SADC MRH PROJECT

SADC GUIDELINE FOR GOOD MANUFACTURING PRACTICE (GMP) INSPECTIONS

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ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
APQR	Annual Product Quality Review
cGMP	current Good Manufacturing Practices
HVAC	Heating Ventilation and Air Conditioning
ICH	International Conference on Harmonisation
MRH	Medicines Regulatory Harmonisation
QA	Quality Assurance
QC	Quality Control
RA	Risk Assessment
SADC	Southern African Development Community
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
TRS	Technical Report Series
WFI	Water for Injection
WHO	World Health Organisation

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FOREWORD

This is the first edition of the SADC GMP guidelines. Generally, SADC subscribes to the WHO current Good Manufacturing Practice (cGMP) guidelines for inspections for pharmaceutical products. The guidelines were developed and formatted based on the WHO requirements. The supplementary guidance documents address issues not explicitly covered in aforementioned WHO GMP guidelines and serves to clarify the SADC expectations.

INTRODUCTION

This document has been prepared to serve as a guidance document on the requirements for current Good Manufacturing Practice (cGMP) applicable to the manufacturing of pharmaceutical products. Pharmaceutical products should be manufactured by GMP approved manufacturers, whose activities are regularly inspected by regulatory authorities. This guideline shall be used as a standard to attain cGMP compliance as required by the SADC member states. The guide is applicable to operations for the manufacture of pharmaceutical products in their finished dosage forms.

SCOPE

The guidelines apply to the SADC member states during the SADC MRH GMP inspections program.

The guidance has been drafted to support the registration and marketing of pharmaceutical products in SADC member states.

It does not create or confer any rights for or on any person and does not operate to bind the SADC medicine regulatory authorities or the public. The guidance has been drafted to support the legal framework set out in the national legislation in member states.

GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts *(adopted from the WHO TRS986 Annex 2).*

Active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

airlock. An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

authorized person. The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

batch (or lot). A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch records. All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product. Any product that has completed all processing stages up to, but not including, final packaging.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Certification: The final review and formal approval of a validation or revalidation, followed by approval of a process for routine use.

clean area. An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

contamination. The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material, intermediate or finished product during production, sampling, packaging or repackaging, storage or transport.

cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

critical operation. An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Certificate of analysis (COA). Specification of analytical product tested to confirm the quality of product

finished product. A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in-process control. Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Joint inspection A joint inspection is a procedure in which the same site is simultaneously inspected by several NRAs, to conduct their evaluations in parallel and share their respective scientific evaluations with each other, potentially join their list of questions or deficiencies to the manufacturer and base their regulatory decision on the outcome of these evaluations.

manufacture. All operations of purchase of materials and products, production, quality control (QC), release, storage and distribution of pharmaceutical products, and the related controls.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

master formula. A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master batch record. A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging. All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product. Any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

qualification. Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification.

quality unit(s). An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

quarantine. The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

reconciliation. A comparison between the theoretical quantity and the actual quantity.

recovery. The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

reprocessing. Subjecting all or part of a batch or lot of an in-process medicine, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch or lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological medicines and, in such cases, are validated and pre-approved as part of the marketing authorization.

reworking. Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due

to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

specification. A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material. A raw material, intermediate, or an API that is used in the production of an API and that incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

validation. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Stringent regulatory authority (SRA)

A National Medicines Regulatory Authority which is strict, precise, exact with effective and well-functioning systems. Among others, it includes regulatory authorities which are:

- Members or observers or associates (prior to 2015) of the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

  Members:

  - European Union member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom
  - Japan
  - United States

  Observers:

  - European Free Trade Association (EFTA) represented by Swiss Medic of Switzerland, and Health Canada (as may be updated from time to time).

  Associates: through mutual recognition agreements: Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

- For medicines used exclusively outside the ICH region, positive opinions or tentative approval under any of the following three special regulatory schemes are recognized as stringent approval: -
    - Article 58 of European Union Regulation (EC) No. 726/2004
    - Canada S.C. 2004, c. 23 (Bill C-9) procedure
    - United States Food and Drug Agency (FDA) tentative approval (for antiretroviral under the PEPFAR programme)
- A regulatory Authority that has been agreed by SADC to have an effective and well-functioning medicines regulation systems.
- **where the inspectorate is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S*)*** https://picscheme.org/en/members , the consideration shall be made on a case to case basis
-

SADC MEMBER STATES

Angola, Botswana, Comoros, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Kingdom of Eswatini, Tanzania, Zambia and Zimbabwe.

