



**PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME**

PI 031-1
Annex
29 July 2009

STANDARD OPERATING PROCEDURE

TEAM INSPECTIONS

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1. DOCUMENT HISTORY

Adoption by Committee of PI 031-1	6 May 2009
Entry into force of PI 031-1	1 September 2009

2. INTRODUCTION

1. At its 24th meeting in Geneva (Switzerland) on 15-16 May 2007, the PIC/S Committee decided to draft a Standard Operating Procedure (SOP) on team inspections to be carried out in non-PIC/S countries. At the 28th meeting of the Committee (Geneva, 5-6 May 2009), it was decided to extend the geographical applicability of this SOP to all inspections carried out in PIC/S countries, when the national legislation does not cover some products (e.g. APIs).

3. PURPOSE

2. The purpose of this SOP is to provide guidance on steps normally necessary to initiate, plan, decide, perform, report upon and follow-up a team inspection (= inspection's process). In the context of this SOP, a team inspection means an inspection carried out by a team of inspectors from different Participating Authorities (PAs).

4. SCOPE

3. This procedure applies to GMP inspections of manufacturers located inside as well as outside of the jurisdictions covered by PIC/S members. The following product categories are covered by this procedure:

- Medicinal products (dosage forms)
- Active pharmaceutical ingredients
- Clinical trial products

5. PREPARATION

a. Planning of inspection

4. The Participating Authority (PA) having identified the need to inspect a manufacturing site fills out the "List of inspections to be carried out by PIC/S inspectors" (PS/W 13/2007).

5. Interested PAs for this specific inspection contact the lead PA (i.e. the PA which entered this inspection into the list PS/W 13/2007) which, then, designates the Lead Inspector who coordinates, with the active collaboration of the other members of the inspection team, the entire inspection process (i.e. from the planning to the evaluation of the corrective measures. A follow-up inspection would trigger a new inspection process).

b. Inspection Team

i. Composition of the team

6. Generally two to three inspectors (incl. Lead Inspector) will be involved per inspection. The composition of the team should be determined based on skills, experience in the type of inspection required, overall travel costs, etc.

ii. Mandate of the Inspection Team

7. The mandate of the Inspection Team is as follows:

- to conduct a GMP inspection;
- to agree on the inspection's scope;
- to discuss and resolve, where possible, any major problems which may occur during the inspection process;
- to ensure that all inspectors play an active role in the inspection process;
- to make decisions on inspection findings by way of consensus; however, where this is not possible, the Lead Inspector makes the final decision;
- to prepare an inspection report;
- to conduct any follow-up measures;
- to rate the inspected site in relation to GMP principles.

iii. Mandate of the Lead Inspector

8. The Lead Inspector is responsible to organize (except logistics, see section 6.a), coordinate, lead during all stages of the inspection and act as spokesperson.

iv. Working language

9. English is the working language. Where translation is necessary, the company to be inspected should be requested to cover interpretation and translation fees.

c. Announcement of the inspection

10. The Lead Inspector should:

- Agree within the team for an inspection period;
- Agree within the team for fees to be invoiced to the company to be inspected (see section 6.b);
- Contact the company three to six weeks in advance in order to propose the inspection dates and to inform it about the fees;
- Once the company is in agreement, send a letter of confirmation;
- Request the company to provide a current site master file (English version) in electronic format. If not available electronically, ask one paper copy per inspector;
- Send a copy of the letter of confirmation to the local regulatory authority, for information. Local authority is welcomed as observer;
- Send the inspection plan to the company at the latest during the week preceding the inspection;

d. Inspection plan

11. The duration of a product (or product class) specific inspection will normally be three to five days for two inspectors. Ensure that the inspection plan is risk-based and covers all critical activities. Key elements in the plan may include:

- the scope and objectives of the inspection;
- when applicable, list of marketing authorisations (incl. applications) or of products registered in countries participating in the joint inspection
- any available post market surveillance information;
- names of the Inspection Team members and their respective roles;
- the time, date and place for the opening meeting;
- the organizational units to be inspected, taking into consideration if the company has multiple sites;
- the expected time and duration for each major inspection activity;
- a schedule of meetings, including a daily briefing to be held with company management;
- a tentative list of documents for review (as attachment to the plan);
- a tentative time, date and place for the final meeting.

12. Be flexible with the inspection plan so as to accommodate any changes needed to meet the site-specific demands or situations encountered or discovered. Notify the

company of any changes to the plan. Document the reasons for not meeting any of the inspection objectives.

6. TRAVEL LOGISTICS, FEES

a. Travel

- International and domestic flights to be booked by each inspector, for domestic flights with the help of the company to be visited, if necessary;
- Hotel proposed by company to be inspected and to be booked either by each inspector or by the company;
- Pickup from hotel to manufacturing site by company to be inspected;
- In case of inspection campaign: transfer from site (hotel) to site (hotel) to be organized in collaboration with involved sites.

b. Fees

13. Travel costs and inspection fees are to be invoiced to the company to be inspected by each inspector according to his/her own agency's rules. It is recommended to invoice before performing the inspection (prepayment).

