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Union procedure on the follow-up of pharmacovigilance inspections

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This guideline replaces document EMA/INS/PhV/192231/2014 “Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products”.

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Union procedure on the follow-up of pharmacovigilance inspections

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1. Introduction

According to Article 19 of Regulation (EC) No 726/2004 and Article 111 of Directive 2001/83/EC, the competent authority of a Member State where medicinal products are authorised, in cooperation with the European Medicines Agency (hereinafter 'the Agency'), shall ensure that the legal requirements governing medicinal products are complied with by means of inspections. The competent authority may inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorisation holder (MAH) or any firms employed by the MAH to perform the activities described in Title IX of Directive 2001/83/EC.

After every inspection, the competent authority is required to report on whether the MAH complies with the requirements laid down in Title IX of Directive 2001/83/EC and the content of those reports shall be communicated to the inspected entity. According to Article 111(8) of Directive 2001/83/EC, if the outcome of the pharmacovigilance inspection is that the MAH does not comply with the pharmacovigilance system as described in the PSMF and with Title IX of Directive 2001/83/EC, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the MAH and give him the opportunity to submit comments, and shall also inform the other Member States, the Agency and the Commission. Any non-compliance identified should be rectified by the MAH in a timely manner through the implementation of a corrective and preventive action (CAPA) plan.

Some pharmacovigilance inspections will require significant follow-up and management due to the nature of the findings identified. Regulation (EC) No 658/2007 empowers the Commission to impose financial penalties on the holders of marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004, and Article 111(8) of Directive 2001/83/EC states that, where appropriate, the Member State concerned shall take the necessary measures to ensure that a MAH is subject to effective, proportionate and dissuasive penalties. A variety of enforcement and infringement options exist within the Member States and are not further described in this guideline.

2. Scope

This procedure defines the steps in the follow-up of pharmacovigilance inspections and the responsibilities of the parties involved. This includes the process for requesting a CAPA plan in writing from the MAH, CAPA plan review and approval by the inspectors, routine interaction within and between Members States and the Agency, actions to be taken following the identification of inspection findings which may impact the robustness of the benefit-risk profile of medicinal product(s), and re-inspection planning. It applies to the follow-up of pharmacovigilance inspections of MAHs with centrally authorised products (CAPs) and nationally authorised products (NAPs), including those authorised via the mutual recognition procedure (MRP) and decentralised procedure (DCP). In addition to inspectors, post-inspection actions may also involve assessors in the Member States, the Agency and other committees such as the Pharmacovigilance Risk Assessment Committee (PRAC).

This procedure does not cover the routine process of exchanging information regarding inspections between Members States, the Agency and the European Commission, including information on the outcome of inspections (covered by the Union procedure on sharing of pharmacovigilance inspection information).

3. Parties involved and responsibilities

3.1. Pharmacovigilance inspectors

- To propose and track appropriate follow-up actions following conduct of inspections.
- To liaise with assessors, inspectors in the Member States and the Agency (as appropriate).
- To present inspection outcomes at PRAC (if required).

3.2. PRAC representative or assessor in the EU Member States

- To review inspection outcomes of Union interest that are escalated by inspectors.
- To comment on priorities for the corrective and preventive action(s).
- To propose appropriate follow-up actions, including use of routine pharmacovigilance tools available to the EU Member States, for the evaluation of any new safety data identified through inspection which may be considered for escalation to PRAC.
- To recommend presentation of findings to PRAC for further EU discussion (if necessary); PRAC discussion is likely to be necessary where non-routine follow-up actions are being considered.

3.3. Supervisory authority, where applicable (if not involved in the inspection)

- To perform a documented review of EU inspection outcomes of Union interest when they are escalated by other inspectors.
- To comment on actions recommended or already taken.

3.4. Pharmacovigilance Risk Assessment Committee (PRAC)

- To consider the inspectors' and assessors' recommendations and define appropriate actions to resolve any safety concerns resulting from inspections.
- Prioritisation of follow-up actions based on the preliminary evaluation of inspection findings and taking account of the products involved and the recommendations from the inspectors and PRAC representative/assessor in lead member state. The PRAC should guide decisions around follow-up actions and evaluate any newly identified safety data in the broader safety monitoring activities and regulatory procedures for particular products/substances.

