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Union procedure on sharing of pharmacovigilance inspection information

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Union procedure on sharing of pharmacovigilance inspection information

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[1] The preparation of a risk-based programme for pharmacovigilance inspections is presented in Annex 1 of the "Union procedures on the coordination of EU pharmacovigilance inspections.

1. Introduction

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

The guideline on good pharmacovigilance practices (GVP) Module III (pharmacovigilance inspections), section III.C.1 states that the Agency and the Member States shall cooperate to facilitate the exchange of information on inspections and in particular:

- Information on inspections planned and conducted in order to avoid unnecessary repetition and duplication of activities in the European Union (EU) and optimise the inspection resources.
- Information on the scope of the inspection in order to focus future inspections.
- Information on the outcome of the inspection, in particular when the outcome is that the marketing authorisation holder does not comply with the requirements laid down in legislation and relevant guidance.

After every inspection the competent authority is expected to report on whether the marketing authorisation holder complies with the requirements laid down in Title IX of Directive 200/83/EC. According to Article 111(8) of Directive 2001/83/EC, if the outcome of the pharmacovigilance (PhV) inspection is that the marketing authorisation holder (MAH) does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file (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. The legislation also states that the competent authority which carried out the inspection shall make the final report available electronically to the Commission, the Member States and the Agency [Article 19(3) of Regulation (EC) No 726/2004 and Article 122(2) of Directive 2001/83/EC]. The aforementioned requirements are based on the general principle that all inspections carried out by the inspection services of any Member States are performed on behalf of the entire Union. The discovery of serious pharmacovigilance non-compliance may have implications not only for the Member State carrying out the inspection but also other, possibly all, Member States. Therefore a mechanism that ensures prompt communication of non-compliance information (critical findings and/or major findings) and consistent, co-ordinated action throughout the Union is required.

GVP Module III also states that a common repository, accessible to all Member States, the Agency and the Commission, should be created to facilitate this information sharing on planned and conducted pharmacovigilance inspections.

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.

[1] The preparation of a risk-based programme for pharmacovigilance inspections is presented in Annex 1 of the “Union procedures on the coordination of EU pharmacovigilance inspections.

2. Scope

This procedure supplements GVP Module III by providing additional guidance on the type of information exchanged between the Member States, the Agency and the European Commission and the tools and procedures developed at EU level to facilitate and optimise the communication across the Union in order to fulfil the legislative requirements. Communication with the public and freedom of information requests are outside the scope of this procedure.

The processes described in this procedure apply to pharmacovigilance inspection information associated with any marketing authorisation holders (or any firms employed by the marketing authorisation holder) of products authorised through a European (centralised/mutual recognition/decentralised) or national procedure that can be subject to inspection in order to verify compliance with the pharmacovigilance obligations described in Title IX of Directive 2001/83/EC in accordance with Articles 111(1) and 111(1)(d).

3. Sharing of information process

A common repository, accessible to all Member States, the Agency and the Commission will be used to facilitate information sharing on planned and conducted pharmacovigilance inspections.

Until a system is in place for the Member States to be able to update directly their information and upload documents to be shared within the Union, the Agency will act as the central point for receipt of all the Member State information to be shared and will ensure that the repository of information is maintained by updating the information on a regular basis.

Member States inspectors and/or assessors may at any stage decide to discuss the information shared and exchange additional information outside the common repository on an *ad-hoc* basis. In those cases the Agency may be requested to support and coordinate the national competent authorities' interactions, as necessary.

3.1. EU inspection programmes and compliance overview

High level information on inspections planned and on the outcome and follow up of inspections conducted will be continuously accessible to all Member States (inspectors and Pharmacovigilance Risk Assessment Committee (PRAC) members), the Agency and the European Commission through the common repository in the form of an "EU list of planned and conducted PhV inspections" described in section 4.1 of this procedure. The EU list of planned and conducted PhV inspections will be a live document maintained continuously by the Agency based on the data sent by the Member States competent authorities using a standardised template. Each competent authority should maintain its own version of the agreed template containing information only on planned and conducted inspections part of their national inspection programme. Updated versions of the national template, or confirmation that there are no changes since the previous update, should be sent by each competent authority to the Agency at least quarterly. In addition, Member States are expected to communicate urgent new information resulting from planned or conducted pharmacovigilance inspections or related topics with relevance/impact for other Member States on an *ad hoc* basis.