HARMONIZED GMP INSPECTION PROCESS OVERVIEW

GMP inspections are conducted in line with current WHO GMP guidelines by inspectors from **at least two (2) member states.** The final GMP inspection reports and compliance/ CAPA reports are reviewed by inspectors from all member states before they are communicated to manufacturers. The final GMP compliance decision, its validity and communication follows individual member state processes.

The harmonized GMP inspections are conducted for the following reasons:

a. To support the registration of products submitted under the collaborative registration pathway;
b. To support the approval of variations submitted for additional sites

Joint inspections maybe considered in the following cases;

a. Routine inspections for sites initially approved under the harmonized GMP inspection route
b. Work sharing for common sites among member states
c. Investigative inspections affecting two or more member states

SADC conducts product line and cost recovery inspections for all manufacturers. The inspection fees applicable vary depending on the number of manufacturing blocks and the dosage forms marketed in SADC or submitted for registration. The inspection process is generally initiated by the SADC inspection coordinator, however manufacturers may send a formal request or enquiry to the SADC GMP inspections coordinator at the implementing agency at gmp@mcaz.co.zw and mcaz@mcaz.co.zw. Manufacturers should provide the current Site Master File, and list of products marketed or submitted for registration under the collaborative SADC registration pathway.

NB: It should be noted that member states reserves the right to conduct independent inspections if considered necessary.

RELIANCE

SADC relies on the work done by other regulatory agencies to make risk informed regulatory decisions. This is done through Desk Reviews of inspection reports from other regulatory Authorities within SADC or Stringent Regulatory Authorities, SRAs and the WHO Pre-qualification program.

The manufacturer must be willing to share all the required documents for evaluation, and these may include, the inspection reports by recognised Authorities, the CAPA, the GMP certificate, APQRs, the Batch processing records. SADC however, reserves the right to determine whether an onsite inspection would be required. All submitted documents shall be treated in confidence by all inspectors in accordance with the SADC Inspectors Code of Conduct. Such information is usually shared redacted. Full information can be shared upon request, where Intellectual Property is preserved.

The application for desk review will be assessed collaboratively by all member states. The outcome/ decision of the desk review process could be approval or recommendation for an onsite inspection. Manufacturers are accordingly expected to send a formal request for a GMP Desk Review to the SADC GMP inspections coordinator at the implementing agency at gmp@mcaz.co.zw and mcaz@mcaz.co.zw.

RECOGNITION

SADC member states are not yet at recognition stage. The harmonisation is still at work sharing stage.

SETTING UP OF NEW PHARMACEUTICAL MANUFACTURING PLANTS IN SADC

Introduction

The setting up of pharmaceutical manufacturing plants is a capital intensive investment and as such requires due diligence and compliance from the conceptual design stages. This will ensure that newly constructed plants meet the acceptable cGMP standards. In this context, the SADC member states are expected to assist committed Greenfield and Brownfield projects through review of their plans from conceptual design up to licensing of the plants.

Steps towards licensing of new pharmaceutical manufacturing premises

a) Prospective pharmaceutical manufacturers must compile the following documentation and then seek a review meeting with the GMP inspectorate of the member states.
   1. Floor plan drawn to scale
   2. Personnel flow
   3. Process and material flow
   4. Spatial surrounding environment
   5. HVAC classification zoning schematic diagrams
   6. HVAC pressurization diagram
   7. Dust extraction schematic diagram (for oral solid dosage forms).
   8. Drainage schematic and Effluent treatment
   9. A brief description of the proposed utilities applicable, e.g, Water system
   10. Quality Control laboratory schematic drawing, including the microbiology laboratory where applicable

b) The manufacturer will proceed with the procurement and civil works after agreeing with the member states GMP inspectorates. Any changes to the agreed plans must be adequately documented, notified and mutually agreed.

c) After completion of construction and submission of a complete application for a Pharmaceutical manufacturer's licence, a physical onsite inspection shall be conducted to verify compliance to the agreed plans and cGMP for non-structural systems, which include a documented quality management system and at least qualification of the areas, major equipment and utilities.

d) After a satisfactory inspection, the site shall hence be licensed as a pharmaceutical manufacturer in the respective SADC member state.

