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THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR QUALITY AUDIT OF MEDICAL DEVICES AND DIAGNOSTICS MANUFACTURING SITES

(*Made under Section 51(c) of The Tanzania Medicine and Medical Devices Act, Cap 219.*

First Edition
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Contents

Abbreviations

CRP	-	Collaborative Registration Procedure
DHF	-	Device History File
DMC	-	Directorate of Human and Veterinary Medicines Control
GHTF	-	Global Harmonization Task Force
GMDN	-	Global Medical Devices Nomenclature
GMP	-	Good Manufacturing Practices
IMDRF	-	International Medical Devices Regulators Forum
ISO	-	International Organization for Standardization
OOS	-	Out -Of -Specification
QC	-	Quality Control
QMS	-	Quality Management System
SMF	-	Site Master File
SRA	-	Stringent Regulatory Authority
TGA	-	Therapeutic Goods Administration
TMDA	-	Tanzania Medicines and Medical Devices Authority
TRC	-	Tracking Number
USFDA	-	United States Food and Drug Administration
WHO	-	World Health Organization
WHO-PQ	-	WHO- Prequalification

Acknowledgements

These guidelines have been developed to outline requirements for the submission of applications for quality audit of medical devices and diagnostics manufacturing facilities. The input contribution to the guidelines was based on experience and knowledge on medical devices quality audit activities carried out by our able auditors and inspectors, available literature and existing international guidelines from Therapeutic Goods Administration, Australia (TGA), United States Food and Drug Administration (USFDA), World Health Organization (WHO) and International Medical Devices Regulators Forum (IMDRF).

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Kissa W. Mwamwitwa
Director, Medical Devices and Diagnostics Control

Foreword

Tanzania Medicines and Medical Devices Authority (TMDA) was established under the Tanzania Medicines and Medical Devices Act, Cap 219 with a mission to protect and promote public health by ensuring quality, safety and effectiveness of medicines, medical devices, diagnostics and other health related products. TMDA grants marketing authorization for products after evaluation for conformance to standards of quality, safety, and performance and upon verification that the manufacturing facility conforms to good manufacturing practice (GMP) requirements.

A quality audit is therefore the act of conducting an official review of documents, records, production practices, and any other resources of a particular medical device manufacturing site as part of the registration assessment of medical devices. The aim is to assess their conformity to the requirements according to relevant standards and the TMDA Control of Medical Devices Regulations. The overall objective of conducting a quality audit is to ensure that medical devices are consistently produced and controlled to the quality standards appropriate to their intended use and as required by TMDA.

Quality audit targets to assess and ascertain the manufacturing facility level of compliance to the set minimum standards as provided in the current ISO 13485 standards for manufacturing of medical devices. These guidelines have been prepared to guide the applicants to ensure that all relevant information is provided when preparing and submitting applications for quality audit to TMDA.

All applicants are therefore urged to familiarize with these guidelines and follow them when preparing and submitting applications for quality audit of their manufacturing facilities. Adherence to these guidelines will ensure that all relevant information for quality audit is provided in the submitted applications. Applicants are also requested to read the guidelines together with the Tanzania Medicines and Medical Devices Act, Cap 219, and Regulations made thereunder. This will facilitate efficient and effective assessments as well as approval of marketing authorization to the products intended to be marketed in Tanzania.

It is anticipated that these guidelines will continue to be revised regularly in response to the experiences gathered from their utilization. Applicants as well as other stakeholders are encouraged to provide comments and views at any time for improvement and updating of these guidelines.

Adam M. Fimbo
Director General

1. Definition of Terms

The definitions given below apply to the terms used in these guidelines. They may have different meaning in other contexts.

Act:
Means the Tanzania Medicines and Medical Devices Act, Cap 219.

Authority:
Means the Tanzania Medicines and Medical Devices Authority, or the acronym "TMDA" established under section 4(1) of the Act.

Applicant:
Means any person or institution or company that applies for marketing authorization of a medical device or a diagnostic in Tanzania.

Audit
Means systematic independent and documented process for obtaining objective evidence and evaluating it objectively to determine the extent to which the audit criteria is fulfilled.