3.5. The Agency Inspections Office (inspection coordinator)

- To coordinate communications between inspectors and assessors.
- To support the Agency product lead in their liaison between PRAC, MAH and inspectors.
- To liaise with the inspectors regarding inspection follow-up actions.
- To prepare documents for PRAC discussion.

3.6. The Agency product lead

- To coordinate assessor/PRAC product-related actions required as a result of inspections.
- To coordinate correspondence with MAHs on product-related actions required as a result of inspections.
- To track product-related inspection follow-up actions and ensure that the Agency inspection coordinator is kept informed in order to provide updates, as necessary, to the lead inspector.
- To take the lead at PRAC for the product specific assessment procedures.

3.7. Marketing authorisation holder

- To ensure that findings identified during an inspection are fully investigated and that appropriate and timely CAPA is implemented to address the findings, with appropriate prioritisation of critical and/or major findings.
- To inform the lead inspector if timelines for agreed CAPA deliverables change.
- To ensure timely evaluation of any new safety data identified through inspection.
- To ensure timely communication about safety concerns to competent authorities, patients and healthcare professionals, in particular notifying changes to the benefit-risk balance of concerned medicinal product(s) according to the urgency required (including implementation of variations to marketing authorisations for safety reasons).
- To respond to requests from competent authorities, including provision of correct and complete information.

4. Routine post-inspection actions

4.1. Provision and review of CAPA plans

For each site inspected an inspection report should be prepared and issued to the MAH (or other inspected organisation) in accordance with the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections. The lead inspector should propose date(s) for the receipt of responses to the findings listed in the inspection report; routinely the responses should be provided by the MAH within a defined time period of 30 working days following receipt of the report, unless there are specific national requirements for provision of responses to inspection reports or the lead inspector determines that an expedited response should be provided. The responses should be provided in the form of a CAPA plan with the aim of addressing the identified non-compliances. The MAH may also take the opportunity to correct misconceptions or misunderstandings in response to the findings. If findings are disputed, the inspector(s) should request relevant documentary evidence supporting the responses.

The CAPA plan should be assessed by the inspector(s) to determine whether the plan is adequate and routinely the assessment should be performed within a defined time period of 30 working days following receipt of the responses. A shorter review deadline of 10 working days for responses to the Committee for Medicinal Products for Human Use (CHMP) requested inspections is stipulated in the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.

Consideration should be given to whether the MAH has proposed adequate corrective action(s) to rectify the identified non-compliance and adequate preventive action(s) to eliminate the underlying root cause of the non-compliance in order to prevent recurrence. The inspector(s) should also establish

whether the MAH has undertaken a further assessment to determine the extent to which the non-compliance exists within the pharmacovigilance system and what impact it may have for all products. Action(s) proposed within a CAPA plan should be SMART (i.e. Specific, Measurable, Achievable, Realistic and Time driven), and the inspector(s) should assess whether the deliverables and timeframes specified in the CAPA plan are clear and reasonable. The template of the pharmacovigilance inspection report provided in appendix 1 of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections includes prompts for this information to be entered by the MAH.

The inspector(s) should seek further information and/or clarification from the MAH if the responses do not adequately address the non-compliances. This may include seeking clarification over proposed timeframes for specific actions. In this instance, consideration should be given to the seriousness of the issue, the nature of the proposed action(s) and whether any interim measures will be put in place to mitigate identified risks. The clarifications/updates required should be documented in writing and a timeframe should be proposed for the receipt of the updated responses. The number of attempts to obtain satisfactory responses should be determined by the inspector(s) using professional judgement and, where necessary, the lead inspector can request a meeting with the MAH to discuss the responses (see section 4.5). Upon receipt of an acceptable CAPA plan proposed by the MAH, the inspection can be closed according to national procedures. The MAH should be instructed that, if the timelines for corrective and preventive actions for critical or major findings change, or if the MAH is no longer able to implement the proposed corrective and preventive actions as intended, the lead inspector should be promptly notified. Changes to proposed corrective and preventive actions should be provided in writing to the lead inspector. For CHMP requested inspections, additional steps to be taken prior to closure of the inspection are outlined in the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.

