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Medicines Control Authority of Zimbabwe

MCAZ/LED/GL 09

# MCAZ GOOD MANUFACTURING PRACTICE GUIDELINE

EFFECTIVE DATE: 07/2023

Medicines Control Authority of Zimbabwe

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Harare

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| Reviewed by: S. Mutyavavir | ..... Signature | 21/7/23 Date |
| Checked by HoD/HoU: | ..... Signature | 21/7/2023 Date |
| Approved by QM: | ..... Signature | 27/7/2023 Date |
| Authorised for use by: Director-General | ..... Signature | 31/7/2023 Date |

## 1.0 APPLICATION

This Good Manufacturing Practice (GMP) guideline applies to;

1.1 Prospective and licensed pharmaceutical manufacturers in Zimbabwe.
1.2 Inspection of international pharmaceutical manufacturers who have products registered with the Authority or intend to register their products with the Medicines Control Authority of Zimbabwe.

## 2.0 PURPOSE

The manufacture of pharmaceutical products must comply with current Good manufacturing practice, cGMP. This is important to give assurance on product quality and ensure that all medicines are safe, effective and of the right quality.

Several GMP guidelines are publicly available and used by different regulatory authorities. The Medicines Control Authority of Zimbabwe fully adopts the World Health Organization, WHO guidelines on cGMP. The manufacturers of pharmaceutical products marketed in Zimbabwe are accordingly expected to comply with the relevant WHO cGMP guidelines as listed in this guideline.

## 3.0 BACKGROUND / INTRODUCTION

The process of setting up acceptable pharmaceutical manufacturing plants has not been clear and elaborate. Many prospective manufacturers have found the Authority's requirements vague or at times undefined. Similarly, the guidance documents used by the inspectorate during GMP inspections have not been outlined to allow manufacturers to proactively assess their compliance to cGMP.

This guidance document therefore seeks to address these grey areas in pharmaceutical manufacturing with the aim of improving cGMP compliance and ensuring that products marketed in Zimbabwe are safe, efficacious and of the right quality.

### 3.1 Contact Information

The GMP inspectorate can be contacted via the following;

3.1.1 Email: gmp@mcaz.co.zw /
3.1.2 Phone: +263 772145191/2/3; +263-242-736981-7
3.1.3 Physical Address:
106 Baines Avenue, Harare, Zimbabwe.
P.O. Box 10559, Harare, Zimbabwe
Authority division: Licensing and Enforcement

## 4.0 DEFINITIONS

**4.1** **Manufacture** includes compound, process or pack for sale but does not include the compounding of a medicine by a medical practitioner, dental practitioner, veterinary surgeon or pharmacist if that medicine—

4.1.2 has not been advertised for sale in Zimbabwe; and

4.1.2 does not contain any component the sale of which is prohibited by this Act; and

4.1.3 is supplied for the treatment of a particular person or animal; (MASCA 15:03)

**4.2** **Manufacturer.** A company that carries out operations such as production, packaging, repackaging, labelling and relabeling of pharmaceuticals *(WHO TRS986 Annex 2)*.

**4.3** **Contamination.** The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport *(WHO TRS986 Annex 2)*.

**4.4** **Cross-contamination**. Contamination of a starting material, intermediate product or finished product with another starting material or product during production *(WHO TRS986 Annex 2)*.

**4.4.1** **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 *(WHO TRS986 Annex 2)*.

**4.4.2** **Medicine,** subject to section seventy-five, means any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in—

i. The diagnosis, treatment, mitigation or prevention of disease or any abnormal physical or mental state or the symptoms thereof in man or in animals; or

ii. Restoring, correcting or modifying any physical, mental or organic function in man or in animals (MASCA: 15:03)

## 5.0 GUIDELINES

### 5.1 Licensing Of New Pharmaceutical Manufacturing Plants

**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 Authority avails itself to assist committed Greenfield and Brownfield projects through review of their plans from conceptual design up to licensing of the plant.

**Steps towards licensing of new pharmaceutical manufacturing premises**

5.1.1 Prospective pharmaceutical manufacturers must compile with the following documentation and then seek a review meeting with the GMP inspectorate.

i. Floor plan drawn to scale
ii. Personnel flow
iii. Process and material flow
iv. Spatial surrounding environment
v. HVAC classification zoning schematic diagrams
vi. HVAC pressurization diagram
vii. Dust extraction schematic diagram (for oral solid dosage forms).
viii. Drainage schematic and Effluent treatment
ix. A brief description of the proposed utilities applicable, e.g., Water system
x. Quality Control laboratory schematic drawing, including the microbiology laboratory where applicable

5.1.2 Upon mutual agreement between the prospective manufacturer and the GMP inspectorate, a file for the prospective manufacturer shall be opened by the Authority.