Audit criteria
Means a set of requirements used as a reference against which objective evidence is compared.

Audit evidence
Means record, statement of fact or other information, which is relevant to the audit criteria and verifiable.

Batch (or lot):
Means a defined quantity of starting material, packaging material or product manufactured in a single process or series of processes so that it is expected to be homogeneous. A batch/lot must be manufactured at essentially the same time, using the same process, same specification of raw materials, common equipment, and be packed in the same type of individual container, using the same packaging materials.

Certified Copy
Means a true copy of the original document certified by a person registered to practice law in the manufacturer's country of origin and endorsed with the practitioner's official stamp and signature.

Corrective Action
Means action to eliminate the cause of a potential non-conformity or other undesirable situation. Corrective action is taken to prevent recurrence.

Desk assessment
Means an evaluation of prior documentary evidence by a competent regulatory authority recognized by the national regulatory authority for compliance to the required standard in support of marketing authorization;

Good Manufacturing Practice
Means the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate for the intended use and as required by the marketing authorization.

In Vitro diagnostics
Means a device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles.

Manufacture
Means all operations involved in the designing, development, production, preparation, processing, compounding, formulating, filling, refining, transformation, refurbishing, packing, packaging, re- packaging and labeling of medical device sand in vitro diagnostic devices.

Manufacturer
Means any natural or legal person with responsibility for manufacture of a medical device and/or in vitro diagnostic devices with the intention of making it available for use, under his name; whether or not such a medical device or in vitro diagnostic devices is designed and/or manufactured by that person himself or on his behalf by another person (s).

Medical Device or Devices
Means an instrument, apparatus, implement, medical equipment, machine, contrivance, implant, in vitro reagent or other similar or related article, including any component, part or accessory, which is: -

a) Recognized in the official National Formulary, or Pharmacopoeia or any supplement to them;

b) Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals; or

c) Intended to affect the structure or any functions of the body of man or other animals and which does not achieve any of its principal intended purposes through chemical action within the body of man or other animals and which is not depended upon being metabolized for the achievement of any of its principle intended purposes.

Medical device's dossier

Means a file that contains detailed information on the device description, designing, manufacturing, quality control and biomedical studies that demonstrates quality, safety and performance of the finished medical devices.

Non-Conformances

Means non-fulfillment of a requirement. Other terms may be used to mean the same as non-conformity (e.g., non-compliance, deficiency)

Notified body

Means an organization designated by European Union country to assess the conformity of medical devices and diagnostics before being placed on the market. The list of notified bodies is published by the European Commission.

Primary Package

Means the package that comes into direct contact with the medical device, it acts as a barrier that protects the product from the external surroundings. Also knows as immediate container.

Process Validation

Means confirmation by objective evidence that a process consistently produces a result or product meeting its pre-determined requirements.

Quality System

Means a system which consists of the organizational structure, responsibilities, procedures, processes and resources for implementing quality management and achieving the objectives.

Quality Management System
Means a management system to direct and control an organization with regard to quality, from establishing quality policy, quality objectives and implementing and maintaining Quality system.

Regulations
Means the Tanzania Medicines and Medical Devices (Control of Medical Devices) Regulations.

Repacking
This is the process of assembly of medical device or in-vitro diagnostic device from its original packing into another packaging, without breach of the primary packaging, before the medical device is sold or supplied.

Risk
Means the possibility of occurrence, and severity of damage, loss or any other undesirable event.

Risk assessment
Means identifying and characterizing the nature, and frequency of the risks associated with the use of a product conducted throughout the product's lifecycle, from the early identification of a product as a candidate, through the pre-marketing development process, and after marketing.

Risk Management
Means systematic application of policies, procedures, and practices to the analysis, evaluation and control of risks.

Site master file (SMF)
Means a document containing specific information about the manufacturing premises and information about the production and/or control of manufacturing process undertaken on the site and is usually prepared by the manufacturer. Its purpose is to provide the auditor with an introduction to the company and its activities prior to the commencement of the inspection and to demonstrate that the site is ready for the inspection.