4.2. Management of unacceptable responses to inspection findings

If, after further clarification has been sought, the responses to the inspection findings are not deemed acceptable, this should be escalated according to national procedures or via the Agency for inspections of MAHs with CAPs. It is a serious matter if the MAH fails to commit to taking appropriate action in response to identified non-compliance. On rare occasions, if the decision is taken to close the inspection when the responses are considered inadequate, the following actions should be taken:

- The conclusions of the inspector(s) with regards to the inadequate responses should be defined in writing, along with specific recommendations for further action, e.g. re-inspection, enforcement action, etc.
- Any irrelevant or inappropriate content added to the inspection report by the MAH should be removed or redacted by the lead inspector.
- The inspection report and the responses (where provided separately) should be shared with other relevant parties in accordance with Union procedures.

4.3. Sharing of inspection reports

For inspections with critical and/or major findings, the inspection report (or, when the inspection report is not written in English, a summary of the report) should be shared in accordance with the Union procedure on sharing of pharmacovigilance inspection information.

The MAH should be encouraged to share the inspection report with relevant service providers to whom it has sub-contracted pharmacovigilance activities, in instances where significant findings have been identified in relation to the activities conducted by the service provider. Service providers should be

reminded that deficiencies that are more broadly applicable to MAHs not subject to the inspection may need to be shared with those affected, such that appropriate CAPA can be derived. The service provider and MAH(s) affected should be able to demonstrate effective assessment and resolution of deficiencies that have been reported during any inspection.

Freedom of information (FOI) laws allows access to data held by national governments by members of the general public. Detailed FOI requirements vary from one Member State to another and public requests for inspection reports should be handled according to these national requirements. Where permitted, certain information within inspection reports should be redacted by a representative of the national competent authority (NCA) prior to release.

4.4. Periodic progress reports

In some instances, it may be necessary for the lead inspector to request that periodic progress reports on CAPA implementation are provided by the MAH. The timing, periodicity and format of these progress reports are at the discretion of the lead inspector and consideration should be given to the nature of the proposed action(s) and the overall timeframes for CAPA implementation. Periodic progress reports can be useful in instances where the MAH has had previously identified issues with CAPA implementation or where a CAPA plan includes actions with long timeframes for implementation, such as safety database re-configuration or large-scale harmonisation of product information (summary of product characteristics (SmPC) and patient information leaflet (PIL)) across multiple Member States.

4.5. Post-inspection meetings

Where deemed necessary by the lead inspector, a post-inspection meeting can be held with the MAH (or other inspected organisation) to discuss the non-compliances identified during the inspection, their impact and proposed action plans. The meeting can be held immediately following the inspection or, alternatively, following provision of a proposed CAPA plan. The purpose of a post-inspection meeting will vary but generally it can provide an opportunity for:

- the lead inspector to further outline specific pharmacovigilance legislative requirements and expectations in relation to statutory guidance;
- the MAH to present supporting information in relation to identified non-compliances and their impact;
- all parties to agree on an acceptable CAPA plan, including timeframes for implementation.

The timing and location of a post-inspection meeting will often be mutually agreed by both the lead inspector and the MAH (and/or other associated organisations, such as a contract service provider), and other representatives from the NCA may also be in attendance. It is recommended that an agenda for the meeting is prepared by the lead inspector and that minutes of the meeting are recorded, including a list of attendees. It is the responsibility of the lead inspector to ensure that any actions agreed at the meeting are adequately documented and are consistent with the final CAPA plan proposed by the MAH.

5. Escalation of inspection outcomes to other inspectors, assessors, PRAC representatives and the Agency

Communication and sharing of information between inspectors and other relevant groups within the NCA of the Member State concerned, and with other relevant national institutions, is important for the

proper follow-up of inspections. Cooperation and coordination of actions among relevant functions should be established taking into account allocation of tasks and responsibilities within Member States.