7. INSPECTION

c. Pre-inspection meeting

14. A face-to-face meeting at the location (hotel) or a teleconference in advance may be organised between the inspectors.

d. Opening meeting

15. Upon arrival at the company, arrange an opening meeting with the company's management and key personnel. The purpose of this meeting is to:

- introduce the members of the Inspection Team;
- outline the purpose, type and scope of the inspection;
- discuss the proposed schedule and make the necessary arrangements;
- review the company's organizational structure;
- discuss any previous inspections, and what corrective and preventative measures were implemented. Discuss any significant changes in facilities, equipment, products and personnel since the last inspection, if applicable;
- give the company the opportunity to present a short (max. 20 minutes) overview of the quality management system and to discuss their current and proposed activities;

16. A record should be made of the main persons met during the inspection (incl. those attending the opening and final meetings).

e. Inspection of plant facilities: scope and procedure

17. Conduct a plant tour. Assess whether the facilities and equipment are of suitable layout and design, if they are maintained properly and if they are suited for the intended operations.
18. Examine the manufacturing process of relevant dosage forms or APIs respectively. Determine the most critical steps in terms of the success of the overall process. Assess how these steps are controlled, monitored and recorded, taking into account the detailed guidelines of GMP.
19. Focus on higher-risk activities, known problems and deviations (incl. list of complaints of the last two years) from standard practices, examine PQR (product quality review) of the last two years.
20. Confirm that the company is effectively implementing its current procedures.
21. Interview all levels of personnel, as deemed necessary. Likewise, request any pertinent documents, e.g. procedures, records, raw data and personnel training records.
22. Confirm the accuracy of the observed deficiencies with the immediate supervisory personnel. Keep management informed of the deficiencies (e.g. wrap up meeting at the end of each day).
23. Depending on the size of the site, the time at disposal, the availability of translators, etc. (partial) splitting of the inspection team may be considered.

f. Critical deficiencies

24. If a critical deficiency is found during the course of the inspection, notify the company's management and request immediate corrective and preventative measures. Investigate which products (name, batch number, customers, dates of supply, etc.) may be affected by the critical deficiency.
25. Notify observed critical deficiencies by using the form "Exchange of information in case of serious GMP non-compliance" (see Annex) which should be sent to the PIC/S Secretariat (info@picscheme.org). The latter will dispatch it immediately to all PIC/S PAs and Partners. Such notification should be done as soon as possible.

g. Review of documentation

26. Assess the company's overall documentation management system, including its change control practices. Evaluate the batch release procedure and the role of the person who is responsible for this duty.
27. Following list of documents which may be reviewed (not exhaustive):
 - master formula and processing instructions;
 - specifications for starting materials, primary packaging materials intermediate, bulk products and finished products;
 - batch manufacturing records;
 - complaints;
 - incident reports;

- relevant standard operating procedures and records, e.g., recall procedure;
- relevant contracts;
- job descriptions and training records;
- validation information;
- laboratory books;
- stability data (incl. on going stability);
- self-inspection program. Self inspection reports are usually not reviewed (only check if they are available).

h. List of deficiencies

28. The team should meet regularly throughout the inspection and prior to the final meeting to discuss the findings and any inspection issues. The list of deficiencies will be presented to the company at the final meeting. Each deficiency should be categorised according to the PIC/S Inspection Report Format and state the inspection rating.

i. Inspection rating

29. Assign the overall inspection rating. There are two possible ratings, conforming (C) or non-conforming (NC) with PIC/S GMP principles. The rating is related to the risk classification of each deficiency. A NC rating may be assigned where a deficiency is rated as critical or where several deficiencies are rated as major. The rating should be assigned at the closing meeting.

j. Final (closing) meeting

30. At the end of the inspection, hold a meeting with the company's management to discuss the outcome of the inspection.

31. Provide the list of deficiencies to the company. Inform them that the Lead Inspector will send the final inspection report within 1 month and that a written response will be requested within the following 1 month.

32. Present a summary of both the positive findings and the GMP deficiencies. The company may wish to further clarify some of the deficiencies. It is important to ensure that all of the deficiencies are accurate and are not subject to misinterpretation.

33. All points of contention should be discussed during this meeting. If the company doesn't accept a deficiency or the inspection rating, inform them that an appeal can be made, by writing to the lead PA.

8. REPORT

34. Each inspector signs the report (based on PIC/S Inspection Report Format) written on the letterhead of the inspectorate of the Lead Inspector. The inspectorate of the Lead Inspector will be the owner of the report.

35. Each deficiency listed in the report should be:

- clear, concise, accurate, factual, objective, complete, not subject to misinterpretation;

- written in the past tense;
- classified according to the PIC/S Inspection Report Format (PI 013);
- referenced to a specific section of the PIC/S GMP Guide (PE 009);
- cover only one issue per observation. Multiple deficiencies dealing with the same issue should be combined.

36. Deficiencies that have been corrected during the inspection should be included in the inspection report with a statement that it has been corrected.

37. The Lead Inspector sends the final report (together with a cover letter giving the timeframe for the plan for corrective measures) to inspected company within 1 month of the final meeting with copy to the team inspectors.

