# Annex 4

## Guidance on good manufacturing practices: inspection report

### Background

The need for revision of the *Guidance on good manufacturing practices: inspection report* (World Health Organization (WHO) Technical Report Series, No. 908, Annex 6, 2003) was brought to the attention of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The intent of this update is to bring it in line with the current format used by the Prequalification Team (PQT) for its inspections and the formats currently used internationally in national and regional inspectorates. In addition, the concepts of risk management, as, for example, included in the *WHO guidelines on quality risk management* (WHO Technical Report Series, No. 986, Annex 6, 2014), have been taken into consideration.

# 1. Introduction

1.1 This guidance describes general principles and a recommended format for inspection reports for use by organizations performing pharmaceutical inspections. It aims to support convergence of practices in drawing up inspection reports so as to facilitate cooperation and information sharing.

# 2. Scope

2.1 These guidelines apply to reports on inspections of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs). A separate template may be used for inspections of contract research organizations and quality control laboratories.

# 3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

**correction.** A correction is any action that is taken to eliminate a nonconformity. However, corrections do not address causes. When applied to products, corrections can include reworking products, reprocessing them, regrading them, assigning them to a different use, or simply destroying them.

**corrective action.** Corrective actions are steps that are taken to eliminate the causes of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again. While corrective actions prevent recurrence, *preventive actions* prevent occurrence. Both types of actions are intended to prevent nonconformities.

**corrective and preventive action.** A system for implementing corrective actions and preventive actions resulting from an investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring.

**deficiency.** Non-fulfilment of a requirement. In this sense this term can be used interchangeably with "nonconformity".

**inspection observation.** An inspection observation is a finding or a statement of fact made during an inspection and substantiated by objective evidence. Such findings may be positive or negative. Positive observations should take the form of a description of the processes that the firm is carrying out particularly well and that may be considered examples of particularly good practice. Negative observations are findings of non-compliance with requirements.

**nonconformity.** Nonconformity refers to a failure to comply with requirements. A requirement is a need, expectation or obligation. It can be stated or implied by an organization, its customers or other interested parties. There are many types of requirements. These include quality requirements, customer requirements, management requirements, product requirements, process requirements and legal requirements. Whenever an organization fails to meet one of these requirements, a nonconformity occurs.

**preventive action.** Preventive actions are steps that are taken to remove the causes of potential nonconformities or potential situations that are undesirable.

## 4. General principles

4.1 When a site at which pharmaceutical products are manufactured is inspected, the inspector(s) responsible should draw up a report. The inspection report should include the items shown in the proposed model inspection report (Appendix 1), adapted as appropriate, according to the national or regional settings and to the scope and purpose of the inspection. Where relevant the appropriate system of good manufacturing practices (GMP) or the nationally appropriate legal basis for GMP, should be indicated.

4.2 The purpose of an inspection report is to provide a factual and objective record of the inspection that includes what was done, the inspection observations or findings (positive and negative) for each activity inspected, as communicated to the company before the end of the inspection, and a conclusion that is applicable at the time that the report is written. Positive findings may include praise for noteworthy efforts in areas that are seen as excellent examples of implementation of the requirements of the guidelines. They could also be conveyed when the company has shown significant improvement in certain areas compared to the findings from previous inspections. Noteworthy efforts do not require any action. Their inclusion in the inspection report is done to highlight areas of strength for future tracking of improvements or areas of decline and to show the organization what areas it can feel proud of.

4.3 The report should be prepared in a timely manner after an inspection, with the participation of all members of the inspection team under the coordination of the lead inspector. The report should be reviewed in accordance with the quality system of the inspectorate.

4.4 The inspection report should, as appropriate, be written in the third person, passive voice and the past tense.

*Example*: "Cleaning logs for rooms and equipment *were maintained* in all areas of the factory."

4.5 All the observations that are considered as deficiencies/noncompliances should be listed under Part 3 of the report. Each observation included in an inspection report should be referenced to the relevant GMP text, WHO guidelines or conditions or commitments under the marketing authorization. An observation that cannot be reasonably referenced should not be listed as a deficiency.

4.6 The non-compliance statement should include the requirement (R), evidence (E) and deficiency (D).

*Example*: (R) The relevant cleaning records and source data should be kept in cleaning validation reports; (E) the source of three samples taken for recovery testing during the process equipment validation was not traceable; (D) cleaning validation reports did not include sufficient data.

4.7 Deficiencies/noncompliance statements should distinguish whether the defect lies in the system itself or in a failure to comply with the system. For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures (SOPs) are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

4.8 Where more than one deficiency relates to the same basic quality system failure, the deficiencies should be grouped and listed as a single observation, under a heading that reflects the basic system failure.