The routine process of exchanging information regarding inspections between Members States, the Agency and the European Commission, including information on the outcome of inspections, is covered by the Union procedure on sharing of pharmacovigilance inspection information.

5.1. Process for escalation of inspection outcomes

Within the NCA of the Member State concerned, inspection findings may need to be communicated to other GxP inspectors, assessors, regulatory affairs, quality defects, marketing or advertising departments. Advice can be sought from assessors regarding appropriate follow-up actions and whether routine pharmacovigilance activities, such as Periodic Safety Update Report (PSUR) submission and signal detection activities, will be sufficient to assess the impact of the inspection findings.

For inspection findings that may impact the benefit-risk profile of a product or have led to significant delays in the introduction of risk minimisation measures, advice should be sought from the PRAC representative in the Member State concerned on priorities for the proposed CAPA, accounting for important missing information for the product concerned. It should also be decided whether the findings require consideration by the PRAC, by assessing whether the completeness of safety data, the robustness of the benefit-risk profile or the correctness of risk communications need to be further discussed during the committee plenary meetings (see section 6). In these circumstances, the Agency Inspections Office should be contacted to coordinate PRAC discussions. For MRP/DCP products, the lead inspector should also inform the appropriate assessors from the reference Member State (RMS).

Where inspection findings are identified that are likely to have a significant impact on other Member States, the lead inspector should communicate to the MAH the expectation that the proposed CAPA plan should ensure that the inspection findings are addressed across all applicable EU Member States. Information about the inspection findings, the proposed CAPA and any recommendations should be communicated to the Agency and concerned Member States in a timeframe commensurate with the seriousness of the issue. In any case it should be prior to the date that the inspection is closed, when the outcome would be routinely shared in accordance with the associated Union procedure. The information should be referred to the Agency and concerned Member States using the template for pharmacovigilance inspection outcome sharing in appendix 3 of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections and/or via discussion at Pharmacovigilance Inspectors Working Group (PhV IWG). Concerned Member States should take account of this information in their national risk-based pharmacovigilance inspection programmes.

Where non-compliance is identified from a national pharmacovigilance inspection of an MAH with CAPs conducted by a non-supervisory authority Member State inspectorate that relates to the global pharmacovigilance system (and not solely to national issues), it may be advantageous for the concerned Member State inspectorate to liaise with inspectors of the supervisory authority regarding the timing of the next supervisory authority inspection. In the event that similar issues are identified at national and supervisory authority inspections, it may be beneficial to discuss whether an integrated CAPA plan can be produced in order to avoid multiple CAPAs for the same or similar non-compliances.

5.2. Examples of inspection findings that may require escalation to relevant stakeholders

This section highlights some examples of inspection findings that may require communication and coordination within and between Member States, the Agency and PRAC representatives. As a general

rule, examples of critical findings which should be shared with the PRAC representative and supervisory authority inspectors include:

- failure to provide pharmacovigilance data to competent authorities or the Agency, which may impact ongoing safety assessments;
- failure to evaluate safety signals which may affect the benefit-risk profile of the concerned product(s);
- failure to take action when a signal assessment demonstrates a new risk;
- failure or significant delays in the implementation of risk-minimisation measures.

The lead inspector should use professional judgement to determine whether inspection findings should be referred to other stakeholders for information and/or coordinated EU actions.

5.2.1. Failure or significant delay in updating authorised product information

Inspection findings in relation to authorised product information can include:

- failures to update SmPCs and PILs in line with current scientific knowledge by means of submission of an appropriate variation application;
- failures to communicate new and changed risks to healthcare professionals and patients due to outdated safety information being published on publicly available platforms and/or obsolete PILs being released in products packs.

Where significant findings of this nature are identified, inspectors should liaise with pharmacovigilance assessors and regulatory affairs personnel within their own Member State, as necessary, to coordinate follow-up and assessment of safety variation applications submitted according to the CAPA plan. Failures in the maintenance of product information, and subsequent submission and approval of safety variations, may warrant further product related actions. Depending on the impact and nature of the safety changes, recall and repackaging of the product or redistribution of advertising materials may be needed. Possible actions should be discussed with the relevant stakeholders, including GMP inspectors, and quality defects and advertising departments. Where failures in the maintenance of product information have been identified for a product which is being studied in a clinical trial, consideration should be given to notifying GCP inspectors in order to assess the impact on the investigator's brochure (IB).

