EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 March 2014
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

Adopted by Pharmacovigilance Risk Assessment Committee	20 February 2014
Adopted by Pharmacovigilance Inspectors Working Group	21 March 2014
Date for coming into effect	01 June 2014

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Table of contents

1. Introduction 4

2. Scope 4

3. Parties involved and responsibilities 5

3.1. Pharmacovigilance inspectors 5
3.2. PRAC representative (for CAPs) or assessor in the EU Member States (for NAPs) 5
3.3. Supervisory authority, where applicable (if not involved in the inspection) 5
3.4. Pharmacovigilance Risk Assessment Committee (PRAC) 5
3.5. The Agency Compliance and Inspections Department (inspection coordinator) 5
3.6. The Agency product leader / procedure manager (as applicable) 6
3.7. Marketing-authorisation holder (MAH) 6

4. Procedure overview 6

5. Interaction between inspectors, pharmacovigilance assessors and PRAC representatives 7

5.1. Inspection findings related to CAPs with the potential to impact the benefit-risk profile 7
5.2. Inspection findings related to NAPs (including MRPs and DCPs) with the potential to impact the benefit-risk profile 8
5.3. Inspection findings affecting multiple products (CAPs and NAPs) with the potential to impact the benefit-risk profile 8
5.4. Failings related to product information affecting multiple Member States 8

6. Considerations before escalation to the Pharmacovigilance Risk Assessment Committee (PRAC) 9

7. Interaction with the Pharmacovigilance Risk Assessment Committee (PRAC) 10

7.1. PRAC discussion 10
7.2. Communicating PRAC recommendations/actions to the MAH 11
7.3. Assessing the fulfilment of post-inspection actions 11
7.4. Persistent non-compliance 11

References **12**
Annexes **12**
Annex I – Process map **13**

1. Introduction

The pharmacovigilance obligations placed on marketing-authorisation holders are laid down in Regulation (EC) No 726/2004, Directive 2001/83/EC and the Commission Implementing Regulation (EU) No 520/2012. Guidelines on the interpretation of these legislative pharmacovigilance requirements are published in the good pharmacovigilance practices (GVPs).

A variety of enforcement and infringement options exist within the Member States and are not further described in this guideline. Regulation (EC) No 658/2007 also 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.

According to 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 or any firms employed by the marketing-authorisation holder (MAH) to perform the activities described in Title IX of Directive 2001/83/EC.

Competent authorities at national and European Union (EU) level have developed a systematic and risk-based approach to make the best use of their surveillance and enforcement resources to ensure the protection of public health. Some pharmacovigilance inspections will require significant follow-up and management due to the nature of the critical findings identified. For those cases where follow-up actions are required, this procedure defines the steps in the follow-up process and the responsibilities of the parties involved.

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

This document applies to the follow-up of pharmacovigilance inspections of MAHs with centrally authorised products (CAPs) and nationally authorised products (NAPs) including those authorised via mutual-recognition procedure (MRP), decentralised procedure (DCP) and national procedure. It describes the actions to be taken following the identification of inspection findings which may impact the robustness of the benefit-risk profile of medicinal product(s). 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 guideline does not cover the routine follow-up of pharmacovigilance inspections, including the process for requesting corrective and preventive action(s) (CAPA) from the MAH (covered by the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections), nor the routine process of exchanging information on 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 (for CAPs) or assessor in the EU Member States (for NAPs)

- To review inspection outcomes of Union interest, which are escalated by inspectors.
- To comment on priorities for the corrective and preventive action(s) (CAPA).
- 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 review EU inspection outcomes of Union interest which 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 Compliance and Inspections Department (inspection coordinator)

- To coordinate communications between inspectors and assessors.
- To support the Agency product leader/procedure manager (as applicable) in their liaison between PRAC, MAH and inspectors.
- To liaise with the inspectors on inspection follow-up actions.
- To prepare documents for PRAC discussion.

3.6. The Agency product leader / procedure manager (as applicable)

- To coordinate assessor/PRAC actions required as a result of inspections.
- To coordinate correspondence with MAHs on actions required as a result of inspections.
- To track product-related inspection follow-up actions.
- To take the lead at PRAC for the product specific assessment procedures.

