Botswana Medicines Regulatory Authority

Approved By: _____ _____

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Date of Approval
(DD/MM//YY)

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1. Preamble

1.1 The Botswana Medicines Regulatory Authority (BOMRA) was established through the Medicines and Related Substances Act of 2013. The act provides for the regulation of medicines, medical devices, and cosmetics to promote human and animal health ensuring safety and efficacy.

1.2 The purpose of this guidelines is to provide guidance to licensed and prospective manufacturers on the requirements for current Good Manufacturing Practice (cGMP). This guideline is applicable to the manufacturing of pharmaceutical products. BOMRA fully adopts the World Health Organization (WHO) guidelines on cGMP. The manufacturers of pharmaceutical products manufactured and marketed in Botswana are expected to comply with relevant WHO cGMP guidelines. This is important to ensure that all medicines are safe, effective and of the right quality. Medicines should be manufactured by approved manufacturers whose activities are regularly inspected by regulatory authorities and comply with cGMP. This guideline will be used as a standard to attain cGMP compliance as required by BOMRA.

2. Laws, Regulations, Policies and Guidelines Applied

These guidelines were developed using principles from the following:

i. Medicines and Related Substances Act, 2013, (MRSA)

ii. Medicines and Related Substances Regulations, 2019

iii. WHO current Good Manufacturing Practice (cGMP) guidelines.

2.1 Legal Consideration

a) MRSA 2013, Section 27 (1): *Manufacture of medicines may only be undertaken in an establishment licensed by the Authority.*

b) *Section 27 (2): A person who wishes to manufacture medicines shall apply in the prescribed form and pay the prescribe fee to the Authority, and shall supply any further information which the Authority may require to satisfy itself that the premises to be used are suitable for the purpose and will be operated in accordance with the standards of good practice in the manufacture and quality control of medicines.*

c) *Section 27 (3): The manufacturer of medicines shall be under the continuous supervisory control of a registered pharmacist who possesses such practical experience as the Authority may prescribe.*

3. Definitions and abbreviations

3.1 Definitions

For the purpose of these guidelines, the following terms shall be defined as follows:

3.1.1 **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.

3.1.2 **Authority**: Means Botswana Medicines Regulatory Authority established under section 3 of MRSA 2013.

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

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

3.1.5 **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.

3.1.6 **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.

3.1.7 **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:

a) 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:

i. 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

ii. Japan

iii. United States

Observers:

i. 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).

b) 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:

i. Article 58 of European Union Regulation (EC) No. 726/2004

ii. Canada S.C. 2004, c. 23 (Bill C-9) procedure

iii. United States Food and Drug Agency (FDA) tentative approval (for antiretroviral under the PEPFAR programme)

c) A regulatory Authority that has been agreed by SADC to have an effective and well-functioning medicines regulation systems.

d) where the inspectorate is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S)

3.1.8 **ZAZIBONA** - a collaborative procedure for Southern African Development Community (SADC) countries in which national regulatory authorities jointly inspect pharmaceutical facilities for licensing purposes.

3.2 Abbreviations

For the purpose of these guidelines, the following abbreviations shall be used:

3.2.1 **cGMP** - current Good Manufacturing Practices

3.2.2 **BOMRA** - Botswana Medicines Regulatory Authority

3.2.3 **HVAC** - Heating Ventilation and Air Conditioning

3.2.4 **ICH** - International Conference on Harmonisation

3.2.5 **SADC -** Southern African Development Community

3.2.6 **SMF** - Site Master File

3.2.7 **WHO** - World Health Organisation

4. Scope

These guidelines are meant to provide guidance to:

a) Prospective and licensed Pharmaceutical manufacturers in Botswana.

b) Inspection of international Pharmaceutical manufacturers who intend to register their products or have their products registered with Botswana Medicines Regulatory Authority.

5. Licensing of a new pharmaceutical manufacturing plant

5.1 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 will assist committed Greenfield and Brownfield projects through review of their plans from conceptual design up to licensing of the plants.

5.2 Application requirements and procedure

5.2.1 Prospective pharmaceutical manufacturers must compile the following documentation and then seek a review meeting with the BOMRA Inspections and Licensing Unit:

a) Floor plan drawn to scale

b) Personnel flow

c) Process and material flow

d) Spatial surrounding environment

e) HVAC classification zoning schematic diagrams

f) HVAC pressurization diagram

g) Dust extraction schematic diagram (for oral solid dosage forms).

h) Drainage schematic and Effluent treatment

i) A brief description of the proposed utilities applicable, e.g, Water system

j) Quality Control laboratory schematic drawing, including the microbiology laboratory where applicable

5.2.2 The manufacturer will proceed with the procurement and civil works after agreeing with the BOMRA inspectors. Any changes to the agreed plans must be adequately documented, notified and mutually agreed. The agreement between the Manufacturer and the Authority shall 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.