Where an inspection has identified failures in the maintenance of authorised product information in a particular territory, there is the potential for a wider issue across multiple Member States to exist. The root cause analysis conducted by the MAH in response to the inspection finding may suggest that the root cause of the failings is a deficiency at a global, rather than a purely national, level. In this instance, the lead inspector should communicate to the MAH the expectation that the proposed CAPA plan should ensure that the inspection findings are addressed across all applicable EU Member States.

Taking into account the severity of the issue and the likely impact on other Member States, the lead inspector should consider referring the issue to concerned Member States and the Agency in accordance with the processes outlined in section 5.1. In addition, the lead inspector should contact the PRAC representative within their own Member State to discuss the safety implications and next steps. Where failures in the maintenance of product information across multiple Member States are confirmed, coordinated EU actions may be required and this should be discussed by the PhV IWG. In the most serious cases, the PhV IWG may recommend escalation to the most appropriate committee

such as the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) or PRAC, particularly if a coordinated approach to the submission of variation applications is required.

5.2.2. Failure or significant delay in the implementation of additional risk minimisation measures

Risk management plan commitments can include the implementation of additional risk minimisation measures, which can consist of targeted communication of educational materials, controlled access to a medicinal product, and interventions aimed at preventing pregnancy during treatment with a medicinal product with known or potential teratogenic effects. Implementation of additional risk minimisation measures will often be performed at a national level in accordance with national requirements.

Where an inspection has identified failure or significant delays in the implementation of additional risk minimisation measures at a national level, the lead inspector should contact the PRAC representative within their own Member State to discuss the safety implications and next steps. For MRP/DCP products, the lead inspector should also inform the appropriate assessors from the RMS.

If the root cause analysis provided by the MAH suggests that the source of the failing is a deficiency at a global, rather than a purely national level, the lead inspector should consider referring the issue to concerned Member States and the Agency in accordance with the processes outlined in sections 5.1.

5.2.3. Failure to provide pharmacovigilance data to NCAs or the Agency

- *Expedited reporting of individual case safety reports*

A routine inspection outcome could include expedited submission of missed individual case safety reports (ICSR) to EudraVigilance by the MAH, with subsequent routine signal detection activities including, where applicable, submission of validated signals by the MAH to the Agency and the competent authorities in Member States where the medicinal product is authorised.

In the event that a significant number of reports for a particular active substance require submission to EudraVigilance, taking into account the size of the safety database and the potential impact of non-submission, inspectors should notify the Agency, where at least one marketing authorisation has been granted in accordance with Regulation (EC) 726/2004, or the lead Member State responsible for monitoring the data in EudraVigilance (where appointed), where the active substance is contained in a medicine authorised in more than one Member State through national, mutual-recognition or decentralised procedures. For such medicinal products or active substances where a lead Member State has not been appointed, inspectors should notify the PRAC representative within their own Member State.

Note: ICSRs submitted by the MAH will routinely appear in the EMA two-weekly or monthly signal detection reports (electronic reaction monitoring reports (eRMRs)) depending on the products. NCAs should confirm any validated signals communicated by a MAH for an active substance/medicinal product authorised in their territory and enter them into the European Pharmacovigilance Issues Tracking Tool (EPITT) in accordance with GVP Module IX – Signal management.

- *Inclusion of data in PSURs*

Where an inspection identifies findings related to inclusion of data in PSURs, this should be communicated to the relevant assessor for the PSUR single assessment procedure (either a Rapporteur appointed by the PRAC or a Member State appointed by the CMDh). Depending upon the urgency and

if considered necessary, the assessor may request an ad-hoc PSUR if the next data lock point is not appropriate or if PSURs are no longer routinely required for that particular product. In order to fully assess whether the new safety information and the inspection findings have an impact on the safety profile of the product(s), it may be appropriate for the MAH to be requested to provide a critical evaluation of the following in the next PSUR:

- whether the new safety information has identified new signals and explain the approach to signal detection taken by the MAH in reviewing this information;
- whether the data suggest a change in frequency of known adverse reactions during the period of failure to report, in which case clear information needs to be provided on the method for calculating frequencies;
- implications of the above for effectiveness of risk-minimisation measures;
- implications for communication of risks to healthcare professionals and patients.