Member States should ensure that during inspection preparation they review the information within the common repository for the MAHs of their concern and, if necessary, contact other inspectorates, to discuss and adapt the inspection scope and/or the timing of inspections in order to avoid unnecessary duplication, make the best use of inspection resources and improve inspection coverage. In order to improve the interaction between inspectors and assessors during inspection preparation and inspection

[1] The preparation of a risk-based programme for pharmacovigilance inspections is presented in Annex 1 of the "Union procedures on the coordination of EU pharmacovigilance inspections.

follow up, the Agency will also circulate the latest version of the "EU list of planned and conducted PhV inspections" within the Pharmacovigilance Risk Assessment Committee meeting documents for information on a quarterly basis.

The Agency may also make accessible via a general folder of the common repository other types of information, such as the risk-based programme for routine inspections of MAHs with centrally authorised products (CAPs), PRAC recommendations on pharmacovigilance inspections, reports extracted from the Eudravigilance database and the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD), as described in section 4 of this procedure.

3.2. Marketing authorisation holder compliance

In addition to the high level information within the "EU list of planned and conducted PhV inspections", additional information on the inspection outcome, information on how the findings are being addressed (e.g. summary of the corrective action preventive action (CAPA) for critical and major findings) and recommendations for follow up will also be made available via the common repository, for inspections with critical findings and/or major findings. For this type of communication the inspection report(s) or, when the inspection report is not written in English, a summary of the inspection report provided 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 will be stored in the respective MAH folder.

For inspections conducted under the national programme, the national competent authorities should provide to the Agency, via the dedicated mailbox, the inspection report(s) and/or the completed template for pharmacovigilance inspection outcome sharing in appendix 3 of the Union procedure on the preparation, conduct and reporting of EU pharmacovigilance inspections. The Agency will include the inspection report(s) and/or the completed template for pharmacovigilance inspection outcome sharing and any other related documents in the relevant MAH folder(s) of the common repository, as applicable. It is recommended that multiple documents associated with a single site inspection are grouped before they are shared within the common repository. In the case of third party inspections the competent authority should indicate whether the inspection outcome is relevant for more than one MAH and provide the list of affected MAHs, so that the Agency can link the documents with all the relevant MAH folders.

For inspections requested by the Committee for Medicinal Products for Human Use (CHMP) it will be the responsibility of the Agency to share the final report via the common repository following circulation to the CHMP/PRAC and the MAH, and therefore the reporting inspectorate will not need to send the inspection report to the dedicated mailbox.

The timelines for the communication of the inspection outcome and any follow up actions required will be judged on a case-by-case basis by the lead inspector, in conjunction with the concerned assessors where applicable, and will depend on the potential negative public health impact of the non-compliance(s) identified. The course of action taken following the discovery of any non-compliance should be commensurate with the level of risk posed by the non-compliance identified and should be in accordance with the steps described in the procedure on Union procedure on the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products.

Sharing of information on serious non-compliance with third country regulators may also be required on a case by case and will be coordinated by the Agency and managed under the framework of applicable confidentiality arrangements.

[1] The preparation of a risk-based programme for pharmacovigilance inspections is presented in Annex 1 of the "Union procedures on the coordination of EU pharmacovigilance inspections.

4. Sharing of information: types of information, source and format

4.1. Inspections planned and conducted

Information on planned and conducted inspections will be shared in the form of an "EU list of planned and conducted PhV inspections". The Agency will populate the EU list with the information sent by each member state national competent authority within the agreed standardised template as information becomes available and at least quarterly.

A colour code will be used to highlight inspections and inspection outcomes within the "EU list of planned and conducted PhV inspections" that require special attention by Member State inspectors and assessors, as follows:

- Red highlight will indicate:
  - Inspection outcomes that require attention and/or action by other Member States. In such cases the comment field may be used to briefly explain the concern(s), the recommended action by other Member states and specify the member states affected, as necessary, or to just make reference to the information included within the template for pharmacovigilance inspection outcome sharing under the specific MAH folder.
  - Inspection outcomes that may be escalated for discussion to the PRAC. 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 describes the process to be followed by inspectors and assessors in order to determine whether escalation to the PRAC is appropriate.
- Green highlight will indicate third country inspections.