Specification

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

Validation Master Plan (VMP)
Means a high-level document which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

2. Introduction

These "*Guidelines on Submission of Documentation for Quality Audit of Medical Devices and Diagnostics Manufacturing Sites, First Edition, July 2022"* is the TMDA publication which sets out procedures and requirements to be followed by applicants when preparing and submitting applications for quality audit as part of the marketing authorization process. It aims at providing detailed submission requirements which need to be met when applying for audit of the manufacturing sites. The guidelines also provide for risk-based approach to be considered when assessing the respective manufacturing sites and provide for documentation requirements based on the assigned risk.

Medical devices including diagnostics are prepared and manufactured from the facilities which have different settings. These guidelines brought forth general requirements that apply to most of the medical devices' and diagnostics' manufacturers. However, some of the requirements may strongly apply to some manufacturers and less to others, but nevertheless the manufacturers should include in the submission of their applications all critical information which is not stated in these guidelines but which is applicable to the manufacturing and quality control.

The conditions for marketing authorization include documented evidence that the medical device is safe with good performance, the premises and manufacturing operations comply with the current good manufacturing practices as laid down in the current ISO 13485 standards or any other requirements as may be prescribed by the Authority.

Quality System audit is part of quality assurance which ensures that medical devices are consistently produced and controlled to the quality standards appropriate for the intended use. The quality system requirements are directed primarily to minimize the risks inherent in any medical devices that cannot be prevented completely through the testing of final products.

Approval of production of medical devices will be based on fulfillment of the requirements prescribed in these guidelines. In addition, the requirements set forth in these guidelines should be considered as minimum and they are not meant to replace other regulatory controls, but rather to complement or supplement them.

3. Submission Requirements

These guidelines describe submission requirements for quality audit applications as well as general and specific guidance to the applicants who intend to market medical devices and in-vitro diagnostics in Tanzania Mainland. The manufacturing site shall comply with the quality management system requirements set forth in the current ISO 13485 standard and TMDA Control of Medical Devices Regulations.

3.1. Submission of Quality Audit Applications

3.1.1. Before quality audit applications are considered, the applicant must have submitted a dossier for registration of the product.

3.1.2. The application for quality audit should include submission of:

a. Current Site Master File (SMF) which has been compiled in accordance to TMDA template of site master file number TMDA/DMD/MDL/T/001.
b. Quality Manual of the manufacturing site.
c. All supporting documents stipulated in these guidelines.
d. A non-refundable Quality audit fees as stipulated in Fees and Charges Regulations in force.

3.1.3. All documents should be in/or translated into English and uploaded electronically to the TMDA Regulatory Information Management System (RIMS).

3.2. Formatting Instructions for Supporting Data

Information and data should be organized for ease of reference (e.g., in a folder hierarchy, bookmarks in PDF document), and a table of contents should be provided. A cover letter that details all correspondence held with the TMDA regarding the application should also be provided.

All supporting data and documents must be provided in a readable electronic format:

3.2.1. Data and documents should be provided in PDF format as individual files (i.e. not joined together in a single PDF file).

3.2.2. The data provided must be searchable (either by generating the documents electronically and converting to PDF format, or by scanning in documents using optical character of recognition (OCR).

3.2.3. Due to archiving and storage requirements, data submitted on USB storage media (or other electronic media such as hard-drives) shall not be accepted.

3.3. Format and Contents of Site Master File

The applicant should submit a duly signed current Site Master File (SMF) of the manufacturing site containing specific and factual information about the production and/or control of manufacturing processes carried out at manufacturing premises. The SMF is a controlled document, it should have an edition number, the date it becomes effective and the date by which it has to be reviewed. Content and arrangement of the SMF should adhere to the template provided in Annex I.

4. General Requirements

4.1. Personnel Management

4.1.1. The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of medical devices rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly understood by the individuals concerned and recorded.

4.1.2. The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

4.1.3. The manufacturer must have an organization chart. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of Quality in the facility.

4.1.4. All personnel should be aware of the principles of Quality Management System that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

4.1.5. Key personnel should be competent and have sufficient knowledge in the particular area and relevant to scope of operation and type of products manufactured.