3.7. Marketing-authorisation holder (MAH)

- To ensure that appropriate and timely corrective and preventive action(s) are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings. To inform the lead inspector if timelines for agreed CAPA actions 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. Procedure overview

As part of the routine follow-up of inspections, inspectors should obtain and review a CAPA plan from the MAH. Unless immediate steps are necessary in order to protect public health, the lead inspector should review the proposed CAPA before making any recommendations for further action or discussion at EU level. The most appropriate post-inspection actions will depend upon the nature of the findings and the product(s) affected (including the way in which products are authorised e.g. CAPs versus NAPs (including MRP/DCPs). This guidance is intended to supplement processes for post-inspection actions which already exist in the Member States. For the purpose of this guidance impact on robustness of the product(s) benefit-risk profile(s) refers not only to cases where the benefit-risk profile itself might be altered, but also to cases where deficiencies in the pharmacovigilance system may have occurred with potential to impact product(s) safety profile(s) e.g. failure to update risk-minimisation measures and/or failure to communicate safety information to healthcare professionals and patients. In practice, the process steps undertaken will vary according to the potential impact of the inspection findings. The main scenarios may be as follows:

- inspection findings, which do not impact the benefit-risk profile (e.g. system failings without evidence of harm (or potential harm) to patient safety or public health) or which have not led to significant delays in the introduction of risk-minimisation measures:
  - the corrective and preventive action(s) (CAPA) proposed by the MAH should be assessed by inspectors according to national procedures (see also Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections),
  - early re-inspection may be considered to assess implementation of the CAPA;

- inspection findings, which may impact the benefit-risk profile or have led to significant delays in the introduction of risk-minimisation measures:
  - the CAPA should be assessed by the relevant inspectors and improvement assessed during the course of re-inspection,
  - the CAPA and any impact assessments produced by the MAH should be reviewed by inspectors and advice sought from assessors in the Member States (where necessary). The relevant assessor at national competent authority level should be asked to comment on whether additional follow-up actions are needed (such as escalation to PRAC), or 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;
- inspection findings, which after discussion with national competent authority assessors, are considered highly likely to impact the benefit-risk profile or have led to significant delays in the introduction of risk-minimisation measures:
  - the CAPA should be tracked by the inspectors. Liaison between those conducting assessment and inspection activities is required. The Agency Compliance and Inspections Department must also be informed of inspection outcomes which require discussion at PRAC in order to coordinate actions and facilitate PRAC discussion,
  - in instances, where the safety and the welfare of patients might be or has been put at risk, referral procedures may be initiated on behalf of the European Union (EU) in order to conduct a scientific assessment of a specific medicinal product, or class of medicines,
  - in the most serious cases where non-compliance may have caused harm to patients, recommendations may include enforcement action against the MAH including referral under Commission Infringement Regulation (EC) No 658/2007.

5. Interaction between inspectors, pharmacovigilance assessors and PRAC representatives

5.1. Inspection findings related to CAPs with the potential to impact the benefit-risk profile

Where inspection findings have been identified with the potential to impact the benefit-risk profile of the concerned product(s), the lead inspector should contact the PRAC representative in their own Member State and the inspectors of the supervisory authority (if different from those conducting the inspection). Information about the inspection findings, the proposed CAPA and the recommendations may be exchanged 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. 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 PRAC representative should provide advice 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 considering 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 7).

5.2. Inspection findings related to NAPs (including MRPs and DCPs) with the potential to impact the benefit-risk profile

Where inspection findings have been identified with the potential to impact the benefit-risk profile of the concerned product(s), the lead inspector should contact pharmacovigilance assessors in their own Member State to discuss the safety implications and next steps. Examples of findings which may need to be shared with assessors do not differ from those described in the section above.

The assessors should provide advice on priorities for CAPA, accounting for important missing information for the product concerned. For MRP/DCP products, the lead inspector should also inform the appropriate assessors from the reference Member State (RMS). In general, inspection issues related to purely nationally-authorised products (not MRP/DCP) should be handled at a national level in collaboration with the national pharmacovigilance assessors (as appropriate). However, depending on the seriousness of the findings detected and the possible implications for the safety profile of the concerned product(s), national assessors may conclude that routine pharmacovigilance activities will not be sufficient and that the topic needs to be brought to PRAC attention (See Section 7). In these circumstances, the Agency Compliance and Inspections Department should be contacted to coordinate PRAC discussions.

