Standard operating procedure

Title: Co-ordination of Pharmacovigilance inspections		
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1. Purpose

This SOP describes how CxMP requested pharmacovigilance (PhV) inspections are co-ordinated by the P-CI-CNC section in connection with human and veterinary medicinal products under the centralised procedure or in the context of a referral procedure.

Routine PhV inspections will be mainly conducted by the EU member states under their national programmes in accordance with the routine PhV inspection plan prepared by EMA in conjunction with EU national competent authorities (NCAs). However, there will be situations where these inspections might be specifically requested by the CxMP (e.g. global PhV sites in third countries).

In addition, PhV triggered inspections will be requested by CxMP. These inspections can be requested as a result of data submitted as part of a MA dossier, data provided as a result of specific obligations/follow-up measures, variations, line extensions, previous inspections or other information received post authorisation, e.g. in relation to safety updates, PSUR, etc.

This SOP should be read in conjunction with the relevant documents mentioned in section 6.

2. Scope

This SOP applies to P-CI-CNC section only.

3. Responsibilities

It is the responsibility of the Section Head to ensure that this procedure is adhered to within his/her own section. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section 9.

4. Changes since last revision

New SOP.

5. Documents needed for this SOP

5.1. The following templates are available under the Oracle Business Intelligence (OBI) link:

http://bi.eudra.org/dashboard/Corporate GxP/GCP and PhV/templates/PHV Templates

- Inspection Request (IREQ).

- Letter to the Applicant.

- Letter to the EEA Inspectors.

- Letter to the EEA Inspectors with contacts.

- Letter to Third Country Inspectors.

5.2. The following documents are saved under X:\Templates\Others\Compliance and Inspection\ PhV \ Payments PhV Inspections

- chek¯¯ Checklist for validating PhV inspection reports-¯EMEA-INS-PhV-344044-2008.

- form¯¯Payment order generation form PhV inspections¯EMEA-INS-PhV-344132-2008.

- form¯¯template Memo to gestionnaire with payment order generation form¯EMEA-INS-PhV-344156-2008.

5.3. The following document is saved in DREAM under: Cabinets/ 04. Inspections/ 1. PhV/PhV Inspections

- EMA/577319/2010 Categorisation of PhV findings.

6. Related documents

1. SOP/EMA/0040 Evaluation of conflicts of interest of experts for involvement in EMA activities.

2. SOP/H/3004 Tasks of the product team on the handling of the initial Marketing Authorisation Application.

3. SOP/INSP/2005 Processing of financial transactions for inspections.

4. SOP/PDM/1004 Core master files of medicinal products for human and veterinary use following the centralised procedure.

5. Core Master File – Compliance and Inspection. Doc. Ref.: EMA/641169/2010.

6. WIN/ INSP/2025 Announcement of Good Clinical Practice/Pharmacovigilance inspection to reporting inspectorate, applicant and 3rd country inspectorate prepared by P-CI-CNC.

7. User Manual for Corporate GxP: CorporateGxP GCP/PhV Inspections Full User Guide (http://corpgxp.eudra.org/corpgxp/us_ext_docs/gcpPhvHelp.pdf)

8. Procedure for Coordinating Pharmacovigilance Inspection requested by the CHMP, INS/PhV/1 which can be found on the EMA public website: Home / Regulatory / Human medicines / Inspections / Pharmacovigilance / Inspections procedure

9. Procedure for Coordinating Pharmacovigilance Inspection requested by the CVMP, INS/PhV-V/1 which can be found on the EMA public website: Home / Regulatory / Human medicines / Inspections / Pharmacovigilance / Inspections procedure

10. Procedure for Reporting of Pharmacovigilance Inspection requested by the CHMP, INS/PhV/3 which can be found on the EMA public website: Home / Regulatory / Human medicines / Inspections / Pharmacovigilance / Inspections procedure

11. Procedure for Reporting of Pharmacovigilance Inspection requested by the CVMP, INS/PhV-V/3 which can be found on the EMA public website: Home / Regulatory / Human medicines / Inspections / Pharmacovigilance / Inspections procedure

7. Definitions

Abbreviations

- Applicant/MAH   Applicant/Marketing Authorisation Holder.

- AR   Assessment Report.

- Corporate GxP   Corporate GxP.

- CxMP   Committee for Medicinal Products for Human/Veterinary Use.

- DDPS   Detailed Description of Pharmacovigilance system.

- HoS   Head of Sector.