4.1.6. Key personnel include the head of production, the head of the quality unit; the head of Quality Assurance, Management Representative, the head of quality control, and the authorized person(s) should be well qualified for the devices produced by the manufacturer. Normally, key posts should have the job description, appointment letter and should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated. Responsibilities of Key personnel should be documented and recorded.

4.1.7. The manufacturer should provide training in accordance with a written programme for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

4.1.8. Consultants and contract staff should be qualified for the services they provide. Evidence of this should be included in the training or other relevant records.

4.1.9. All personnel, prior or and during employment, as appropriate, should undergo health examinations that is relevant to the operations they are involved into and risk of the product. Personnel conducting visual inspections should also undergo periodic eye examinations.

4.2. Documentation and Records

Good documentation constitutes an essential part of the quality assurance system. The company should provide information on its policy related to control of document and documented information. The policy should include description of documentation system (i.e., electronic or manual); and when documents and records are stored or archived off-site (including vigilance data, when applicable): list of types of documents/ records; name and address of storage site; and an estimate of time required to retrieve documents from the off-site archive.

Documents should be designed, prepared, reviewed, approved, signed, dated by appropriate authorized persons and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

4.2.1. Documents should contain unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents

from master documents must not allow any error to be introduced through the reproduction process**.**

4.2.2. Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specified period of time.

4.2.3. Where documents require the entry of data, these entries should be clear, legible, and indelible. Sufficient space should be provided for such entries.

4.2.4. Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.2.5. Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of devices are traceable. Records and associated standard operating procedures should be retained for at least one year after the expiry date of the finished product.

4.2.6. Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked.

4.2.7. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked.

4.2.8. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

4.3. Authorized manufacturing activities

4.3.1. Indicate whether the site has been approved by the competent National Authority, or it has undergone a successful audit by a foreign NRA.

4.3.2. Quote the relevant document (license) as issued by the Competent Authority. State the period of validity of license/certificate document

(if the validity of the document is given in the country concerned). Any conditions and/or restrictions should be stated.

4.3.3. Information about the use of outside administrative or other technical assistance in relation to the operation should be provided.

4.4. Quality management

Short description of the quality management system of the company should be provided including;

4.4.1. Company's Quality Policy.

4.4.2. Responsibility of the Quality Assurance function.

4.4.3. Elements of the Quality Assurance system e.g., organizational structure, responsibilities, procedures, processes.

4.4.4. Audit programme (self-inspection or audits by external organizations undertaken).

4.4.5. How results are reviewed to demonstrate the adequacy of the quality system in relation to the objective i.e., quality, efficacy and safety of the product.

4.4.6. Records if the company has been certified to industry standards (e.g., ISO9000, ISO13485).

4.4.7. Brief description of quality risk management (QRM) policy implemented by the company.

4.5. Premises and equipment

4.5.1. Premises

Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of product.

4.5.1.1. Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products. Plan/layout or description of manufacturing areas with indication of scale should be provided.

4.5.1.2. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures and records should be maintained.

4.5.1.3. Electrical supply, lighting, temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the products during their manufacture and storage, or the accurate functioning of equipment.

4.5.1.4. Premises should be designed and equipped so as to provide maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

4.5.1.5. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations, materials flow, personnel movement and to the requisite cleanliness levels

4.5.1.6. Pipe work, light fittings, ventilation points, and other services should be designed and to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

4.5.1.7. Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary, they should be shallow to facilitate cleaning and disinfection.

4.5.1.8. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: raw and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned, or recalled products.

4.5.1.9. Where special storage conditions are required (e.g., temperature, humidity) these should be provided. The conditions should be controlled, monitored and records maintained.

4.5.1.10. Segregation should be provided for the storage of quarantined, approved, rejected, recalled, or returned materials or products.

4.5.1.11. Printed packaging materials are considered critical to the conformity to its labeling, and special attention should be paid to sampling, the safe and secure storage of these materials

4.5.1.12. Quality control laboratories should be separated from production areas. Areas where biological or microbiological test methods are employed should be separated from each other

4.5.1.13. Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), and records.