4.9 Deficiencies should be reported with a focus on risk to patient health and/or need for corrective and preventive action (CAPA).

4.10 The report should not include comments that could be construed as proposed specific solutions to issues raised. Recommendations should relate to recommended regulatory action as appropriate.

4.11 Each deficiency should be classified as critical, major or other, according to the following definitions, which may be adapted according to the national or regional legal context.

4.11.1 A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

4.11.2 A *major* deficiency may be defined as a non-critical observation that:

a) has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
b) indicates a major deviation from the GMP guide;
c) indicates a failure to carry out satisfactory procedures for release of batches;
d) indicates a failure of the person responsible for quality assurance/ quality control to fulfil his or her duties;
e) consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

4.11.3 A deficiency may be classified as *other* if it cannot be classified as either *critical* or *major*, but indicates a departure from GMP. A deficiency may be *other* either because it is judged as minor or because there is insufficient information to classify it as *major* or *critical*.

4.11.4 Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of an *other* deficiency may be categorized as *major*.

4.11.5 A deficiency that was reported at a previous inspection and was not corrected may be reported with a higher classification.

4.11.6 One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer during the inspection.

4.11.7 The status of compliance with WHO GMP guidelines should be determined by the nature and number of deficiencies:

a) When there are *other* deficiencies only:

i. the site is considered to be operating at an acceptable level of GMP compliance,
ii. the manufacturer is expected to provide CAPAs,
iii. CAPAs are evaluated and followed up during the next routine inspection.

b) When there are *other* and a few *major* deficiencies (e.g. < 6[1]):

   i. the site is compliant with GMP after assessing the CAPAs,
   ii. CAPAs for *all* deficiencies to include actions implemented and/or planned, timelines and documented evidence of completion, as appropriate,
   iii. CAPAs are evaluated on paper and may or may not include an on-site, follow-up inspection.

c) When there are *critical* or several *major* deficiencies (e.g. ≥ 6):

   i. the site is considered to be operating at an unacceptable level of compliance with GMP guidelines,
   ii. another inspection will normally be required,
   iii. administrative and/or legal enforcement actions are applied as necessary.

4.12 The next date for inspection of the site should be determined depending on the level of compliance and risk category as defined under national or regional procedures. Appendix 2 provides an example of how the next inspection date may be determined. Other approaches may be used.

4.13 The report shall be signed by all inspection team members, but may be signed by the lead inspector after consultation with and on behalf of the inspection team, and reviewed in accordance with the quality system of the inspectorate.



[1] The number six is related to the six systems to be inspected, as listed in Appendix 1.

# Appendix 1

## Guidance on good manufacturing practices: inspection report

### Model inspection report

| Part 1 | General information |
|---|---|
| **Manufacturer details** | |
| Company information | Name of manufacturer<br>Corporate address of manufacturer (including telephone, fax, email and 24-hour telephone numbers)<br>Contact person, telephone number and email address |
| Inspected site | Address of inspected manufacturing site if different from that given above (including global positioning system (GPS) coordinates<br>in World Geodetic System (WGS) 84: latitude and longitude expressed in decimal degrees, taken at the main entrance of the site; data universal numbering system (D-U-N-S) number: NNNNNNNNN, where each N represents a number from 0–9, if available) and specific production blocks or workshops inspected if the whole site was not inspected<br>Site number (e.g. unit number, site master file number or number allocated by the responsible authority)<br>Manufacturing licence number (if applicable)<br>Key personnel |
| Summary of activities performed at the site | For example, manufacture of active pharmaceutical ingredient(s) (APIs), manufacture of finished pharmaceutical products (FPPs), intermediates or bulk packaging, laboratory testing, batch release, distribution and importer activities |
| **Inspection details** | |
| Date(s) of inspection(s) | … |
| Type of inspection | For example, initial, routine, follow-up, special |
| Inspector(s) | Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers |

Table *continued*

| Part 1 | General information |
|---|---|
| Competent regulatory authority | For foreign inspections, state whether the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection |
| GMP guidelines used for assessing compliance | List the relevant guidelines stating the title of the guidelines, the title of the publication and web address where the guidelines can be accessed, for example:<br>1. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf?ua=1) |
| **Introduction** | |
| Brief summary of the manufacturing activities | Description of main activities (including, e.g. FPP(s) or API(s) manufactured and their reference/registration/active pharmaceutical ingredient master file (APIMF)/drug master file (DMF)/certificate of suitability to the monographs of the European Pharmacopoeia (CEP) numbers, as appropriate); other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development); use of outside scientific, analytical or other technical assistance in manufacture and quality control<br>Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available |
| History | Previous inspection date and history of regulatory agency inspections<br>Summary of past inspections; observations on CAPA from previous inspection<br>Major change since previous inspection and planned future changes<br>GMP-related recalls from the market of any product in the past two years |

