



Medicines Control Authority of Zimbabwe

MCAZ GOOD MANUFACTURING PRACTICE GUIDELINE

APPROVED DATE: 10/12/2019

EFFECTIVE DATE: 10/12/2019

Medicines Control Authority of Zimbabwe

106 Baines Avenue

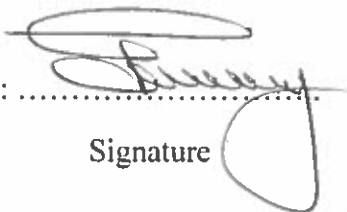
P O Box 10559

Harare

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Website: www.mcaz.co.zw

Approved by Director General:



Signature

10/12/2019
.....

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 the current World Health Organisation (WHO) 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—
 - 4.4.2.1** 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
 - 4.4.2.2** 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

5.1.1 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.

5.1.2 Steps towards licensing of new pharmaceutical manufacturing premises

5.1.2.1 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

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

5.1.2.3 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.

5.1.2.4 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.

5.1.2.5 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 Routine inspections

5.2.1 Risk based routine inspections

5.2.1.1 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.

5.2.2 Recognition

The inspectorate recognises manufacturers under the jurisdiction of well-resourced 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 currently exempted from GMP inspections.

5.2.3 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 well-resourced 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 inspection would be required.

5.2.4 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 individual regulatory agencies and promotes harmonisation within the African region.

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

5.2.5 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.

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

5.2.3 GMP Inspection Guidelines

NB: The reference guideline documents listed below are the current WHO guidelines and may be 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. <i>Short name: WHO TRS No. 986, Annex 2</i> 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. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2. <i>Short name: WHO TRS No. 970, Annex 2</i> http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
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. <i>Short name: WHO TRS No. 1010, Annex 8</i> http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/
4.	Good practice in Quality Control	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. <i>Short name: WHO TRS No. 1019</i> http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1019/en/
		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. <i>Short name: WHO TRS No. 957, Annex 1</i> http://www.who.int/medicines/publications/44threport/en/

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. <i>Short name: WHO TRS No. 961, Annex 2</i> 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. <i>Short name: WHO TRS No. 961, Annex 6</i> 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. <i>Short name: WHO TRS No. 961, Annex 9</i> 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. <i>Short name: WHO TRS No. 992, Annex 5</i> 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. <i>Short name: WHO TRS No. 981, Annex 2</i> http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
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. <i>Short name: WHO TRS No. 992, Annex 3</i> http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO TRS 992_web.pdf

10.	Data integrity	<p>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. <i>Short name: WHO GDRMP guidance or WHO TRS No. 996, Annex 5</i> http://www.who.int/medicines/publications/pharmrep/WHO_TRS_996_annex05.pdf</p>
11.	Hold time studies	<p>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. <i>Short name: WHO TRS No. 992, Annex 4</i> http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf</p>
12.	Site Master File	<p>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. <i>Short name: WHO TRS No. 961, Annex 14</i> http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1</p>
13.	Sampling	<p>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. <i>Short name: WHO TRS No. 929, Annex 4</i> http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1</p>
14.	Validation - HVAC - Water system - Analytical methods - Computerised systems - cleaning - Guideline on qualification - Non sterile process validation	<p>WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report (WHO Technical Report Series, No. 1019). <i>Short name: WHO TRS No. 1019, Annex 3</i> https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1</p>

15.	Hazardous substances	<p>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. <i>Short name: WHO TRS No. 957, Annex 2</i> http://www.who.int/medicines/publications/44threport/en/</p>
16.	Chemical reference standards	<p>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. <i>Short name: WHO TRS No. 943, Annex 3</i> http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1</p>
17.	Technology transfer	<p>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 Series, No. 961), Annex 7. <i>Short name: WHO TRS No. 961, Annex 7</i> http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1</p>
18.	Biological products	<p>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</p>
19.	Blood products	<p>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</p>
20.	Stability studies	<p>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</p>

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.	Pharmacovigilance	Zimbabwe National Pharmacovigilance Policy Handbook, 2 nd Edition, December 2016 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; 1. International Society of Pharmaceutical Engineering https://ispe.org/

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
N/A	N/A	N/A