Botswana Medicines Regulatory Authority

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Revision status sheet

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1. Purpose

The purpose of this guideline is to inform applicants intending to acquire licensing for manufacture of medical devices about requirements for operating a premises for manufacturing of medical devices.

2. Scope

This guideline is applicable to manufacturing of Medical Devices in line with internationally recognised Quality Management Standards or specifically ISO 13485 - Medical Devices – Quality Management System – Requirements for Regulatory purposes, The quality standards are applicable to the manufacturing of Class A, B, C and D medical devices. There may be additional requirements for Classes B, C, and D based on the level of risk posed by the device.

3. Definitions and Abbreviations

The following definitions shall apply:

3.1 Definitions

3.1.1 Authorized Manufacturer

Any entity licensed by BoMRA for the purpose of compliance with minimum requirements to conduct operations for manufacturing of medical devices and to ensure compliance with the laws and regulation in force in Botswana.

3.1.2 Intended use/ purpose

The objective intent of the manufacturer regarding the use of Medical Devices as reflected in the specifications, instructions, and information provided by the manufacturer of the medical device.

3.1.3 In Vitro diagnostic Device (IVD)

Means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimen derived from the human or animal; solely or principally to provide information for diagnostic, monitoring or compatibility purposes which includes but not limited to – reagents used for IVD purposes, calibrators, control chemicals, specimen receptacles, software and related instruments or apparatus or other articles and are used for the following test purposes;

diagnosis; aid to diagnosis; screening; monitoring; predisposition; prognosis; prediction; determination of physiological status.

Note: An accessory is not considered to be a medical device. However, where an accessory is intended specifically by its manufacturer to be used together with the 'parent' medical device to enable the medical device to achieve its intended purpose, it should be subject to the same procedures and guidance as apply to the medical device itself. Note: The definition

of a device for in vitro examination includes, for example, reagents, calibrators, sample collection devices, control materials, and related

3.1.4 Manufacturer

A company that carries out at least one step of the manufacture of a medical devices, which includes the responsible person and/or company that manufactures a medical devices with the intention of making it available for use, under his/her/its name, whether or not such device is designed and/or manufactured by that person or on behalf of that person by another person(s).

3.1.5 Manufacture (process/manufacturing)

All operations of generating a medical device, including purchase of materials and components, production, quality control, packing, labelling, release, storage, and shipment.

3.1.6 Medical device

Any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article:

a) intended by the manufacturer to be used, alone or in combination, for humans or animals for;

i. diagnosis, prevention, monitoring, treatment or alleviation of disease

ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury

iii. investigation, replacement, modification or support of the anatomy or of a physiological process

iv. supporting or sustaining life

v. control of conception

vi. disinfection of medical devices; or

vii. providing information for medical or diagnostic purpose by means of in vitro examination of specimens derived from the human body and;

b) which do not achieve its primary intended action in or on human or animal body by pharmacological, immunological or metabolic means but which may be assisted in its intended function by such means

3.1.7 Responsible Person

The RP is responsible for ensuring product manufactured is not harmful to the users and prevent potential harm arising from the methods and the materials used to produce the product.

The responsibilities also include:

a) to ensure that the provisions of the licence are observed

b) to ensure that the operations do not compromise the quality of medical devices

c) to ensure that an adequate quality system is established and maintained
d) to oversee audit of the quality system and to carry out independent audits
e) to ensure that adequate records are maintained
f) to ensure that all personnel are trained
g) to ensure that all processes and methods are validated and approved for use.
h) to ensure full and prompt cooperation with product licence holders in the event of recalls.
i) To be the liaison person with the regulatory authority on issues of compliance
j)

3.2 Abbreviations

WHO - World Health Organization
SMF - Site Master File

4 Classification of Medical Devices

4.1 Medical devices are grouped into risk classes according to their potential harm to the patient or user, the following are classes of medical devices--

a. **Class A –** Low Risk
b. **Class B –** Low Moderate Risk.
c. **Class C –** Moderate-high Risk
d. **Class D –** High Risk

4.2 Classification Scheme for In-Vitro Diagnostic Devices

a. **Class D –** Highest Risk
b. **Class C –** Moderate public health risk, but high individual risk
c. **Class B –** Low public health risk and/ or moderate individual risk
d. **Class A –** Low individual risk

4.3 All Medical devices shall be appropriately classified in accordance with classification rule as specified in Global Harmonization Task Force-GHTF/SG1/N15:2006 and International Medical Device Regulator's Forum- IMDRF/IVDWG/N64FINAL:2021

5 Application Requirements

The following documents are required to be part of the documentation that are to be submitted together with the applications forms specified in Annexure I, II, III.