Any queries, clarifications, contributions and feedback should be submitted to the Head of Agency of the respective National Medicines Regulatory Agency.

GMP INSPECTION REFERENCE GUIDELINES

NB: The reference guideline documents listed below are the current WHO guidelines and maybe updated from time to time.

	GMP TOPIC/AREA	REFERENCE GUIDANCE DOCUMENT
1.	**GMP main principles**	WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/ TRS1025 Annex 6
2.	**Water for Pharmaceutical Use**	WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.***Short name: WHO TRS No. 970, Annex 2*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/ TRS 1025 Annex 3; Production of water for injection by means other than Distillation and
3.	**Heating Ventilation and Air-conditioning, HVAC**	Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

		Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 8. **Short name: WHO TRS No. 1019** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1019/en/
4.	**Good practice in Quality Control**	WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1. ***Short name: WHO TRS No. 957, Annex 1*** http://www.who.int/medicines/publications/44threport/en/ **Good chromatography practices**. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025, Annex 4. ***Short name: WHO TRS No. 1025, Annex 4*** https://www.who.int/publications-detail/978-92-4-000182-4
5.	**Pharmaceutical Microbiology**	WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2. ***Short name: WHO TRS No. 961, Annex 2*** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
6.	**Sterile products**	WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6. ***Short name: WHO TRS No. 961, Annex 6*** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

7.	**Finished goods transportation validation**	Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO TRS No. 961, Annex* 9** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1 WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
8.	**Quality risk management**	WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. ***Short name: WHO TRS No. 981, Annex 2*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/ International Conference on Harmonisation, ICH, Q9 Quality Risk Management https://database.ich.org/sites/default/files/Q9_Guideline.pdf Include the PICS guidance

9.	**Non-sterile process validation**	WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. ***Short name: WHO TRS No. 992, Annex 3*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
10.	**Data integrity**	Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5. ***Short name: WHO GDRMP guidance*** or ***WHO TRS No. 996, Annex 5*** http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
11.	**Hold time studies**	WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. ***Short name: WHO TRS No. 992, Annex 4*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
12.	**Site Master File**	WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. ***Short name: WHO TRS No. 961, Annex 14*** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
13.	**Sampling**	WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4. ***Short name: WHO TRS No. 929, Annex 4*** http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

14.	**Validation** -HVAC -Water system -Analytical methods -Computerised systems -cleaning - Guideline on qualification of equipment and systems - Non sterile process validation	WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report (WHO Technical Report Series, No. 1019). ***Short name: WHO TRS No.* 1019*, Annex 3*** https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1
15.	**Hazardous substances**	WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 3*** http://www.who.int/medicines/publications/44threport/en/
16.	**Chemical reference standards**	General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3*** http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

17.	**Technology transfer**	WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7. ***Short name: WHO TRS No. 961, Annex 7*** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
18.	**Biological products**	WHO Expert Committee on Biological Standardization Sixty-sixth report **WHO Technical Report Series, No. 999, 2016 Annex 2** https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1
19.	**Blood products**	WHO guidelines on good manufacturing practices for blood establishments, Annex 4; World Health Organization **WHO Technical Report Series, No. 961, 2011** https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1
20.	**Stability studies**	WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-second report **WHO Technical Report Series, No. 1010, Annex 10** http://apps.who.int/medicinedocs/documents/s23498en/s23498en.pdf
21.	**Herbal medicines**	WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-second report **WHO Technical Report Series, No. 1010, Annex 2** http://apps.who.int/medicinedocs/documents/s23498en/s23498en.pdf
22.	**Biosimilars**	WHO Expert Committee on Biological Standardization Sixtieth report; **WHO Technical Report Series, No. 977, 2013 Annex 2** https://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1

23.	**Pharmacovigilence**	https://www.fda.gov/media/71546/download
24.	**New premises**	The manufacturers are free to use any reference engineering texts that help them attain the WHO cGMP Compliance. The following organization can be used as an example; 1. International Society of Pharmaceutical Engineering https://ispe.org/ The supplementary guidance in this document also assist with the process for establishing acceptable new pharmaceutical plants within the SADC member states.