5.1.3 The manufacturer will proceed with the procurement and civil works according to the agreed plans. Any changes must be adequately documented, notified and mutually agreed. The agreement between the manufacturer and the Authority will be valid for 24 months, beyond which the prospective manufacturer should get the documents reviewed and agreement renewed by the Authority, if the committed works have not been commenced.

5.1.4 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.

5.1.5 After a satisfactory inspection, the site shall hence be licensed as a pharmaceutical manufacturer in Zimbabwe.

**NB:** Kindly note that the premises shall be expected to comply with other requirements according to the City By-laws, the Factories Act and the Environmental Management Act.

Any queries, clarifications, contributions and feedback should be submitted to the Director-General, MCAZ, 106 Baines Avenue, Box 10559, Harare Telephone +263-4-736 981-5; email mcaz@mcaz.co.zw and copied to the GMP inspections office at gmp@mcaz.co.zw .

## 5.2 GMP Inspections

### 5.2.1 Inspection team composition

The inspections team shall be comprised of the following officers;

i. The Lead inspector, who shall be an experienced and competent inspector with adequate knowledge, training and qualifications to conduct the inspection of a particular dosage form.
ii. The co-inspector, who shall who shall be an experienced and competent inspector with adequate knowledge, training and qualifications to conduct the inspection of a particular dosage form. The co-inspector may be at competence level below the Lead inspector and will be gaining experience to lead future similar inspections.

**NB**: Senior regulatory officers from other departments like Chemistry, Microbiology, Pharmacovigilance or Dossier assessment will be considered for inspections requiring more specialised knowledge on their expert fields.
iii. Observer inspector, who shall be undergoing training on GMP inspections.

### 5.2.1 New inspections

New inspections are conducted to support product registration before the issuance of marketing authorisation. These inspections are product based and are triggered through submission of a dossier for registration.

### 5.2.3 Risk based routine inspections

The Authority conducts routine quality assurance surveillance activities on all registered medicines in Zimbabwe. This is done through risk derived routine cGMP inspections.

i. Local manufacturers are inspected annually or at a frequency based on the compliance risk determined after each inspection.
ii. Product based inspections are conducted for International manufacturers, with a risk based routine inspection frequency from one year to three years. Re-inspections may be applicable as follow up verification of the adequacy of corrective and preventive actions.

### 5.2.4 Recognition

The inspectorate recognises manufacturers from Stringent Regulatory Authorities which include the International Conference on Harmonisation, ICH countries. These countries include the European Union, USA, Australia, Canada and Japan. These manufacturers are exempted from GMP inspections.

### 5.2.5 Reliance

The Authority relies on the work done by other Authorities to make risk-informed regulatory decisions. This is done through Desk Reviews of inspection reports from other regulatory Authorities and the WHO Pre-qualification program. To qualify for Desk review GMP clearance, the manufacturing site must have been inspected and cleared by Stringent Regulatory Authorities including WHO Prequalification inspections, for the same dosage form and manufacturing block and line. The manufacturer must be willing to share all the required documents for evaluation, and these include, the inspection reports by recognised Authorities, the CAPA, the GMP certificate, APQRs for the products, the Batch processing records. The Authority, however, reserves the right to determine whether an onsite or virtual inspection would be required. New foreign facilities in jurisdictions without an SRA shall not be legible for reliance. Reliance through desk reviews will only be considered for routine inspections of these facilities. This shall be for a maximum of two desk reviews.

### 5.2.6 Collaboration and work sharing

The Authority collaborates with other SADC countries in a work-sharing model called the ZAZIBONA harmonisation initiative. The member countries select representatives to participate in harmonised GMP inspections and the outcome compliance recommendations are used for internal decision making at individual country level. This reduces the work burden on the regulatory agency and promotes harmonisation within the African region.

To participate in the ZAZIBONA inspections, manufacturers must submit the same dossier in at least two active SADC member states, and the inspection is done to support product registration in the Southern African region. Correspondence can be send to the MCAZ GMP inspectorate at gmp@mcaz.co.zw as the coordinating implementing agency within SADC.

### 5.2.7 GMP Inspection fees

The Authority conducts product based and cost recovery inspections for all international manufacturers. The inspection fees applicable vary depending on the scope of products marketed in Zimbabwe or submitted for registration. The manufacturing site factors are also taken into consideration. Manufacturers are accordingly expected to send a formal request for a GMP inspection to gmp@mcaz.co.zw and mcaz@mcaz.co.zw and provide the current Site Master File, and list of products marketed or to be marketed in Zimbabwe. This will allow the inspectorate to accurately calculate the relevant inspection fees applicable.

Local manufacturers do not pay for inspection fees as this cost is factored into the licensing fees. However, if there be need for re-inspections within the same calendar year, re-inspection fees are applicable in line with the published Fee Schedule.