- IO   Inspection Overview.

- IR   Inspection Report.

- IREQ   Inspection Request.

- JAR   Joint Assessment Report.

- MA   Marketing Authorisation.

- MAH   Marketing Authorisation Holder.

- NCA   National Competent Authority.

- OBI   Oracle Business Intelligence.

- P-CI-CNC   Clinical and Non-clinical Compliance section, in the Compliance and Inspection sector in the Patient Health Protection unit.

- PhV   Pharmacovigilance.

- PRAC   Pharmacovigilance Risk Assessment Committee.

- PSMF   Pharmacovigilance System Master File.

- PSUR   Periodic Safety Update Reports.

- PTL   Product Team Leader.

- PTM   Product Team Member.

- QPPV   Qualified Person for Pharmacovigilance.

- RI/LI   Reporting Inspector/ Leading Inspector.

- SH   Section Head.

- SMDB   Scientific Memory Database.

PhV Inspection: The act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the PhV activities and that may be located at the site of the QPPV or at other affiliates, or at other establishments which the competent authority sees fit to inspect.

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 EMA Inspection sector. The reporting inspector and the EMA inspection sector are responsible for the communication between the inspectorates, inspectors involved, the (co)-rapporteurs and the CxMP. 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 PhV 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 PhV 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 inspectees;

- Leading the conduct of the inspection on site;

- Communication between the inspectees and the reporting inspector/EMA Inspection sector. The system of communication should, however, 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):

An inspection report (IR) is prepared for each site inspected. It is written by the lead inspector and signed by the lead inspector and other inspectors as required by local legal requirements and SOPs. The inspection report will be written in English, unless required by local regulations to be in local language. In the latter case the inspection report will be translated / modified to English under the responsibility of the lead inspector prior to signature by all involved inspectors. The timelines for the finalisation of the IR will be extended as needed.

Inspection Overview (IO):

For multiple site inspections, an inspection overview (IO) will also be prepared, addressing the major and critical findings recorded for all sites, providing an evaluation of the impact of the findings, and a recommendation on the actions to be taken. For each PhV inspection request made by the CxMP one inspection overview is prepared. This report is in English, and summarises the critical and major findings of the inspection of all sites involved.

The IO is written and signed by the reporting inspector, and reviewed and signed by the lead inspectors. The IRs are attached to the IO as appendices. Signature may be obtained by fax, and the originals mailed to the reporting inspector. Where there is only one site inspected, the IO and IR can be one document provided that they are in English and provided that a summary of the findings and conclusion is given – the report should fulfil the objectives of the IO and IR.