GUIDANCE ON RISK BASED CLASSIFICATION OF DEFICIENCIES

Introduction

This document helps ensure consistency among SADC inspectors during GMP inspections when classifying good manufacturing practices (GMP) observations according to risk. It also informs industry of the situations SADC considers unacceptable that may result in a non-compliant (NC) rating and/or compliance.

Guidance to assigning risk to an observation

DEFINITIONS

Critical deficiency

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.

Major deficiency

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

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- 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.

Minor/ Other deficiency

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

Inspectors will generally consider the following when assigning risk ratings:

- Risk will be assigned in relation to the nature of the product, nature of the deviation, and frequency of occurrences.
- Risks maybe upgraded/ downgraded from one class to the next depending on the evidence supporting the non-conformance and the nature of the deficiency and how critical the observation is to the dosage form.
- When making a Critical observation—or when re-evaluating a Major observation as a Critical observation —inspectors should bring this situation to the attention of the company's senior management.
- All observations should be discussed with the auditee and agreed upon during the inspection. In the event of disagreement, the auditee should be able to defend their position with clear reputable references on the finding in a CAPA response.
- Recurring observations from previous inspections maybe upgraded.

NB: The following are typical GMP non-conformances inspectors may observe during an inspection. It is not intended to be an all-inclusive/ exhaustive list, and inspectors may identify other observations.

GMP SYSTEM	CRITICAL	MAJOR	MINOR/ OTHER
PREMISES	i. *No air filtration system* ii. *Generalized malfunctioning of the ventilation system(s)- Contamination evident.* iii. *Inadequate segregation of manufacturing or testing areas from other manufacturing areas for high risk products such as highly sensitizing drugs, biological, hormones,cytotoxic drugs or highly active drugs*	i. *Malfunctioning of the ventilation system that could result in possible localized or occasional cross-contamination.* ii. *Maintenance/periodic verification such as air filter replacement, monitoring of pressure differentials not performed.* iii. *Accessory supplies (steam, air, nitrogen, dust collection, etc.) not qualified.* iv. *Heat, Ventilation, Air Conditioning (HVAC) and purified water system not qualified.* v. *Temperature and humidity not controlled or monitored when necessary (for example, storage not in accordance with labelling requirements).* vi. *Damages (holes, cracks or peeling paint) to walls/ceilings immediately adjacent or above manufacturing areas or equipment where the product is exposed.*	i. *Un-screened/Un-trapped floor drains.* ii. *Outlets for liquids and gases not identified.* iii. *Damages to surfaces not directly adjacent or above exposed products.* iv. *Non-production activities performed in production areas.* v. *Inadequate rest, change, wash-up and toilet facilities.* vi. *Magnehelic gauges used to monitor pressures in the rooms, not temper sealed after calibration.*

	iv. *Design of premises does not allow logical flow of material and personnel - cross contamination/ mix up evident*	vii. *Un-cleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipment.* viii. *Surfaces finish (floors, walls and ceilings) that do not permit effective cleaning.* ix. *Unsealed porous finish in manufacturing areas with evidence of contamination (mildew, mould, powder from previous productions, etc.).* x. *Insufficient manufacturing space that could lead to mix-ups.* xi. *Physical and electronic quarantine accessible to unauthorized personnel/Physical quarantine area not well marked and/or not adhered to.* xii. *No separate area/Insufficient precautions to prevent contamination or cross-contamination during raw material sampling.*	