### 5.3 GMP Inspection Guidelines

**NB: The reference guideline documents listed below are the current WHO guidelines and maybe updated from time to time by the WHO. The latest published WHO guidelines must be used for each system, even before the review period of this guideline.**

| | 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/ |
| **2.** | **Water for Pharmaceutical Use** | WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.***Short name: WHO TRS No. 1033, Annex 3*** https://www.who.int/publications/m/item/annex-3-trs-1033 |
| **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/<br><br>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/ |

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| **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. Fifty Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2. ***Short name: WHO TRS No. 1044, Annex 2*** https://www.who.int/publications/m/item/trs1044-annex2 |
| **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<br><br>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/ |

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| **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**<br>-HVAC<br>-Water system<br>-Analytical methods | 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 |

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| | -Computerised systems<br>-cleaning<br>- Guideline on qualification<br>- Non sterile process validation | |
| **15.** | **Hazardous substances** | WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on<br>Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO<br>Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 2***<br>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<br>Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization<br>2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***<br>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<br>for Pharmaceutical Preparations. Fifty Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report<br>Series, No. 1044), Annex 4. ***Short name: WHO TRS No. 1044, Annex 4***<br>https://www.who.int/publications/m/item/trs1044-annex4 |
| **18.** | **Biological products** | WHO Expert Committee on Biological Standardization Sixty-sixth report **WHO Technical Report Series, No. 999, 2016 Annex 2**<br>https://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1 |

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| **19.** | **Blood products** | WHO guidelines on good manufacturing practices<br>for blood establishments, Annex 4; World Health Organization **WHO Technical Report Series, No. 961, 2011**<br><br>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<br>**WHO Technical Report Series, No. 1010, Annex 10**<br>http://apps.who.int/medicinedocs/documents/s23498en/s23498en.pdf |
| **21.** | **Herbal medicines** | WHO Expert Committee on Specifications for Pharmaceutical Preparations Fifty-second report<br>**WHO Technical Report Series, No. 1010, Annex 2**<br>http://apps.who.int/medicinedocs/documents/s23498en/s23498en.pdf |
| **22.** | **Biosimilars** | WHO Expert Committee on Biological Standardization Sixtieth report;<br>**WHO Technical Report Series, No. 977, 2013 Annex 2**<br>https://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1 |
| **23.** | **Pharmacovigilance** | Zimbabwe National Pharmacovigilance Policy Handbook, 2nd Edition, December 2016<br>https://www.mcaz.co.zw/index.php/downloads/category/15-guidelines?download=157:zimbabwe-national-pharmacovigilance-policy-handbook |
| **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;<br>1. International Society of Pharmaceutical Engineering https://ispe.org/ |
| **25** | **Reliance and recognition** | The MCAZ Reliance policy |
| **26** | **Remote inspection** | MCAZ Remote GMP inspections guideline |

## 6.0 KEY RELEVANT DOCUMENTS

**6.1** Medicines and Allied Substances Control Act 15:03

**6.2** 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

## 7.0 HISTORY

| DOCUMENT HISTORY | | |
|---|---|---|
| Revision Number | Date Approved | Reason for Change and Amendments |
| 0 | November 2019 | To align with GBT evaluation recommendations<br><br>Details of change<br><br>5.2 changed from "Routine inspections" to "GMP inspections"<br><br>5.2.1 Inclusion of the **Inspection team composition**<br><br>The inspections team shall be comprised of the following officers; …….. (Added)<br><br>5.2.2 Inclusion of **New inspections**<br>New inspections are conducted……. (added)<br><br>Numbering changed<br><br>5.2.1 to 5.2.3<br><br>5.2.2 Recognition Changed from "…….These manufacturers are currently exempted from GMP inspections." to 5.2.4 "…….These manufacturers are exempted from GMP inspections"<br><br>5.2.3 to 5.3<br><br>5.3 **GMP Inspection Guidelines**<br>GMP topic/area<br>24. New premises: …..International Society of Pharmaceutical Engineering https://ispe.org/ (added) |

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| | | 25 Reliance and recognition: MCAZ Reliance guideline (added)<br>26 Remote inspection: MCAZ Remote GMP inspections guideline (added) |
| 1 | July 2023 | <u>System Improvement</u><br><br>Section 5.2.5<br>Added<br>New foreign facilities in jurisdictions without an SRA shall not be legible for reliance. Reliance will only be considered for routine inspections of these facilities. This shall be for a maximum of two desk reviews.<br><br>5.3 GMP Inspection Guidelines<br>Update in links for the following guidelines<br>1. Water for Pharmaceutical Use from WHO TRS 971 to WHO TRS 1033 Annex 3<br>2. WHO good manufacturing practices for sterile pharmaceutical products from WHO TRS 961 Annex 6 to WHO TRS 1044 Annex 2<br>3. WHO guidelines on transfer of technology from WHO TRS 961 Annex 7 to WHO TRS Annex 4 |