4.5.1.14. A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture, and other external factors, or where it is necessary to isolate the instrument

4.6. Equipment

The layout, design and location of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

4.6.1. Manufacturing equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

4.6.2. Repairs and maintenance operations should not present any hazard to the quality of the products.

4.6.3. Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in clean and dry condition.

4.6.4. Non-dedicated equipment should be cleaned according to validated cleaning procedures between productions of different devices to avoid cross contamination.

4.6.5. Cleaning and drying equipment should be chosen and used so as not to be a source of contamination’

4.6.6. Equipment should be installed in such a way as to minimize any risk of error or of contamination

4.6.7. Production equipment should not present any hazard to the products. The parts of the 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.

4.6.8. Current drawings of critical equipment and support systems should be maintained.

4.6.9. Fixed pipework should be clearly labeled to indicate the contents and, where applicable, the direction of flow

4.6.10. All service piping's and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

4.6.11. Water pipes should be sanitized, according to written procedures that detail the action limits for microbial contamination and the measures to be taken.

4.6.12. Control-laboratory equipment and instruments should be suited to the testing procedures undertaken.

4.6.13. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

4.7. Production

Master Production Documents including device master record, Handling of materials, Handling of Rejected Materials and products, Process Validation should be put in place and records should be retained.

4.8. Quality control

Description of the Quality Control (QC) activities carried out on the site in terms of physical, chemical, microbiological and biological testing should be provided. Details should be provided on any QC services obtained from external testing facilities

4.9. Contract manufacturing and analysis (if any)

Brief description and list of any contract manufacturing and analysis should be provided.

4.10. Distribution, complaints and product recalls

Brief description of the system for distribution, handling complaints, product defects and recalls.

4.11. Self – inspection/ internal audit

Short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

4.12. Heating, Ventilation and Air-Conditioning (HVAC) Systems (If applicable)

HVAC systems are essential to maintaining a controlled environment in cleanrooms. They help regulate humidity, temperature, and pressure, as well as control airflow and ensure the environment remains contaminant free.

4.12.1. Key objectives to be achieved by the HVAC systems;

4.12.1.1. Mechanical services that deliver the anticipated levels of comfort and functionality.
4.12.1.2. A zero-tolerance approach to patient safety and infection control.
4.12.1.3. Compliance with the applicable codes and standards.
4.12.1.4. Appropriate pressure differentials between adjacent spaces and departments in clinical facilities.
4.12.1.5. Adherence to air changes per hour requirements as per code.
4.12.1.6. Reliable operation at the extreme outside design temperatures.
4.12.1.7. Reducing operating and maintenance costs shall be a key component in all new constructions.
4.12.1.8. Flexibility for future modification and expansion.
4.12.1.9. An appropriate level of consistency across facilities, recognizing the specific demands of each facility.

4.12.2. Maintenance

4.12.2.1. There should be a planned preventive maintenance programme, procedures and records for the HVAC system. Records should be kept.
4.12.2.2. There should be appropriate training for maintenance personnel.
4.12.2.3. Filters should be changed only by specialists or trained personnel.
4.12.2.4. Any maintenance activity should be critically assessed to determine any impact on product quality including possible contamination.
4.12.2.5. Maintenance activities should normally be scheduled to take place outside of production hours, and any system stoppage should be assessed with a view to possible re-qualification of

an area that may be required as a result of an interruption of the service.

4.13. Water Treatment (If applicable)

The following should be considered in the water treatment:

4.13.1. Water treatment systems should be designed, constructed, installed, maintained and adapted to ensure a consistently reliable production of water of an appropriate quality;

4.13.2. Water treatment system components, equipment, control and measuring instruments should be tagged;

4.13.3. Pipelines, valves, monitoring and measuring instruments should be marked and labelled and the direction of flow should be indicated;

4.13.4. All measuring instruments should be calibrated and the calibration recorded. It is recommended that the individual instruments be labelled as proof of calibration (date of calibration, done by, due date for calibration) where possible;

4.13.5. All water treatment systems components, including stills, should be subject to routine and planned maintenance, validation and monitoring;