5.2.3 After completion of construction, Pharmaceutical manufacturer shall submit a fully completed Application for Premises License; **BOMRA/IL/IL/P01/F02** - which shall be checked by the officer in charge, stamped and applicant given a copy, declaration form.

5.2.4 The applicant shall also submit the following:

a) A certified copy of the pharmacist's registration certificate issued by a professional body

b) A certified copy of a valid Blue card

c) A copy of a site master file

d) A list of products to be manufactured

e) Proof of payment (use facility name as reference)

f) Certified copy of identity card or passport

5.2.5 All applications must be submitted to BOMRA at plot 112, International Finance Park or emailed to inspections@bomra.co.bw

5.2.6 Upon receipt of a complete application for a Pharmaceutical manufacturer's license, the Authority through the Inspections and Licensing unit, shall conduct a physical onsite inspection to verify compliance to the agreed plans and cGMP for non -structural systems such as documented quality management system and at least qualification of the areas, major equipment and utilities.

5.2.7 After a satisfactory inspection, the site shall hence be licensed as a pharmaceutical manufacturer and registered to the BOMRA database.

NB: Kindly note that the premises shall be expected to comply with requirements of other national regulatory agencies such as licenses, permits or any other approvals.

6. GMP inspection of international manufacturers

6.1 cGMP inspections are conducted on international manufacturing sites to support the registration of products in Botswana and the approval of variations submitted for structural site changes including addition of new sites/blocks.

6.1.2 Application requirements and procedure

6.1.2.1 Pharmaceutical manufacturer shall submit the following:

a) Completed Application Form **BOMRA/IL/IL/P08/G01-F01**

b) A copy of current master file (not more than a year old)

c) A list of products submitted to BOMRA for registration

d) A proof of payment (use facility name as reference)

6.1.2.2 All applications must be submitted to BOMRA at Plot 112, Gaborone International Finance Park or emailed to inspections@bomra.co.bw

7. Routine inspections

7.1 Risk based routine inspections

7.1.1 The Authority shall conduct routine quality assurance surveillance activities on all medicines registered in Botswana which will be done through risk-based cGMP inspections.

7.1.2 Local manufacturers shall be inspected annually or at the frequency based on compliance risk determined after each inspection

7.1.3 Product based inspections will be conducted for international manufacturers with risk based routine inspection frequency from 1 year to three years.

7.1.4 Re-inspections may be applicable as follow up verification of adequacy of corrective and preventive actions.

8. Harmonized GMP Inspections

8.1 The Authority collaborates with other Southern African Development Community (SADC) member states through a work sharing model known as the ZAZIBONA harmonisation initiative. 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 cGMP compliance decision, its validity and communication follows individual member state processes. This reduces the work burden on individual regulatory agencies and promote harmonisation within SADC region.

8.2 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.

8.3 Joint inspections maybe considered in the following cases:

a) Routine inspections for sites initially approved under the harmonized GMP inspection process.

b) Work sharing for common sites among member states.

c) investigative inspections affecting two or more-member states.

8.4 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 reserve the right to conduct independent inspections if considered necessary.

9. Recognition

9.1 The Authority recognises the manufactures under jurisdiction of Stringent Regulatory Authorities which include International Conference on Harmonisation, ICH countries. These countries include the European Union, USA, Australia, Canada and Japan.

9.2 The authority also recognises the manufacturers inspected and approved by SADC countries through ZAZIBONA collaborative initiative.

9.3 These manufacturers shall be exempted from GMP inspections.

10. Reliance

10.1 Botswana Medicines Regulatory Authority (BOMRA) 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.

10.2 To qualify for desk review GMP clearance, the manufacturing site must have been inspected by SADC (ZAZIBONA collaboration initiative), Stringent Regulatory Authorities including WHO Pre-qualification inspections for the same manufacturing block, line and dosage form.

10.3 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. BOMRA however, reserves the right to determine whether an onsite inspection would be required.

10.3 The outcome/ decision of the desk review process could be approval or recommendation for an onsite inspection.

10.4 Manufacturers are expected to send a formal request for a GMP Desk Review to BOMRA at inspections@bomra.co.bw.

11. References

a) Medicines and Related Substance Act 2013

b) Medicines and Related Substances Regulations, 2019

c) 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

12. Appendix

a) Application Form 8 - **BOMRA/IL/IL/P01/F02**

b) Declaration Form for Continuous Supervision by Pharmacist - **BOMRA/IL/IL/P01/F03**

c) GMP application form for international manufacturers - **BOMRA/IL/IL/P08/G01- F01**

d) GMP inspection reference guidelines.

Annexure - 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
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.	**Pharmacovigilance**	reportadr@bmra.co.bw
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.