38. The timeframe for corrective measures may be dependent on the risk category of the deficiencies and the inspection rating. Generally, the company is given 1 month to respond to the inspection report.

9. GMP CERTIFICATE

39. Any GMP certificate may be issued by PAs of directly involved inspectors on their own letterhead. No GMP certificate will be issued by the PIC/S Secretariat.

10. FOLLOW-UP

40. The company sends its response letter (including plan for corrective measures) to the Lead Inspector. The latter sends it to the Inspector team for review. If the company fails to respond to the inspection report, the Lead Inspector sends a reminder letter to the company.

41. Within 1 month, the Lead Inspector prepares a response letter. This letter should:

- acknowledge receipt of the company's plan for corrective measures;
- state the dates of the inspection and the address of the site inspected;
- provide an assessment of their corrective measures: this assessment may be carried out in collaboration with the other participating inspectors;
- include a statement of appreciation for co-operation with the Inspection Team;
- request for further correspondence, if needed.

42. Deficiencies may be considered as resolved if the company's response letter:

- states that corrective and preventative measures have been implemented;
- includes supporting documentation;
- if necessary, includes a written commitment, providing a clear and reasonable schedule for implementation of corrective and preventative measures.

43. If the corrective and preventative measures taken by the company are not considered being acceptable, further correspondence between the inspection team and the company may be necessary.

44. In case of NC rating of the inspected site the need for a follow-up inspection to ensure that corrective measures have been implemented should be discussed within the inspectors' team. Such follow-up inspection would represent a new inspection's process to be dealt according this procedure.

11. FLOW OF DOCUMENTS

45. All communications and exchange of documents (e.g. SMF, inspection plan, inspection report, corrective measures, etc.) should be made directly between the company and the Inspection Team.

a. Distribution of the inspection report

46. The report will be available for PIC/S PAs upon request at the Lead Inspector's inspectorate.

b. Archiving of inspection information

47. The Lead Inspector will retain all inspection information, including inspection reports and any further correspondence. Inspectors will retain their inspection notes. The information will be kept in a manner which ensures the integrity, confidentiality and traceability and shall meet the requirements of PIC/S.

48. At the end of the team inspection process, the Lead Inspector should provide the following information to the PIC/S Secretariat (for statistical purposes):

- composition of the inspection team (names and PAs represented);
- name and address of the company inspected;
- exact dates of the team inspection;
- conclusions of the team inspection.

12. REFERENCE DOCUMENTS

- PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PE 009);
- PIC/S Quality System Requirements for Pharmaceutical Inspectorates (PI 002);
- PIC/S Inspection Report Format (PI 013);
- PIC/S Explanatory Notes for Industry on the Preparation of a Site Master File (PE 008).

13. ANNEX

Annex: Form for Exchange of information in case of serious GMP non-compliance

14. REVISION HISTORY

Date	Version Number	Reasons for revision

Exchange of information in case of serious GMP non-compliance

1. Details of Manufacturing Site/ Products		
Inspected site(s):		
Activities carried out	<i>Manufacture of active substances</i>	<input type="checkbox"/>
	<i>Manufacture of bulk/ intermediates</i>	<input type="checkbox"/>
	<i>Manufacture of finished medicinal products (dosage forms)</i>	<input type="checkbox"/>
	Investigational medicinal products	<input type="checkbox"/>
	Packaging	<input type="checkbox"/>
	<i>Laboratory Testing</i>	<input type="checkbox"/>
2. Details of Inspection		
Inspection date(s)		
	<i>First inspection</i>	<input type="checkbox"/>
	<i>Follow-up inspection</i>	<input type="checkbox"/>
Date and brief description of the previous inspection, if any		
Scope of the inspection	<i>Product related inspection</i>	<input type="checkbox"/>
	<i>General GMP inspection</i>	<input type="checkbox"/>
	<i>Other (please explain):</i>	<input type="checkbox"/>
Dosage form (s)		
Name/ Type of product(s)	<input type="checkbox"/> <i>human use</i>	
	<input type="checkbox"/> <i>veterinary use</i>	
Reference number(s), if any		
Marketing Authorisation (Product Licence) Holder (MAH)		

Inspected area(s): (Were several production units are in place)	<i>Unit Nr:</i> <i>Unit Nr:</i> <i>Unit Nr:</i> <i>Laboratory</i> <input type="checkbox"/> : <i>Comments:</i>	
List of deficiencies and observations (critical only)		
Proposed corrective action by company where available (for critical deficiencies only)		
Inspectors evaluation of the manufacturer's action plan and response to the inspection findings (critical only)		
Planned follow-up inspection	<input type="checkbox"/> <i>no</i>	
	<input type="checkbox"/> <i>yes, in</i> <i>(Month, year)</i>	<i>Type:</i> <input type="checkbox"/> <i>routine</i> <input type="checkbox"/> <i>follow-up</i>
Action taken/ proposed by inspectors		
Additional comments : 		
Name of Lead inspector's authority		
Phone Number Fax Number E-Mail		
Name of lead inspector (not mandatory)		
Signature of authorised person at responsible authority		
Date		