4.13.6. All maintenance, validation and monitoring operations should be documented;

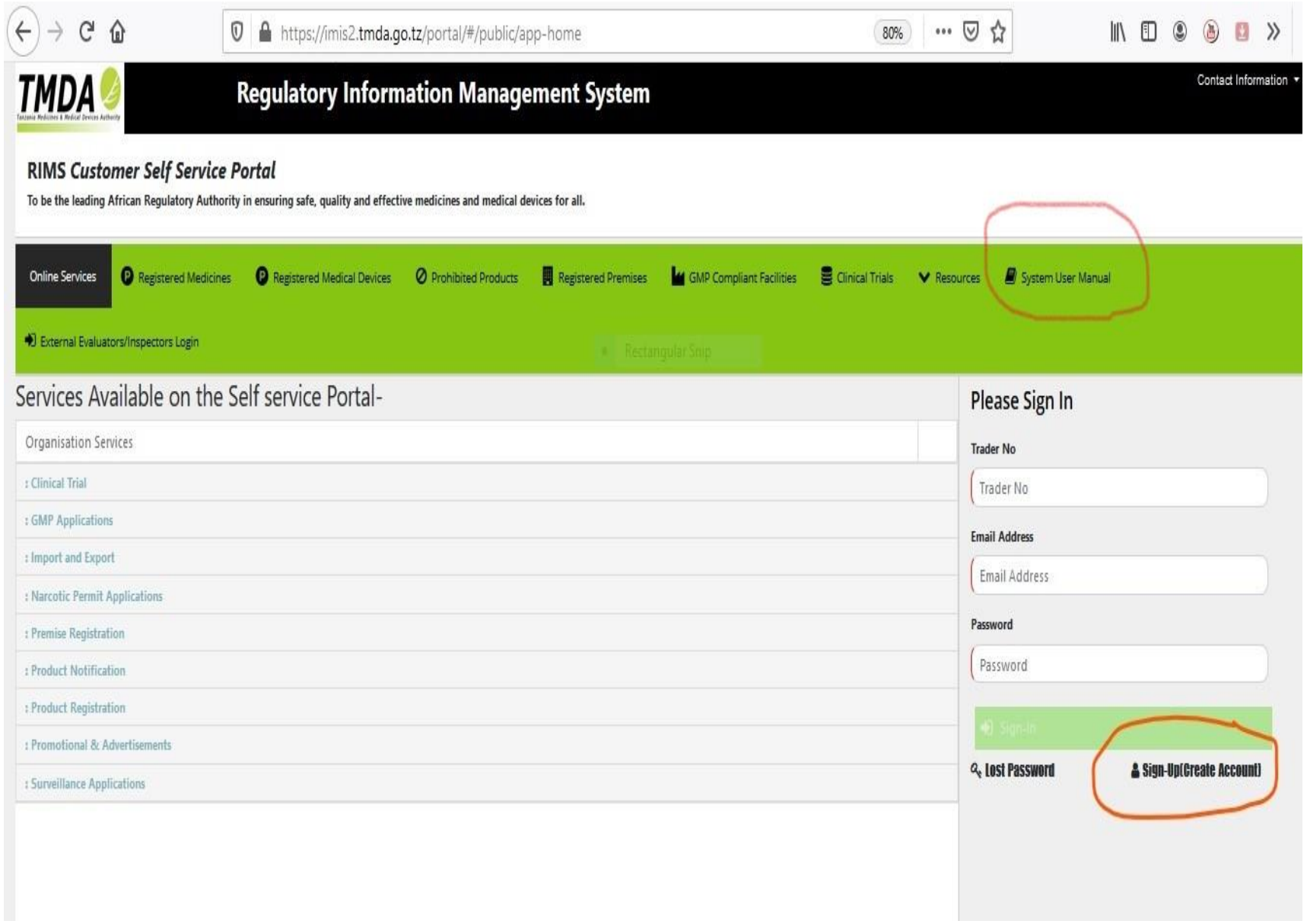
4.13.7. The manufacturer should monitor all components of the water treatment system and processing stages to ensure that water complies with the required specification;

4.13.8. Water sources, treatment procedures, water treatment system efficiency, treated water quality for production, and microbiological or contamination with endotoxins monitoring results should be within limits in accordance with the specification and