5.1 Manufacturer's Information details

The manufacturer shall be required to provide information on;

a) Name of the Company

b) Trading name if applicable

c) Location of the plant or other premises where the manufacturing process will take place (provide physical address and coordinates)

Contact details (Phone Number, Postal and email address)

5.2 Responsible Person's Information Details

The Responsible Person shall apply to the authority on behalf of the Manufacturer and shall provide details on

a) Copies of identity (Omang) or Passport

b) Relevant Qualifications Copies

c) Summary of Curriculum Vitae (CV)

d) Copies of registration with a professional body

5.3 Technical documentation

Technical information about the device to be manufactured shall be provided. The information documented shall be clear, unambiguous, organised, legible and shall have details on the following

5.3.1 Device description and specification

This shall entail;

a) product or trade name and a general description of the device including its intended purpose and intended users,

b) Device classification according to Global Harmonization Task Force-GHTF/SG1/N15:2006 and International Medical Device Regulator's Forum- IMDRF/IVDWG/N64FINAL:2021

c) Device specifications

d) Indications, *contra*-indications, warnings

e) Where applicable technical agreement with any Medical Device Manufacturing entity

5.3.2 Device Risk Management Plan

There shall be a plan in place to identify and manage risk emanating from the use of the device throughout the lifecycle of the device.

5.3.3 Device Manufacturing Information

There shall be information on;

a) All the stages of the Manufacturing processes
b) Continuous process monitoring
c) Environmental Condition/Status of manufacturing area
d) Product functionality checks and testing
e) Design and Layout of manufacturing Plant and Utilities
f) Production, materials, and Personnel flow chart
g) List of Critical Equipment
h) Suppliers and Subcontractors

5.3.4 Device Labelling Information (See to section 7)

5.4 Up to date Site Master File (SMF)

This shall be required for Manufacturers applying for license renewal. (*See Section 6.3*)

6 Requirements for the manufacturing of Medical Devices

6.1 Competence

a. Competent technical person who shall be in charge of all operations shall be a graduate in a relevant branch such as Engineering, Chemistry, Pharmacy, Biomedical Engineering, Biochemistry, Biotechnology, physics, or any applicable science discipline.
b. The competent technical person shall have at least 2 year experience in the manufacturing or testing of the medical device for which application is made.
c. diploma in engineering (in relevant branch) from a recognised institute and shall have the experience of not less than four years in manufacturing or testing of medical devices.
d. Registration with a relevant professional body

6.2 Manufacturer's Site Master File

The manufacturer shall be required to create and maintain a SMF detailing the following,

a) List of products produced at the facility,
b) Organizational structure (Organogram),
c) Personnel Responsibilities and Qualifications,
d) Product Manufacturing flow chart,
e) Layout of the manufacturing plant and Utilities,
f) Equipment and Utilities used in production,
g) Quality Management System/Quality Assurance
h) Maintenance Plan.

6.3 Manufacturing Site

6.3.1 Personnel

6.3.1.1. Operations shall be done under supervision of a suitably qualified Responsible person

6.3.1.2. All personnel involved in manufacturing activities shall be trained in ISO 13485 or Good Manufacturing Practices-WHO, TRS 987

6.3.1.3. Personnel involved in the distribution activities must receive initial and continuing training on SOP'S relevant to their tasks, role or responsibilities

6.3.1.4. All personnel in the Manufacturing activities must have employment contracts or job descriptions specific to their role/ activities/responsibilities.

6.3.1.5. There should be suitably trained and adequate personnel heading the different departments of Manufacturing plant.

6.3.1.6. Change of the responsible person in charge shall be communicated to the Authority within 30 working days.

6.3.1.7. Replacement of the responsible person shall be carried out within 30 working after the last working day of the Responsible Person.

6.3.2 Layout

6.3.2.1 The premises shall have segregated areas for the Storage of materials and finished products, Receiving area, dispatch area, Production area and quality control area. The areas shall be clearly demarcated and labelled.

6.3.2.2. Measures should be taken to protect products and materials from direct sunlight, rain and extreme weather conditions labelled.