5.3. Inspection findings affecting multiple products (CAPs and NAPs) with the potential to impact the benefit-risk profile

Where inspectors detect a system failure that has an impact on a wide range of products (for example multiple CAPs or a combination of CAPs and NAPs), the lead inspector should contact the PRAC member in their own Member State to discuss the implications. See section 6.1 for guidance on the interaction with the PRAC representative. Other local pharmacovigilance assessors in the Member State(s) can also be informed, if considered necessary. If it is decided to discuss the topic at PRAC, a complete list of affected products (CAPs and NAPs) should be supplied to the Agency Compliance and Inspections Department by the lead inspector. The Agency Compliance and Inspections Department will be responsible for coordinating actions at a European level in conjunction with the Agency product leader / procedure manager, as applicable.

5.4. Failings related to product information affecting multiple Member States

Where inspections have identified failures in the maintenance of product information (summary of product characteristics (SmPC) and patient information leaflet (PIL)) across multiple Member States, coordinated EU actions may be required. The inspection findings should be shared with other EU inspectors 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 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 co-ordinated approach to submission of variations is required.

6. Considerations before escalation to the Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC mandate includes reviewing the safety profile of all medicinal products (including CAPs and NAPs). From a pharmacovigilance inspection perspective, all Member States (inspectors and PRAC), the Agency and the European Commission will have continuous access to information on planned and conducted inspections and inspection outcome of MAHs (of CAPs and NAPs) through a common repository and will receive in addition regular updates for information via an overview Excel spread sheet report, as described in the Union Procedure on sharing of pharmacovigilance inspection information. Discussion of inspection topics at PRAC should not occur routinely and it is not intended that every critical finding detected during pharmacovigilance inspection would require discussion at PRAC.

In cases where the inspectors and assessors consider routine pharmacovigilance activities are sufficient to address the inspection findings, the topic will not be escalated for discussion to PRAC. Routine pharmacovigilance activities may include:

- **routine CAPA follow-up** including periodic updates on MAH progress against the CAPA commitments;
- **expedited submission of missed cases** to EudraVigilance (and Member States in the transitional period) with subsequent routine **signal detection** activities. ***Note:*** Individual Case Safety Reports (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;
- **inclusion in PSURs**. The integrated benefit-risk evaluation in PSURs provides an opportunity to critically evaluate relevant new safety information that could have an impact on the benefit-risk balance of the medicinal products. Depending upon the urgency and if considered necessary, the assessor may request an ad-hoc PSUR if the next date lock point (DLP) 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 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 in information to healthcare professionals (HCPs) and patients.

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 e.g. as part of the CAPA, 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.

This information when relevant to the inspection finding should be reported within the template for pharmacovigilance inspection outcome sharing (appendix 3 of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections).

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

7.1. PRAC discussion

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.

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 Compliance and Inspections Department is responsible for coordinating discussions at PRAC together with the Agency product leader / procedure manager 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 Compliance and Inspections Department and provide the inspection report and any other supporting documentation. The Agency Compliance and Inspections Department 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 leader(s)/ procedure manager(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 Compliance and Inspections Department should liaise with the inspectors to facilitate the process.

Following PRAC discussion, the Agency Compliance and Inspections Department or product leader / procedure manager (as appropriate) 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 Compliance and Inspections Department and/or the product leader / procedure manager should also ensure that the topic will be discussed and adopted at the following plenary meeting of the Committee for Medicinal Products for Human Use (CHMP), as appropriate.

7.2. Communicating PRAC recommendations/actions to the MAH

Following discussion at PRAC, the PRAC advice will be sent to the MAH by the product leader / procedure manager, after adoption by PRAC and if necessary, after adoption by the CHMP.

7.3. Assessing the fulfilment of post-inspection actions

The lead inspector is primarily responsible for assessing the MAH compliance against CAPA commitments in accordance with national processes for inspection follow-up.

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.

7.4. 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 a marketing-authorisation holder is subject to effective, proportionate and dissuasive penalties. Moreover Regulation (EC) No 658/2007 also empowers the Commission, to impose financial penalties on the holders of marketing authorisations 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.

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 procedures 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.
- Countdown to July 2012: the establishment and functioning of the PRAC

Annexes

Annex I

Process map

Annex I – Process map