Table *continued*

| **Part 1** | **General information** |
|---|---|
| **Brief report of inspection activities undertaken** | |
| Scope and limitations | For example, blocks inspected, areas of interest, focus of inspection<br>Out-of-scope: areas, activities or product lines not inspected<br>Restrictions: constraints noted in inspecting specific areas |
| Areas inspected | For example, dosage form(s) included in the inspection |
| Key persons met | Names and job titles |

| **Part 2** | **Brief summary of the findings and recommendations (where applicable)** |
|---|---|
| | This part of the report is arranged based on the WHO Guidance for good manufacturing practices: main principles. It may also be arranged according to six inspection systems, namely:<br>1. pharmaceutical quality system,<br>2. production system,<br>3. facilities and equipment system,<br>4. laboratory control system,<br>5. materials system,<br>6. packaging and labelling system.The observations made during the inspection that are considered to be non-compliant with GMP should be listed. Where positive observations are included in the report, a clear distinction should be made between positive and non-compliant.<br>Non-compliant observations can be classified, e.g. as *critical*, *major* and *other* if the Member State concerned has defined these terms<br>The date by which corrective action and completion are requested in accordance with the policy of the NRA should be given. |
| 1. Pharmaceutical quality system | Describe the pharmaceutical quality system (PQS) in place and how well the elements are institutionalized and implemented, including the quality risk management (QRM) and product quality review (PQR) |

Table *continued*

| Part 2 | Brief summary of the findings and recommendations (where applicable) |
|---|---|
| 2. Good manufacturing practices for pharmaceutical products | Briefly describe how the elements of GMP are implemented |
| 3. Sanitation and hygiene | Describe procedures and records relating to sanitation and hygiene for personnel, premises, equipment, production materials, cleaning materials and others that could become a source of contamination |
| 4. Qualification and validation | Describe policies, procedures, records and any other evidence for qualification and validation and how the validation status is monitored and maintained |
| 5. Complaints | Describe procedures, responsibilities and records for handling complaints, including extension of investigation to other batches, possibility of counterfeits, trending and consideration for recall and notification of competent authorities |
| 6. Product recalls | Describe the existence of a recall procedure and evidence of its effectiveness; provisions for notification of customers and competent authorities and segregation of recalled products |
| 7. Contract production, analysis and other activities | Describe how contractors are evaluated, how compliance with marketing authorization is ensured, existence of comprehensive contracts and clarity of responsibilities and limits |
| 8. Self-inspection, quality audits and suppliers' audits and approval | a) Self-inspection:<br>describe the procedures and items for self-inspection and quality audits; constitution of self-inspection team(s); frequency of self-inspection; existence of self-inspection schedules and report; system for monitoring follow-up actions.<br>b) Suppliers' audits and approval:<br>describe procedures for evaluation and approval of suppliers including applications of risk management principles, especially determining the need and frequency for on-site audits. |

Table *continued*

| Part 2 | Brief summary of the findings and recommendations (where applicable) |
|---|---|
| 9. Personnel | Describe availability of adequate numbers of sufficiently qualified and experienced personnel, clarity of their responsibilities, limits and reporting hierarchy. Qualifications, experience and responsibilities of key personnel (head of production, head(s) of the quality unit(s), authorized person) and procedures for delegation of their responsibilities |
| 10. Training | Describe comprehensiveness of procedures and records for induction, specialized and continuing training and evaluation of its effectiveness; coverage of GMP and concepts of quality assurance during training; training of visitors and evaluation consultants and contract staff |
| 11. Personal hygiene | Describe system in place for initial and regular health examination of staff appropriate to their responsibilities. Measures and facilities to impart, maintain and monitor knowledge of a high level of personal hygiene. Measures to ensure personnel do not become a source of contamination to the product, including hand-washing and gowning. Appropriate restriction of smoking, eating, drinking, chewing and related materials from production, laboratory and storage areas |
| 12. Premises | Description of the appropriateness of the location, design, construction and maintenance of premises to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; measures for dust control; specific measures for ancillary areas, storage areas, weighing areas, production areas and quality control areas; measures for appropriate segregation and restricted access; provisions for appropriate lighting, effective ventilation and air-control to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity |
| 13. Equipment | Describe the adequacy of the numbers, type, location, design and construction, and maintenance of equipment to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; use, cleaning and maintenance procedures, records and logs; calibration of balances and other measuring instruments; status labelling |

