GUIDANCE ON GOOD MANUFACTURING PRACTICES:

INSPECTION REPORT

(AUGUST 2015)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr S. Kopp, Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms (kopps@who.int) with a copy to Ms Marie Gaspard (gaspardm@who.int) by 1 October 2015.

Medicines Quality Assurance working documents will be sent out electronically only and will also be placed on the Medicines website for comment under “Current projects”. If you do not already receive our draft working documents please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.
<table>
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<tr>
<th>Draft proposal presented to and discussed at the informal consultation on inspection, GMP and risk management guidance in medicines’ manufacturing</th>
<th>28–30 April 2014</th>
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<td>Presentation of meeting recommendations to the fortieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>13–17 October 2014</td>
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<td>Preparation of draft proposal for revision by Mr D. Mubangizi, Head of the WHO Prequalification Team-Inspections, based on the current trends; formats used for convergence purposes of the format</td>
<td>October 2014–April 2015</td>
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<td>Document sent out for comments</td>
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<td>Submission to fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
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BACKGROUND

During an informal consultation held in 2014 discussion took place regarding the possible revision of the *Guidance on good manufacturing practices: Inspection report* (World Health Organization (WHO) (Technical Report Series, No. 908, Annex 6, 2003) to bring it in line with the current format used with the Inspection Group of the Prequalification Team (PQT) and the formats currently used internationally in national and regional inspectorates.

The need for revision was brought to the attention of the WHO Expert Committee on Specifications for Pharmaceutical Preparations by the PQT inspectors. It agreed that, in light of the new developments, a draft for revision be prepared.

This proposed update was drafted over the past months reviewing the various formats and considering efforts of inspectorates and regulatory agencies, as well as the Pharmaceutical Inspection Co-operation Scheme (PIC/S) towards convergence.
GUIDANCE ON GOOD MANUFACTURING PRACTICES: INSPECTION REPORT

1. INTRODUCTION

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

This guideline applies to reports on inspections of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs). A separate template is provided for inspections of contract research organizations (CROs) and quality control laboratories.

3. GLOSSARY

- 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, regarding 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 correction actions and preventive actions resulting from an investigation of complaints, product rejections, nonconformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring.

- deficiency. Non-fulfilment of a requirement. This sense it 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 regulated practice. Negative observations are 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. Some of these include quality requirements, customer requirements, management requirements, product requirements, and legal requirements. Whenever an organization fails to meet one of these requirements, a nonconformity occurs.

**observations.** The term “observations” is often limited to areas pointed out by the inspector as being in compliance but very close to becoming a nonconformance or that given additional evidence could transform into a nonconformance. In this sense, observations can be looked as “accidents waiting to happen”.

**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/regional settings and to the inspection scope and purpose. Where relevant the appropriate system of good manufacturing practices (GMP) or the national 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 findings (positive and negative) for each activity inspected, as shared with the company before the end of the inspection, and a conclusion that is applicable to the time that the report is written. Positive findings may include praises or noteworthy efforts in areas that are seen as excellent examples of implementation of the requirements of the guideline. Noteworthy efforts are also given when the practices are seen as best in class. They could also be issued when the company has shown significant improvement in certain areas from prior inspections. Noteworthy efforts do not require any action. When provided in the inspection report it is done for reporting purposes only and to show to the organization areas where they 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 style and in 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 5 of the report. Each observation included in an inspection report should be
referred to the relevant legal 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 between 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 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, they 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 preventative action (CAPA).

4.10 The report should not include comments that could be construed as proposed specific solutions to issues observed. 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/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 which does not comply with its prequalification application (including variations); and/or
b) indicates a major deviation from the GMP guide; and/or
c) indicates a failure to carry out satisfactory procedures for release of batches; and/or
d) indicates a failure of the person responsible for quality assurance /quality control to fulfil his/her duties; and/or
e) consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.

4.11.3 A deficiency may be classified as other if the deficiency 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 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 not corrected may be reported in 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):
   i. compliance of the site with GMP is made after the CAPAs have been assessed,
   ii. CAPAs for major deficiencies to include documented evidence of completion,
   iii. CAPAs paper evaluated and may or may not include an on-site follow up inspection;

b) 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.

4.12 The next due date for inspection of the site should be assigned depending on level of compliance and risk category as defined under national/regional procedures. The following is an example of how the next due date may be determined.

1 The number six is related to the six systems to be inspected, as listed in Appendix 1.
| RISK CATEGORY: | Acceptable | | | Unacceptable |
|---------------|------------|------------|-------------|
|               | Good       | Satisfactory | Basic       | Determine on a case-by-case basis |
| 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 |

4.13 The report shall 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.