6. Interaction with the Pharmacovigilance Risk Assessment Committee (PRAC)

6.1. Escalation to PRAC

In cases where routine pharmacovigilance practices are considered insufficient to address the inspection findings or the topic is considered relevant for PRAC discussion, the lead inspector in collaboration with the PRAC representative and/or pharmacovigilance assessor should escalate the topic for discussion at PRAC. This decision should be based upon a thorough assessment of the implications of the inspection findings on the safety profile of the concerned product(s). Examples of critical inspection findings which may be considered for discussion at PRAC include:

- findings which may challenge the established benefit-risk profile of the product(s) or may have resulted in significant delays in introduction of appropriate risk-minimisation measures and therefore need EU-wide discussion;
- findings related to the non-reporting of ICSR data in significant volumes which may affect one or more products;
- findings which may result in enforcement actions including the potential to trigger an infringement procedure under Commission Regulation (EC) No 658/2007.

In order for inspectors and assessors to determine whether PRAC escalation may be appropriate, the inspection findings should be placed into context of their potential public health impact. Additional information may be requested post-inspection, for example as part of the CAPA plan, in order to clarify the public health impact where appropriate data are not available from retained inspection documents. The appropriate contextual measures will be dependent upon the nature of the findings but could include:

- the total number of ICSRs within the global safety database for the concerned product(s) versus the number of missed ICSRs to understand the extent/proportion of missed cases;
- the nature, seriousness and source of the missed ICSRs (if known);
- the next PSUR date (to determine whether the issues can be adequately assessed in a forthcoming PSUR or whether more urgent actions may be required);

- the total number of patients exposed to the concerned product(s) by EU and non-EU region (where known), including information on exposure to products concerned over time period of failure to report, and any off-label use;
- others, as appropriate, which may include whether the missed ICSRs include unlabelled adverse reactions.

6.2. PRAC discussion

Discussion of pharmacovigilance inspections at PRAC could have different outcomes depending on the situation and the nature of the findings detected and will not necessarily require an ad-hoc assessment of the benefit-risk profile of the concerned product(s) by the PRAC. Actions for the PRAC will be decided on a case-by-case basis.

The Agency Inspections Office is responsible for coordinating discussions at PRAC together with the Agency product lead of the concerned product(s) (or the appointed lead when several products are affected), as applicable. In order to facilitate the PRAC discussions, the lead inspector should notify the Agency Inspections Office and provide the inspection report and any other supporting documentation. The Agency Inspections Office should prepare the draft PRAC advice document that will form the basis for the PRAC discussion and circulate this draft to the relevant PRAC representatives and inspectors for comments/agreement prior to the PRAC meeting. A copy of the final draft version should be circulated to all relevant parties (for example, the product lead(s) of the concerned products, PRAC secretariat, PRAC representatives and relevant inspector(s)).

In cases where multiple products are affected, both CAPs and NAPs, different PRAC representatives may be appointed. PRAC representatives will be responsible for assessing the impact of the inspection findings on the safety profile of the products concerned. When considered appropriate, a lead PRAC rapporteur may be appointed to facilitate the discussion at PRAC. The appointment of a lead PRAC rapporteur should take into account the Member State that conducted the inspection and/or the Member State in which the PSMF is located. In addition, where considered appropriate a representative of the inspection team will also be invited to attend the PRAC meeting and present the inspection findings. The Agency Inspections Office should liaise with the inspectors to facilitate the process.