Table *continued*

| Part 2 | Brief summary of the findings and recommendations (where applicable) |
|---|---|
| 14. Materials | Describe measures in place to select, store, approve and use materials (including water) of appropriate quality and how these measures cover starting materials, packaging materials, intermediate and bulk products, finished products, reagents, culture media and reference standards. Describe also the measures for the handling and control of rejected, recovered, reprocessed and reworked materials; recalled products; returned goods; and waste materials |
| 15. Documentation | Describe the comprehensiveness and adequacy of the documentation system in place (labels; specifications and testing procedures, starting, packaging materials, intermediate, bulk products and finished products; master formulas; packaging instructions; batch processing and packaging records; standard operating procedures (SOPs) and records) and how principles of good documentation and data management (attributable, legible, contemporaneous, original, accurate (ALCOA)) are institutionalized, implemented and maintained |
| 16. Good practices in production | Describe procedures, facilities and controls in place for production (processing and packaging); prevention of risk of mix-up, cross-contamination and bacterial contamination during production |
| 17. Good practices in quality control | Describe the extent of the organizational and functional independence of the quality control function and the adequacy of its resourcing.<br>Describe the procedures, facilities, organization and documentation in place which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the requirements.<br>Describe the procedures for the control of starting materials and intermediate, bulk and finished products; test requirements; procedures and responsibilities for batch record review; procedures, records and facilities for initial and ongoing stability studies; policy, procedures, facilities and records for retention samples. |

Table *continued*

| **Part 2** | **Brief summary of the findings and recommendations (where applicable)** |
|---|---|
| Samples taken | (if applicable) |
| Assessment of the site master file | (if applicable) |
| Annexes attached | … |

| **Part 3** | **List of deficiencies** | |
|---|---|---|
| **List of deficiencies** | Deficiencies should be listed by category with reference to the relevant section(s) of GMP guidelines. This may be presented in a tabular format, giving references to the relevant GMP requirement: | |
| | Deficiencies | References |
| 1. Critical | 1.1 …<br>1.2 … | …<br>… |
| 2. Major | 2.1 …<br>2.2 … | …<br>… |
| 3. Other | 3.1 …<br>3.2 … | …<br>… |

| **Part 4** | **Outcome** |
|---|---|
| Initial conclusion | Statement regarding the GMP status, including information on any restrictions in scope.<br>The following guidance may be used to determine the outcome of the inspection based on the nature and number of deficiencies observed:<br>• *other* deficiencies only: operating at an acceptable level of compliance with GMP guidelines;<br>• *other* and a few (e.g. < 6) *major* deficiencies: decision on level of compliance to be made after receipt and evaluation of CAPAs;<br>• *any critical* or several (e.g. ≥ 6) *major* deficiencies: operating at an unacceptable level of compliance with GMP guidelines. |

| Part 5 | List of GMP guidelines referenced in the inspection |
|---|---|
| References | List of GMP guidelines referred to in the inspection, for example: |

1. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; http://www.who.int/medicines/publications/pharmprep/en/index.html)
2. WHO good manufacturing practices for sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 6 (WHO Technical Report Series, No. 961; http://www.who.int/medicines/publications/pharmprep/en/index.html)
3. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 3 (WHO Technical Report Series, No. 957; http://www.who.int/medicines/publications/pharmprep/en/index.html)
4. WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; http://www.who.int/medicines/publications/pharmprep/en/index.html)
5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 5 (WHO Technical Report Series, No. 961; http://www.who.int/medicines/publications/pharmprep/en/index.html)
6. General guidelines for the establishment maintenance and distribution of chemical reference substances. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-first report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 937; http://www.who.int/medicines/publications/pharmprep/en/index.html)

| Part 6 | Assessment of company response, final conclusion, risk rating and next due date |
|---|---|
| Brief narrative on the adequacy of the company's response to issues to be addressed | … |
| Final conclusion | Final statement of GMP compliance, including information on any restrictions in scope |
| Risk rating following the inspection | For example, low (L), medium (M), high (H), critical (C) |
| Date next inspection due (for planning purposes) | The inspectorate may decide to include this information for internal use only |
| Name(s) (all inspectors or lead inspector) | |
| Signature(s) (all inspectors or lead inspector) | |
| Date | |

# Appendix 2

## Example of a risk category assessment of the site depending on level of compliance and inspection frequency

| Risk category of the site | GMP compliance rating and related inspection frequency (in months) | | | |
|---|---|---|---|---|
| | Acceptable | | | Unacceptable |
| | Good | Satisfactory | Basic | |
| **Critical (C)** | 24 | 18 | 12 | Determine on a case-by-case basis |
| **High (H)** | 30 | 20 | 15 | Determine on a case-by-case basis |
| **Medium (M)** | 36 | 24 | 18 | Determine on a case-by-case basis |
| **Low (L)** | 48 | 36 | 24 | Determine on a case-by-case basis |