6.3.2.3. There shall be labels in the warehouse prohibiting unauthorised entry, drinking and eating.

6.3.2.4 Layout of this areas shall be documented in an approved QA document

6.3.3 Fire Safety

6.3.3.2. Fire detection and protection equipment shall be available, serviced and easily accessible in the different parts of the manufacturing plant.

6.3.3.2. A procedure for fire prevention, detection and control should be available. Staff should be trained to carry out regular fire drills. Training records shall be maintained.

6.3.3.3. Smoking shall be prohibited in all areas.

6.4 Manufacturing process

6.4.1 Components/or Material used

The Manufacture shall keep a list of the materials used to:

a. produce the medical device,
b. preserve the device,
c. package the device.

6.4.2. Qualification and Validation

Qualification and validation should establish and provide documentary evidence that:

a) the premises, supporting utilities, equipment and processes have been designed meet the requirements for use, safety, risk and performance as outlined in ISO 13485, GMP and other International recognised standards.

b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ)

c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ)

d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).

6.4.3. Documentation

The manufacture is required to have in place the following

6.4.2.1. Documents, including records, determined by the organization to be necessary to ensure the effective planning, operation, and control of its processes

6.4.2.2. Documented procedures and records of the manufacturing process from start to finish.

6.4.2.3. Documents in use that are approved, signed and dated by the appropriate responsible persons.

6.4.2.4. Quality manual detailing the scope of quality management system, documented procedures or their reference, processes interactions and documentation structure.

6.4.2.5. Other required documentation include;

a) Product design and development documents
b) Technical Documentation
c) Batch Manufacturing Record
d) In process testing records or results

e) Quality Control Results
f) Validation protocols, procedures and results
g) Risk assessment, mitigation and Monitoring documents
h) Cleaning and Pest Control Records
i) Training plan and training records
j) Measuring and Monitoring of product and processes
k) Procurement Records
l) Product instructions, labels, Packaging Information
m) Any Other documentation that is not specified in this list that is part of the manufacturing process or a requirement of an international standard.

6.5 Equipment

6.5.1. Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.
6.5.2 The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and Maintenance.
6.5.3. Production lines should be clearly labelled to indicate use and status.
6.5.4. Measuring equipment should be securely kept and should be calibrated according to a fixed schedule.
6.5.5. Laboratory equipment and instruments should be suited to the testing procedures undertaken.
6.5.6. Production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.
6.5.7. Defective equipment should be removed from manufacturing and QC areas. If this is not possible, it should be clearly labelled as defective to prevent use.
6.5.8. Current drawings of critical equipment and support systems should be maintained.
6.5.9. Equipment list and mantaince plan or schedule should be in place to enable periodic servicing.

6.6 Quality Management System

There shall be a quality management system implemented by the Manufacturer and its effectiveness maintained by the Manufacturer to ensure customer satisfaction regarding health and safety.

These shall be

a) ISO 13485- Medical Device- Quality Management Systems- Requirements for Regulatory Purposes.
b) Good Manufacturing Practices

6.7 Product Standards for Medical Devices in Botswana

(1) The medical device shall conform to the standards laid down by the Botswana Bureau of Standards (BoBS).

(2) Where no relevant Standard of any medical device has been laid down under sub rule-1, such device shall conform to the standard laid down by the International Organisation for Standardization (ISO) or the International Electro Technical Commission (IEC), or by any other pharmacopoeia standards.

(3) In case of the standards which have not been specified under sub rule-1 and -2, the device shall conform to the validated manufacturer's standards

7 Labelling and instructions

7.1 The label or Device manual shall bear the following information

a. The name or trade name of the device
b. Identification of the devices and Model Number (Where applicable)
c. Intended purpose of the device
d. Registered name, trade name or registered trademark of the authorized manufacturer and the address of its registered place of business
e. The lot number or the serial number of the device preceded by the words LOT NUMBER or SERIAL NUMBER or an equivalent symbol, as appropriate
f. The date Manufactured and the Expiry date
g. An indication of any special storage and/or handling condition applicable
h. Warnings or precautions to be taken that need to be brought to the immediate attention of the user of the device, and to any other person
i. Indication of single use or multiple uses
j. Where the information above cannot be placed on the device this may be included in the accompanying user manual/instruction