In order to fulfil the requirement of Article 111(1) of Directive 2001/83/EC for cooperation between the Member States and the Agency in the coordination of inspections in third countries, the Agency will use the "EU list on planned and conducted PhV inspections" as a basis for the maintenance of a list of third country site inspections, as described in the Union procedure on the coordination of EU pharmacovigilance inspections. The third country site inspection list will be also made accessible to EU/EEA national competent authority inspectorates via the common repository. National inspectorates should provide details of the outcome of these third country inspections in accordance with section 4.2 of this procedure.

4.2. Inspection outcome, MAH CAPA and follow up actions / recommendations

For inspections with critical findings and/or major findings the final pharmacovigilance inspection report(s) or, if the final report is written in a local language, a summary of the inspection outcome should be made available 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. National competent authorities should complete each section of the template for pharmacovigilance inspection outcome sharing, as applicable, and with focus on:

- findings that relate to the global pharmacovigilance system (and not solely to national issues) and for which inadequate CAPA have been provided;
- findings with the potential to impact the benefit-risk profile of the concerned medicinal products;

[1] The preparation of a risk-based programme for pharmacovigilance inspections is presented in Annex 1 of the "Union procedures on the coordination of EU pharmacovigilance inspections.

- findings that require action by other Member States.

The areas where major and critical findings have been identified will be indicated by selecting from the predefined list (ticked in the template). In addition, if applicable, any findings that need attention should be highlighted and further information, should be provided in the text field, as necessary. Summary text provided does not need to be the exact translation of the original inspection report.

Information on the marketing authorisation holder CAPA are also to be provided by completing the template, if not provided as part of the inspection report (written in English). Member States will share information on CAPA status (clearly indicating whether the CAPA is completed or on-going) and a list of outstanding issues, as applicable. Clear recommendations, implications for other Member States and actions required by other Member States should be clearly stated, where required. This type of CAPA information sharing is essential when non-compliances are identified from national pharmacovigilance inspection(s) of an MAH conducted by non-supervisory authority Member State(s). In such cases communication between the concerned Member State inspectorate(s) and the supervisory authority, when applicable, should be facilitated, when necessary, in order to produce an integrated CAPA and avoid multiple CAPAs for the same or similar non-compliances, as described in the Union procedure on the coordination of EU pharmacovigilance inspections. In addition, inspectors should include in the template information on CAPA status for product specific findings and product specific concerns requiring follow up that may be relevant and useful for assessors.

For third country inspections the final inspection report(s) or, if the final report is not in English, a summary of the inspection outcome should be made available using the template for pharmacovigilance inspection outcome sharing, as described above.

Contractors may be inspected in the margins of an MAH inspection or as part of a routine programme of system inspections of contractors [Article 111(1)(d) of Directive 2001/83/EC]. In this last case, the sharing of information within the common repository and the processes to be followed in the context of nationally authorised products (NAPs) and CAPs are to be further developed by the Pharmacovigilance Inspectors Working Group (PhV IWG).

4.3. Other pharmacovigilance related information

Other information shared within the common repository may include:

- information from EudraVigilance (standard predefined EudraVigilance queries including reports on MAH reporting compliance, issues revealed from EudraVigilance data management activities);
- information generated from queries within XEVMPD (e.g. pharmacovigilance system master file (PSMF) location, information on the products covered by a specific PSMF, qualified person for pharmacovigilance (QPPV) contact details);
- information on committee (PRAC/CHMP) decisions/recommendations in relation to inspections; other ad-hoc communication related to medicinal product safety and pharmacovigilance (including notifications from the MAH);
- additional information provided by Member States or the Agency (e.g. assessor's input) that may not refer to a distinct inspection or MAH but may nevertheless be relevant for national competent authorities performing pharmacovigilace inspections.

It is noted that when the information is MAH related the relevant documents will be made accessible under the corresponding MAH folder.

[1] The preparation of a risk-based programme for pharmacovigilance inspections is presented in Annex 1 of the "Union procedures on the coordination of EU pharmacovigilance inspections.

Definitions

For the definition of pharmacovigilance inspection specific terms please refer to the Union procedure on the coordination of EU pharmacovigilance inspections.

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 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 the management of pharmacovigilance inspection findings which may impact the robustness of the benefit-risk profile of the concerned medicinal products.

[1] The preparation of a risk-based programme for pharmacovigilance inspections is presented in Annex 1 of the "Union procedures on the coordination of EU pharmacovigilance inspections.