		xiii. *Doors giving direct access to exterior from core manufacturing and packaging areas used by personnel* xiv. *Lack of proper facilities to prevent contamination when moving from areas of lower classification to areas of higher classification, for instance airlocks, change rooms.* xv. *Lack of proper chemical/ biochemical waste disposal infrastructure and procedures*	
EQUIPMENT	i. *Equipment used for complex manufacturing operations of critical products not qualified and with evidence of malfunctioning or lack*	i. *Equipment does not operate within its specifications.* ii. *Equipment used during the critical steps of fabrication, packaging/labelling, and testing, including computerized systems, is not qualified.*	i. *Insufficient distance between equipment and walls to permit cleaning.* ii. *Base of immovable equipment not adequately sealed at points of contact.*

	of appropriate monitoring. ii. *Evidence of contamination of products by foreign materials such as grease, oil, rust and particles from the equipment.*	iii. *Tanks for manufacturing of liquids and ointments not equipped with sanitary clamps.* iv. *Stored equipment not protected from contamination.* v. *Inappropriate equipment for production: surfaces porous/ potentially reactive and non-cleanable/material sheds particles.* vi. *No covers for tanks, hoppers or similar manufacturing equipment.* vii. *No inadequate precautions taken when equipment such as oven or autoclave contains more than one product (possibility of cross-contamination or mix-ups).* viii. *Equipment location does not prevent cross-contamination or possible mix-ups for operations performed in common area.* ix. *Purified water system not maintained or operated to provide water of adequate quality.* x. *Leaking gaskets with potential impact on product quality.*	iii. *Use of temporary means or devices for repair.* iv. *Defective or unused equipment not removed or appropriately labelled.* v. *Minor equipment used for non-critical products not qualified*

		xi. *No calibration program for automatic, mechanical, electronic or measuring equipment/no records maintained.* xii. *No preventative maintenance program for major equipment/no records maintained.* xiii. *No equipment usage logs.* xiv. *Inadequate cleaning of equipment with evidence of residue carry over* xv. Long campaigns during which Contamination accumulates xvi. Risks from machine lubricants xvii. *Poor control over metal items – in-particular sieves*	
PERSONNEL	i. *Individual in charge of Quality Control (QC) or production for a fabricator of critical/high risk products does not hold a relevant qualification in a*	i. *Individual in charge of QC or Production for a manufacturer of a low risk product does not hold a relevant qualification in a science related field to the work being conducted and does not have sufficient practical experience in their responsibility area.*	i. *Inadequate training records.* ii. *Insufficient written training program*

	science related field to the work being conducted and does not have sufficient practical experience in their responsibility area.	*ii. Delegation of responsibilities for QC or Production to insufficiently qualified persons.* *iii.* Insufficient personnel for QC or Production operations resulting in a *high probability of error.* *iv. Insufficient training for personnel involved in production and QC resulting in related GMP deviations* *v. Key personnel lack defined job responsibilities.*	
SANITATION & HYGIENE	*i. Evidence of widespread accumulation of residues/extraneous matter indicative of inadequate cleaning.* *ii. Evidence of gross infestation.*	*i. Sanitation program not in writing but premises in acceptable state of cleanliness.* *ii. No standard operating procedures (SOP) for microbial/environmental monitoring, no action limits for areas where susceptible non-sterile products are manufactured.* *iii. Cleaning procedures for production equipment not validated (including analytical methods).*	*i. Incomplete written sanitation procedure.* *ii. Incomplete implementation of the written sanitation program.*

		iv. *Inadequate written health requirements and/or hygiene program.* v. *Health requirements and/or hygiene program not properly implemented or followed.*	
GOOD PRACTICE IN PRODUCTION	i. *No written Master Formula.* ii. *Master Formula or manufacturing batch document showing gross deviations or significant calculation errors.* iii. *Evidence of falsification or misrepresentation of manufacturing and packaging orders.*	i. *Master Formula prepared/verified by unqualified personnel.* ii. *Lack of or incomplete validation studies/reports for critical manufacturing process (lack of evaluation/approval).* iii. *Inadequate validation of changeover procedures.* iv. *Unapproved/undocumented major changes compared to Master Production Documents.* v. *Deviations from instructions during production not documented and not approved by QC.* vi. *Discrepancies in yield or reconciliation following production not investigated.*	i. *Incomplete SOPs for handling of materials and products.* ii. *Access to production areas not restricted to authorized personnel.* iii. *Inadequate checks for incoming materials.* iv. *Written procedures incomplete for packaging operations.* v. *Incomplete recall procedure.* vi. *No agreement between the wholesaler, the importer*