8 Packaging

8.1 Packaging shall be as follows;

a) All documents should be in English or Setswana (For Local Market)
b) For sterile devices Information on the package must indicate ('Sterile packaging')
c) Statement confirming that the packaged device is in a sterile condition
d) The sterilization Method shall be indicated (if sterile)
e) Name and address of Manufacturer
f) Device description and Model Number (Where applicable)

g) Intended Use, intended users and contra-indications
h) The month and year of Manufacturing
i) Instructions to check what to do if the sterile packaging is damaged or unintentionally opened before use (Where applicable)

9 Complaints

9.1 All complaints and other information concerning potentially defective devices should be carefully reviewed according to written procedures and the corrective action should be taken.
9.2 If the Responsible person is not responsible for handling complaints they should be made aware of any complaint, investigation or recall.
9.3 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

10 Device Recalls

10.2 There should be a system in place to enable device recall from the market, promptly and effectively, devices known or suspected to be defective.
10.2 The Responsible person should be responsible for the execution and coordination of recalls. He or she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.
10.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any prompt recall activity down to the required level in the distribution chain.
10.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.
10.5 In case of an Intention to recall, all competent authorities of all countries to which the medical device has been distributed should be promptly informed.
10.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers.

11 Post licensure notifications

Post licensure changes to the processes and structure of the facility shall be made by the person representing the company to the Authority of any post licensure notifications. These shall not be made 3 months prior to license expiry (Application for license renewal shall be made in that case).

11.1 Changes in respect of following shall be considered as major changes

a. material of construction.

b. design which shall affect quality in respect of its specifications, indication for use; performance and stability of the medical device.

b. the intended use or indication for use.

d. the method of sterilization.

e. the approved Shelf life.

f. the name or address of

(i) the domestic manufacturer or its manufacturing site

(ii) overseas manufacturer or its manufacturing site

g. label excluding change in font size, font type, colour, label design

h. manufacturing process, equipment or testing which shall affect quality of the device

i. primary packaging material.

11.2 Changes in respect of following shall be considered as minor change;

1. design which shall not affect quality in respect of its specifications, indication for use, performance and stability of the medical device

2. in the manufacturing Process, equipment, or testing which shall not affect quality of the device

3. packaging specifications excluding primary packaging material

12 Processing of Application

12.1 Application shall be submitted in Form 8 along with other required documents (see cl. 8.8 below). Upon receiving the application, BoMRA shall assess it to verify whether all the requirements have been fulfilled.

12.2 If the application meets the prescribed requirements, the authority shall proceed to carry out an inspection of the manufacturing plant.

12.3 An application will be rejected if it does not meet the minimum requirements for manufacturing operations. The applicant shall receive an inspection report outlining reasons for not awarding a license. (See Annexure 2)

12.4 New operations shall be inspected within forty five (45) working days after submission of an application, the applicant shall be notified of date and time prior to inspection.

12.5 License renewal shall be inspected within fifteen (15) working days after date of application.

12.6 Application for renewal of existing license shall be submitted three (3) months prior to license expiry.

12.6 Applications for prospective medical device manufacturer licence and license renewal shall be addressed to the Chief Executive Officer, BoMRA.

12.7 The applicant shall fill and submit Form 8 (annexure 1), together with Document Checklist (Annexure 2) and the Declaration Form (Annexure 3). The submitted documents shall be checked for confirmation by the officer responsible, stamped and copy of acknowledgement given to the applicant

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

13. Release of Customer Information

13.1 BOMRA Inspections and licensing department holds the information relating to customers in strict confidence as the terms and conditions of services provided. Except for information that the customer places in the public domain or when agreed between the Inspectorate and the customer, all other information is considered proprietary information and shall be regarded as confidential.

13.2 The inspection body shall seek authorization and clearance from the Chief Executive Officer, before any customer information is placed in the public domain or shared with a third party.

13.3 The inspection body shall notify the customer in advance, unless prohibited by law, when the inspection body is required, by law or authorized by contractual arrangements, to release confidential customer information.

13.4 Information about the customer obtained from other sources other than the customer (e.g. complainant), shall remain confidential between the inspection body and the customer. Identity of the source can only be shared with the customer if the source has agreed to it in writing.

13.5 The following information about the customer shall be shared through BoMRA public domains

1. Company Name (licensee and business name)
2. License number
3. Business address (physical address)
4. Type of business (authorized activity)

5. Premises contact details (email, telephone line)
6. RP Name
7. License validity

14 Inspection of Manufacturing Premises

14.1 Objectives for carrying out an Inspection/audit

a. The overall intent of the manufacturing site inspection is to assess the safety, performance and quality of commercially available medical devices including IVDs.

b. The specific objectives of this process are to assess compliance of the manufacturer's quality management system and manufacturing practices with international standards to:

i. determine the effectiveness of the implemented quality management system in meeting appropriate quality standards,
ii. verify the data supporting the claims presented in the submitted pre-submission form and product dossier,
iii. inspect the quality management system according to the manufacturer's own requirements.