8. Process map(s)/ flow chart(s)

```
                          ┌─────────┐
                          │  START  │
                          └────┬────┘
                               ▼
                  ┌─────────────────────────┐
                  │ 1. Identify need to request
                  │    inspection at CxMP
                  │    meeting              │
                  └────────────┬────────────┘
                               ▼
                  ┌─────────────────────────┐
                  │ 2. Check PhV
                  │    summary/latest DDPS to
                  │    identify QPPV, PSMF,
                  │    location, RI and
                  │    supervisory authority (if
                  │    applicable)          │
                  └────────────┬────────────┘
                               ▼
                  ┌─────────────────────────┐
                  │ 3. Prepare draft IREQ using
                  │    Corporate GxP        │
                  └────────────┬────────────┘
                               ▼
                  ┌─────────────────────────┐◄──────────────────┐
                  │ 4. Circulate draft IREQ to                   │
                  │    (co)-rapporteurs, PTL and                 │
                  │    inspectors for comments                   │
                  └────────────┬────────────┘                   │
                               ▼                                │
                        ╱─────────────╲         Yes  ┌─────────────────────┐
                       ╱   5.          ╲───────────► │ 5.1 Implement comments│
                       ╲  Comments     ╱             └──────────┬──────────┘
                        ╲ received?   ╱                         │
                         ╲───────────╱                          │
                               │ No                             │
                               ▼                                │
                  ┌─────────────────────────┐◄─────────────────┘
                  │ 6. Obtain final sign off
                  │    from P-CI-CNC SH     │
                  └────────────┬────────────┘
                               ▼
                  ┌─────────────────────────┐
                  │ 7. Table IREQ for adoption
                  │    at next CxMP meeting │
                  └────────────┬────────────┘
                               ▼
         ┌─────┐   No    ╱─────────────╲    Modification
         │ END │◄───────╱   8.CxMP      ╲──────────────────────┘
         └─────┘        ╲  adoption?    ╱
                         ╲─────────────╱
                               │ Yes
                               ▼
                  ┌─────────────────────────┐
                  │ 9. Confirm inspection team│
                  └────────────┬────────────┘
                               ▼
                  ┌─────────────────────────┐
                  │ 10. Check experts' DoI  │
                  └────────────┬────────────┘
                               ▼
                             ○
                    Continue with step 11
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Proceed from step 10

○

11. Prepare announcement letters

12. Check the documents provided by the applicant/MAH

13.1 Inform CxMP and update Corporate GxP ← Cancellation — 13. Update on adopted inspection? — IO → 13.2 Change in IO target date or other changes? — Scope /site → 13.4 Update inspection request

13.1 Inform CxMP and update Corporate GxP → END

13. Update on adopted inspection? — No (down)

13.2 Change in IO target date or other changes? — IO target date (down) → 13.3 Inform CxMP/update Corporate GxP

13.4 Update inspection request → ○ Continue with step 4

14. Receive IO

15. Valid report? — No → 15.1 Request clarification/amendment according to validation outcome

15. Valid report? — Yes ↓

16. Circulate IO to (co)-rapporteurs, CxMP/PRAC members, concerned inspectors, GCP mailbox and PTL

17. Send IO to applicant MAH/

18. Prepare payment order and inspection memo

19. Sign payment order and provide it to Initiating Agent along with inspection memo

20. Categorise inspection findings and enter data in Corporate GxP

21. Finalise inspection in Corporate GxP

END

9. Procedure

Step	Action	Responsibility
1.	• <u>Pre-authorisation applications</u> (human products only): Identify the need for a CHMP requested inspection in the (co)-rapporteurs Day 80 (D80) AR. Exceptionally need for an inspection can be reflected in D150 JAR. For human medicinal products, the AR is circulated by the PTL to all PTMs in accordance with step 21 of SOP/H/3004. • <u>Post-authorisation applications</u> – Post-authorisation procedures: Identify the need for a CxMP requested inspection as a consequence of data submitted as part of an application, data provided as a result of specific obligations/follow-up measures, variations, line extensions, previous inspections or other information received post authorisation, e.g. in relation to safety updates, PSUR, etc.	P-CI-CNC PTM
2.	Check PhV summary/latest DDPS (as applicable) to identify QPPV, PSMF, location, RI and supervisory authority (if applicable).	P-CI-CNC PTM
	Preparation of the IREQ **Inspection Request's status in Corporate GxP: Draft**	
3.	Prepare draft IREQ after entering information in Corporate GxP using the template available in Corporate DWH <u>http://bi.eudra.org</u>/dashboard/Corporate GxP/GCP and PhV/Templates/PhV templates/Inspection Request.	P-CI-CNC PTM
4.	Circulate draft IREQ to (co)-rapporteurs, PTL and potential Inspectorate/Inspectors for comments within a given deadline.	P-CI-CNC PTM
5.	Are comments received? - If yes, go to step 5.1. - If no, go to step 6.	P-CI-CNC PTM