		vii. *Line clearance between production of different products not covered by SOP and not documented.* viii. *No regular checks for measuring devices/no records.* ix. *Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups.* x. *Inadequate labelling/storage of rejected materials and products that could generate mix-ups.* xi. *Upon receipt, bulk and in-process drugs, raw material and packaging material not held in quarantine until released by QC.* xii. *Labels are not properly controlled.* xiii. *Production personnel using bulk and in-process drugs, raw material and packaging material without prior authorization by QC.*	*and the distributor relative to a recall of a drug when the importer or distributor assumes wholesaler's responsibilities with respect to recalls.* vii. *Incomplete/inaccurate annual product quality review.*

		xiv. *Inadequate/inaccurate labelling of bulk/in-process drugs, raw material and packaging material* *xv.* *Raw material dispensing not done by qualified persons, according to an SOP.* *xvi.* *Master Formula incomplete or showing inaccuracies in the processing operations.* *xvii.* *Changes in batch size not prepared/verified by qualified personnel.* *xviii.* *Inaccurate/incomplete information in manufacturing/packaging batch documents.* *xix.* *Although documented, combination of batches done without QC approval/not covered by SOP.* *xx.* *No written procedures for packaging operations.* *xxi.* *Non-standard occurrences during packaging not investigated by qualified personnel.* *xxii.* *Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, disposal).*	

		xxiii. *Inadequate handling of outdated/obsolete packaging material.* *xxiv.* *No or inadequate self-inspection program/Program does not address all applicable sections of GMPs/Records incomplete or not maintained.* *xxv.* *Fabrication, packaging/labelling and testing operations carried out at a site not holding a valid manufacturing licence.* *xxvi.* *No agreement between the contractor, the importer and the distributor covering the fabrication and packaging/labelling operations.* *xxvii.* *Recall:* *i.* *Absence of recall procedure combined with distribution practices that would not permit an adequate recall (distribution records unavailable or not kept).* *ii.* *Improper quarantine and disposal practices that would allow*	

		recalled/rejected units to be returned for sale. xxviii. Incomplete validation of content uniformity and blending due to sample size taken *xxix. Intermediate and bulk products – holding time not set, or justified, or respected.*	
QUALITY CONTROL DEPARTMENT	*i. No person in charge of QC available on premises.* *ii. Quality Control department is not a distinct and independent unit, lacking real decisional power, with evidence that QC decisions are often overruled by production department or management.* *iii.*	*i. Inadequate facilities, personnel and testing equipment.* *ii. No authority to enter production areas.* *iii. No SOPs approved and available for sampling, inspection and testing of materials.* *iv. Products made available for sale without approval of QC department.* *v. Products released for sale by QC without proper verification of manufacturing and packaging documentation.* *vi. Master production documents not in compliance with marketing authorization.* *vii. Out of specification test results, deviations and borderline conformances not properly*	*i. No agreement between the contract laboratory and the establishment covering the testing activities.* *ii. Investigations of non-conformances not completed in timely manner.*

		investigated and documented, according to a SOP. *viii. Raw material/packaging material used in production without prior approval of QC.* *ix. Reprocessing/Reworking done without prior approval of QC department.* *x. Lack of or inadequate system for complaint handling.* *xi. Returned goods are made available for sale without assessment and/or approval by QC.* *xii. SOPs covering operations that can affect the quality of a product such as transportation, storage, etc...not approved by QC department/not implemented.* *xiii. Inadequate evidence to demonstrate that storage and transportation conditions are appropriate.* *xiv. Lack of or insufficient change control system.* *xv. For testing laboratories (in house or contract), the systems and controls in place*	

		for the proper qualification, operation, calibration and maintenance of equipment, standards, solutions, and records keeping do not assure that the results and conclusions generated are accurate, precise and reliable. *xvi.* *Products tested at a site not holding a valid GMP licence/ certificate and not adequately approved/ certified.* *xvii.* *Sterility testing not performed in a Grade A environment within a Grade B background or in an isolator of a Grade A within an appropriate background and limited access to non-essential personnel* *xviii.*	
Quality Control Raw Material Testing	*i.* *Evidence of falsification or misrepresentation of analytical results.* *ii.* *No evidence of testing Certificate of Analysis*	*i.* *Reduced testing program in place without adequate certification of the vendors/suppliers.* *ii.* *Water used in the formulation is not of acceptable quality.* *iii.* *Insufficient testing of raw material.*	*i.* *Lots identified for confirmatory testing used in production without QC approval.* *Incomplete validation of test methods*

