agency for adherence to applicable reference texts and the Agency/Union guidelines.</b>	[5 ] days *
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\*Times allowed to complete each step of the initiation, conduct and termination of the inspection are provided in this table. These times, shown in square brackets, should be considered as indications and can be modified if necessary e.g. the times for the preparation of the inspection report can be extended when the inspectors request information from the inspected entity, which is necessary for the completion of the report.

<sup>1</sup>Shorter reporting timelines for pre-authorisation inspections.

<sup>2</sup>The Agency should be notified as soon as possible by the reporting inspector of any urgent critical finding relating to the functioning of the MAH pharmacovigilance system and in particular the risk-benefit of the product(s) concerned by this inspection.