5.1	Implement the comments on the request and go to step 6.	P-CI-CNC PTM
	Inspection Request's status in Corporate GxP: Requested	
6.	Ask P-CI-CNC assistant to obtain final sign-off from P-CI-CNC SH once the draft IREQ is finalised. Save in DREAM the final version of the IREQ within the MAHs (H/V) core master file documents. Change the status in Corporate GxP from draft to requested.	P-CI-CNC PTM
7.	Table via MMD the final version of the IREQ for adoption at the next CxMP meeting.	P-CI-CNC Assistant
	Adoption of the IREQ **Inspection Request's status in Corporate GxP: Adopted**	P-CI-CNC PTM
8.	Has the IREQ been adopted by the CxMP? - If yes, go to step 9. - If no, end of process. - If the IREQ has been modified, go to step 4.	P-CI-CNC PTM
9.	Confirm inspection team to be involved (RI, LI and if the case, supporting inspector) and third countries contact point for those sites outside the EU. Enter information in Corporate GxP and change status from requested to adopted.	P-CI-CNC PTM

Step	Action	Responsibility
10.	Prepare binders for IREQ original hard copy as described in the WIN/INSP/2025. Check experts' Declaration of Interest in accordance with SOP/EMA/0040. If expert has risk level 2 or 3 proceed as described in section 3.4 of WIN/INSP/2025. ***Note: DoI of Experts with risk level 3 will be reviewed by Scientific Administrator in accordance with SOP/EMA/0040***	P-CI-CNC Assistant
11.	Prepare the announcement letters using templates in accordance with WIN/INS/2025. Update Corporate GxP accordingly and give the letters to the P-CI-CNC PTM for final sign off. Provide also a copy of letter to reporting inspectorate to the Initiating agent according to step 1 of SOP/INSP/2005. Save in DREAM the final version of the announcement letters within the MAHs (H/V) core master file documents. Go back to step 9 if there are changes in the inspection team, as applicable.	P-CI-CNC Assistant
	Initiation of the inspection **Inspection Request's status in Corporate GxP: Initiated**	
12.	Check the documents provided by the applicant/MAH as per announcement letter and confirm dates of inspection. Update Corporate GxP accordingly and change the status from adopted to initiated at the latest the day before the first inspection takes place. If the inspections dates change, update Corporate GxP accordingly and notify payments shared mailbox.	P-CI-CNC PTM
13.	Updates on the inspection request? - In case of cancellation of the inspection, go to step 13.1. - In case of changes in the IO, go to step 13.2. - If NO updates on the inspection request, go to step 14.	P-CI-CNC PTM
13.1	Inform the CxMP, update accordingly Corporate GxP and inform Inspection_Payment@ema.europa.eu. End of process.	P-CI-CNC PTM
13.2	Changes in the IO: - Target date (i.e. postponed for 1 month), go to step 13.3. - Changes on scope and/or site, go to step 13.4.	P-CI-CNC PTM
13.3	Inform the CxMP, update Corporate GxP and continue with step 14.	P-CI-CNC PTM
13.4	Update inspection request and go to step 4. Send the link of the new IREQ to Inspection_Payment@ema.europa.eu only in case of changes in the sites.	P-CI-CNC PTM
	Integrated Overview report **Finalise or amend without status change in Corporate GxP**	
14.	Ensure the IO is sent to EMA by the reporting inspector according to agreed deadline. Any possible delay in providing the IO should be notified by the RI to EMA.	P-CI-CNC PTM
15.	Validate the IO received within 5 days, as outlined in the document INS/PHV/01, against the currenlty used checklist, see under point 5.2. Does validation fail? - If yes, go to step 15.1 - If no, go to step 16.	P-CI-CNC PTM
15.1	Contact the reporting inspector in writing and ask for clarification	P-CI-CNC PTM

Step	Action	Responsibility
	on the failure(s) detected and request amendment of the IO if needed in which case, go back to step 15.	
16.	Circulate the IO to (co)-rapporteurs, CxMP/PRAC members, (human medicinal products only), concerned inspectors, GCP mailbox and PTL. Save in DREAM the final version of the IO within the MAHs (H/V) core master file documents. Ensure the topic is added to the next CxMP/PRAC Agenda.	P-CI-CNC PTM
17.	Send the IO to the applicant/MAH after circulation to the CxMP/PRAC.	P-CI-CNC PTM
18.	Prepare payment order and inspection memo in accordance with the templates listed under point 5.2 and send an e-mail with links of these documents saved in DREAM to Inspection_Payment@ema.europa.eu	P-CI-CNC PTM
19.	Sign off the payment order and provide it to the Initiating Agent along with the inspection memo.	P-CI-CNC PTM
20.	Categorise the inspection findings detected in the IO in accordance with the document EMA/577319/2010 Categorization of PhV findings. Enter the data in Corporate GxP.	P-CI-CNC PTM
	Finalisation of the inspection **Inspection Request's status in Corporate GxP: Finalised**	
21.	Change the inspection status from Initiated to Finalised within one year by the completion of the inspection or at the time of the next PhV inspection, whichever is earlier and only when the complete set of data for the product has been reviewed in Corporate GxP for data quality purpose.	P-CI-CNC PTM

10. Records

All completed forms and other records relating to the operation of this procedure will be collected by the P-CI-CNC PhV co-ordinators and will be stored in DREAM under:

Cabinets/04. Inspections/2. PHV/PHV Inspections/MAHs Human or MAHs Vet.

The document "Core master file - Compliance and Inspection. Table of contents – GxP inspections": EMA/641169/20120 should be followed with regard to core master file documents to be saved in DREAM.

Hard copies will be saved under the appropriate product binder.

Note: Product mailboxes should always be copied for relevant correspondence.