	(COA) available from the supplier/synthesizer and no testing done. iii. *Use of raw material after the expiration date.*	iv. *Incomplete specifications.* v. *Specifications not approved by QC.* vi. *Test methods not validated.* vii. *Use of raw material after retest date without proper retesting.* viii. *Multiple lots of the same raw material, comprising of one reception, are not considered as separate for sampling, testing and release.* ix. *No SOP for conditions of transportation and storage.* x. *Certification of brokers or wholesalers allowed without proper documentation.* xi. *Lack of adequate SOPs and/or SOPs not followed consistently. For example;* i. Inadequate or lack of sampling plan, ii. unrepresentative sample size, iii. lack of microbial testing of primary packaging material.	
PACKAGING MATERIAL TESTING		i. *Reduced testing program in place without adequate certification of vendors/suppliers.*	i. *Inadequate procedures of transportation and storage.*

		ii. *Lack of or insufficient testing of packaging material.* iii. *Inadequate specifications.* iv. *Specifications not approved by QC.* v. *No identity test done by the packager/labeller after receipt on its premises.* vi. *Certification of brokers or wholesalers done without proper documentation.*	ii. *Inappropriate environment and/or precautions to prevent contamination of packaging material during sampling.*
FINISHED PRODUCT TESTING	i. *Finished product not tested for compliance with applicable specifications by the manufacturer.* ii. *Evidence of falsification or misrepresentation of testing results / forgery of COA.*	i. *Incomplete/inadequate/ outdated specifications.* ii. *Finished product specifications not approved by QC.* iii. *Incomplete testing.* iv. *No identity testing upon receipt at site and/or no periodic complete confirmatory testing.* v. *Lack of or insufficient validation of test methods.* vi. *No SOP for conditions of transportation and storage.*	i. *Inadequate method transfer for a validated analytical method.* ii. *Method validation report does not specify the revision of the analytical method used at the time of validation.*

	iii. *Non-compliant products made available for sale.*	vii. *Use of unique identifier principles not meeting the acceptable options.*	
DOCUMENTATION	*Evidence of falsification or misrepresentation of records*	i. *Lack of or incomplete Master Production Documents.* ii. *Unavailability of documentation from suppliers in a timely manner.* iii. *Lack of or incomplete records of sale.* iv. *Lack of or incomplete records of complaints received respecting the quality of a drug.*	i. *Incomplete plans and specifications for the manufacturing buildings* ii. *Insufficient retention time for evidence and records to be maintained.* iii. *No organization charts.* iv. *Incomplete records for the sanitation program.*
SAMPLES		i. *Retained samples not kept for finished products.* ii. *Failure to submit retained samples when alternative sample retention granted.*	i. *Samples of raw material not available.* ii. *Insufficient quantity for finished products or active pharmaceutical ingredients (API).* iii. *Improper storage conditions.*

STABILITY	i. *No data available to establish the shelf-life of products.* ii. *Evidence of falsification or misrepresentation of stability data/forgery of COA.*	iii. *Insufficient number of lots to establish shelf-life.* iv. *Insufficient data to establish shelf-life.* v. *No action taken when data shows that the products do not meet their specifications prior to the expiry date.* vi. *Lack of or inadequate continuing stability program.* vii. *No stability studies pertaining to changes in manufacturing (formulation)/packaging material.* viii. *Testing methods not validated.* ix. *No consideration given to enroll worst case scenarios (for example, reworked/reprocessed lots).* x. *Inappropriate storage conditions for stability samples.*	i. *Stability testing not performed at the time required by the written program.* ii. *Review of stability data not performed in a timely manner.*
STERILE PRODUCTS	i. *Lack of or inadequate validation of critical sterilization cycles.*	i. *Aqueous-based products not subject to terminal steam sterilization without proper*	i. *Inadequate control on the maximum number of*