Following PRAC discussion, the Agency Inspections Office or product lead should prepare the final PRAC advice summarising the inspection finding(s), the conclusions and recommendations made by PRAC on follow-up actions, as applicable. The PRAC advice should clearly indicate who will be responsible for coordinating post-inspection actions and/or evaluating additional data provided by the MAH. For example, it will define which issues are system-related and to be followed up by inspectors and which are product-related and to be undertaken by PRAC through their routine activities. The Agency Inspections Office and/or the product lead should also ensure that the topic and related PRAC recommendations (PRAC advice) will be communicated and adopted at the following plenary meeting of the CHMP, where at least one centrally authorised product is within the scope of the PRAC recommendation, or of the CMDh, where no centrally authorised product is within the scope of the recommendation, as appropriate.

6.3. Communicating PRAC recommendations/actions to the MAH

Following discussion at PRAC, the PRAC advice will be sent to the MAH by the product lead after adoption by PRAC and, if necessary, after adoption by the CHMP or CMDh. The Agency inspection coordinator will be kept informed by the product lead and will provide updates to the lead inspector.

6.4. Assessing the fulfilment of post-inspection actions

The lead inspector is primarily responsible for assessing the MAH compliance against CAPA commitments in accordance with the processes described in sections 4 and 7 of this procedure. Any additional steps to encourage compliance or the provision of further information arising during the PRAC discussion should be included and adopted within the PRAC advice.

6.5. Persistent non-compliance

According to GVP Module III, when non-compliance with pharmacovigilance obligations is detected, the necessary action will be judged on a case-by-case basis. The action taken will depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action. Action may be taken by the Agency, the Commission or the competent authorities of the Member States as appropriate. As stated in Article 111(8) of Directive 2001/83/EC, where appropriate, the Member State concerned shall take the necessary measures to ensure that an MAH is subject to effective, proportionate and dissuasive penalties. Moreover, Regulation (EC) No 658/2007 also empowers the Commission to impose financial penalties on MAHs to ensure the enforcement of certain obligations connected with marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004.

Reference should also be made to legislation at EU and national level on penalties and sanctions and the implementing procedures relating to these.

7. Re-inspection planning

At the point where an inspection can be closed, the lead inspector should include a recommendation for the timing of a re-inspection to assess appropriate implementation of the CAPA plan. The timing should be defined using a risk-based approach. Where critical findings have been identified, an early re-inspection within 12 to 18 months should be considered. Where significant major findings have been identified, a timeframe of 24 to 36 months should be considered. In other situations, a re-inspection should be performed as part of a routine risk-based inspection programme. The recommendation for the re-inspection should be recorded in the inspection report or other documents according to national procedures. The re-inspection should be included in the inspection programme for nationally or centrally authorised products.

Coordination and cooperation may be required for the re-inspection in order to review the implementation of CAPA 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. Inspectors and/or assessors from a Member State that is not the supervisory authority may request to participate in the next supervisory authority inspection which can then replace the national re-inspection.

The scope of re-inspection will depend on many factors as listed in the GVP Module III. It is recommended that the inspection team records any information that would be beneficial to the inspection team performing the re-inspection. This includes data on the inspection conduct, any special circumstances and areas which were insufficiently addressed to make an assessment of compliance.

If it is identified during a subsequent inspection that corrective and preventive actions have not been implemented as described and no justification for this exists, this may lead to a new inspection finding (potentially critical grading) and/or escalation of the issue.

8. Communication of inspection findings to regulatory authorities outside of the EU

Sharing of information on serious non-compliance identified during EU/EEA site inspections with third country regulators may be required on a case by case basis. Such sharing of information will be coordinated by the Agency and managed under the framework of applicable confidentiality arrangements.

For inspections conducted in sites located in third countries, as part of its coordination role the Agency will contact local authorities in third countries, as appropriate, to notify them of the inspection and invite them to observe the inspection. However, the inspection outcome may only be shared whenever confidentiality arrangements are in place to facilitate this.

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.
- Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council.
- Guideline on good pharmacovigilance practices (GVP) - Module I – Pharmacovigilance systems and their quality systems.
- Guideline on good pharmacovigilance practices (GVP) - Module III – Pharmacovigilance inspections.
- Union procedure on the coordination of EU pharmacovigilance inspections.
- Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections.
- Union procedure on sharing of pharmacovigilance inspection information.
- Union recommendations on the training and experience of inspectors performing pharmacovigilance inspections.