14.2 Stages of Inspections/Audit

a. Desk inspection/audit (Stage 1)

i. These is the first assessment of the documents related to the quality management system to establish the readiness for the on-site inspection, and to determine the scope and objectives of the on-site inspection. **(See 5.1-5.4)**
ii. Any issues of concern or clarifications required will be communicated to the manufacturer.
iii. When the desk assessment is complete, proposed inspection date will be communicated.

b. On-site inspection (Stage 2)

a. These Stage is the inspection of the premises where manufacturing will take place. It evaluates the effective implementation of the quality management system and implemented production processes through an on-site(s) inspection.
b. A preliminary report detailing Non-Conformities (if any) will be provided on the final day of the inspection.
c. A final inspection report including the classified nonconformities will be issued after the inspection.

14.3 Special Inspection

A special inspection may be required when,

a) Effective implementation of corrective actions to prevent the recurrence of nonconformities needs to be verified in a follow-up inspection

b) substantial changes are made to the medical device design, composition, safety and/or performance,

c) serious concerns have been raised about the ongoing quality of the medical device

d) production has been suspended and then recommenced; and/or

e) there is a significant change in the quality management system

14.4 Inspection carried out by Conformity Bodies

a). Conformity Assessment Bodies

These are competent bodies accredited to carry out audit of manufacturing sites of medical devices to verify conformance with the Quality Management System and other applicable standards. These bodies can be mandated by the regulatory Authority to carry inspection of medical device manufacturing sites as specified under the regulations,

The conformity Assessment body shall;

(i) impart training to its staff covering all the evaluation and verification operations for which the Confirmation assessment body has been designated.

(ii) ensure that staff has adequate knowledge and experience of the requirement of the control.

(iii) carry out the evaluation and verification operations with the highest degree of professional integrity independently with technical competence.

(iv) ensure that manufacturing site and products comply with prescribed standards referred in regulation.

(v) not provide training or consultancy to the manufacturers whose site is being audited.

(vi) ensure that their auditors possess required qualification and expertise in the relevant field for carrying out assessments of manufacturing site and medical device that they are undertaking.

(vii) establish and maintain procedure and record which demonstrate its compliance with quality management system.

14.5 Inspection by Expert Consultant

The authority may engage the expertise of a technically competent person to participate in the inspection of a medical device Manufacturer. In this capacity the technical expert may assume the role of lead inspector or Co-inspector and is expected to act in a manner and responsibilities equal to that of the authority's inspectors.

14.6 Responsibilities of the manufacturer

Responsibilities of the manufacturer will be communicated prior to the inspection among other things, the manufacturer's responsibilities will be to;

a. Agree the objectives of the scope of the inspection with the Authority team.

b. Inform the Authority team of any issues that may affect an effective and efficient inspection process,

c. Cooperate with the inspectors to ensure that the objectives of the inspection are achieved,

d. Avail the responsible person for coordinating and facilitating, on behalf of the manufacturer, the inspection process,

e. Inform relevant employees and personnel about the objectives and the scope of the inspection,

f. Appoint responsible members of staff to accompany members of the inspection team,

g. Ensure inspectors are aware of health, safety and other applicable requirements,

h. Provide on-site resources, such as a meeting room, for the inspection team in order to ensure an effective and efficient inspection process,

i. Provides full access to the manufacturing facilities, documents and records and other evidence as requested by the inspectors in a timely manner to ensure an effective and efficient inspection process and so that the inspection timetable can be met.

j. Implement corrective and preventive actions against raised non-conformities within 60 working days of receipt of final inspection plan

k. Address all the corrective and preventive actions within two report submissions to the Authority.

15 References

a. WHO: Regional Publication, Eastern Mediterranean Series – Regulation of Medical Devices, A Step by Step Guide

b. WHO: Medical Device Regulation, Global Overview and Guiding Principles

c. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices

d. Technical report Series 986, Annexure 2 - WHO good manufacturing practices for pharmaceutical products: main principles1

e. ISO 13485 - Medical Devices – Quality Management System – Requirements for Regulatory purposes