	ii. *Water for Injection (WFI) systems not validated with evidence of problems such as microbial/endotoxin counts not within specifications.* iii. *No media fills performed to demonstrate the validity of aseptic filling operations.* iv. *No environmental controls/No monitoring for viable microorganisms during filling for aseptically filled products.*	*justification or approval through the marketing authorization.* ii. *Inadequate room classification for processing/filling operations.* iii. *Aseptic manufacturing suites under negative pressure compared to clean areas (C-D). Clean areas (C-D) under negative pressure to unclassified areas.* iv. *Insufficient number of samples taken for environmental monitoring/inadequate sampling methods.* v. *Insufficient environmental controls/Insufficient monitoring for viable microorganisms during filling for aseptically filled products.* vi. *Disinfectants not qualified or adequately monitored.* vii. *Premises and equipment not designed or maintained to minimize contamination/generation of particles.* viii. *Inadequate maintenance of purified water*	*personnel present in clean and aseptic areas.*

	v. *Aseptic filling operations continued following unsatisfactory media fill results obtained.* vi. *Batches failing initial sterility test released for sale on the basis of a second test without proper investigation.* vii. *Inadequate environmental conditions for aseptic operations.* viii. *Absence of leak test for products sealed through fusion method, for example; ampules*	*and WFI systems.* ix. *Inadequate re-validation of purified water and WFI systems after maintenance, upgrading, out-of-specs trends.* x. *Inadequate training of personnel.* xi. *Personnel involved in aseptic filling prior to completing successful media fill.* xii. *Inadequate gowning practices for clean and aseptic areas.* xiii. *Inadequate sanitation/disinfection program.* xiv. *Inadequate practices/precautions to minimize contamination or prevent mix-ups,* xv. *Non-validated time lapse between cleaning, sterilization, and use of components, containers and equipment.* xvi. *No consideration given to bio burden prior to sterilization.* xvii. *Non-validated time lapse between start of manufacturing and sterilization or filtration.* xviii. *Inadequate program for media fill.*	

		xix. *Capability of media to grow a wide spectrum of microorganisms not demonstrated.* *xx.* *Misinterpretation of results for media fills.* *xxi.* *Samples for sterility testing insufficient in number or not representative of the entire production run or from parts of the batch considered to be most at risk of contamination.* *xxii.* *Each sterilizer load not considered as a separate lot for sterility testing.* *xxiii.* *Purified water is not used as the feed water for the WFI system and the clean steam generator.* *xxiv.* *Inadequate testing program for WFI.* *xxv.* *The WFI used for the final rinsing of containers and components used for parenteral drugs is not tested for endotoxins when those containers and components are not depyrogenated subsequently.* *xxvi.* *Inappropriate environment/controls for crimping following aseptic filling.*	

		xxvii. *Inadequate inspection for particles and defects.* *xxviii.* *Gases used to purge solutions or blanket products not passed through a sterilizing filter.* *xxix.* *Inadequate integrity testing of sterilizing or vent filters.* *xxx.* *Steam used for sterilization not monitored to assure suitable quality.*	
Pharmaceutical Quality system	*i.* *Non existing pharmaceutical quality system, no SOPs or policies on OOS, deviations, change management, market complaints handling.*	*i.* *Inadequate product quality reviews* *ii.* *Deviations, market complaints and OOS not recorded or adequately investigated.* *iii.* *Changes affecting marketing authorization not properly documented, notified and authorized.* *iv.* *Lack of application of Quality Risk Management principles.*	*i.* *Lack of / inadequate periodic trending or review of deviations, incidents, OOS, complaints, water system, changes, risk assessments.*

Key relevant guidance document

1. WHO good manufacturing practices for pharmaceutical products: main principles. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report* Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2 http://www.who.int/medicines/publications/pharmprep/en/index.html

UPDATE HISTORY

Version Number	Date Approved	Reason for Change and Amendments
01		New draft GMP guidance document