5. Application Procedures

STEP 1: Create an Account/ sign up

Before making an application, the applicant must hold an account in the TMDA online portal *rims2.tmda.go.tz/portal*. The RIMS account provides applicant with an integrated point of entry to TMDA Online Services. The primary objective of TMDA -RIMS is to provide clients with the ability of viewing and managing their entire web-based application activity with the TMDA from a single user portal. Applicant can create an account by signing up as shown below;


https://imis2.tmda.go.tz/portal/#/public/app-home
80%
TMDA
Regulatory Information Management System
Contact Information
RIMS Customer Self Service Portal
To be the leading African Regulatory Authority in ensuring safe, quality and effective medicines and medical devices for all.
Online Services
Registered Medicines
Registered Medical Devices
Prohibited Products
Registered Premises
GMP Compliant Facilities
Clinical Trials
Resources
System User Manual
External Evaluators/Inspectors Login
Services Available on the Self service Portal-
Organisation Services
: Clinical Trial
: GMP Applications
: Import and Export
: Narcotic Permit Applications
: Premise Registration
: Product Notification
: Product Registration
: Promotional & Advertisements
: Surveillance Applications
Please Sign In
Trader No
Trader No
Email Address
Email Address
Password
Password
Sign-In
Lost Password
Sign-Up(Create Account)

STEP 2: Lodge an application

Once the applicant has gained access to RIMS, with guidance from the system user manual shown on the screen print above, applicant shall be able to obtain instructions on how to lodge an electronic application for quality audit.

STEP 3: Submission of Application

After successful lodging and submission of application an invoice will be generated and the application will be assigned a tracking number (format TRC-WEB00YY/M/O/, e.g., TRC-WEB0020/M/O/). All documents and correspondence regarding the application should reference the assigned tracking number.

6. Processing Of Applications

6.1. Once the confirmation of payment is received through RIMS system, the Authority shall process the application as per the time frame set out in TMDA Client Service Charter.

6.2. After preliminary review of the application in detail, in case of missing information queries will be sent through the applicant's online portal account.

6.3. The application shall not be processed until all queries raised are appropriately addressed.

6.4. The manufacturer shall be notified in advance that an audit is to be conducted.

6.5. There shall be a quality audit plan which shall be communicated to and agreed with the manufacturer two weeks before inspection.

7. Conduct of the Audit

7.1. General Requirement

7.1.1. The authority shall plan for and conduct quality audit to verify compliance of the facility with good manufacturing practices requirements as laid down in ISO 13485 quality management system standard. The quality audit referred under this guideline shall apply to facilities manufacturing medical devices and diagnostics categorized as class C, D, and class A, B invasive and/or sterile products. Quality audits for manufacturers of class A and class B products may be conducted depending on the risk of the product(s) and as established during assessment of marketing authorization applications.

7.1.2. The submitted quality audit application and its accompanying documents shall be evaluated and risk assessment shall be done. Outcome of preliminary assessment and risk category shall be used in deciding on the scope of the audit, number and qualification of auditors and number of days required for audit. Based on the perceived risk, the Authority may also establish if the site requires on site audit or it can be assessed by desk review mechanism.

7.2. DESK REVIEW

7.2.1. Desk Review Mechanism Criteria

Desk assessment process involves submission of current, accurate and authentic documentary evidence by applicant/manufacturer to the Authority to demonstrate the conformity of all processes involved in manufacturing of medical devices and diagnostics with regulatory requirements and GMP.

The following criteria shall be considered for facilities to be subjected for Desk assessment

7.2.1.1. Located and audited in the original founding member states of Global Harmonization Task Force (GHTF) (later changed to International Medical Device Regulators Forum (IMDRF) countries i.e., Australia, Canada, Japan, European Union and United States of America.

7.2.1.2. Located and audited by members of IMDRF excluding China, Brazil and Russia or as may be updated from time to time

7.2.1.3. Other sites as established through quality risk management

7.2.1.4. Manufacturing sites audited and approved by World Health Organization (WHO) under prequalification program, MDSAP (excluding Brazil and China), EMA and any other regional harmonization initiatives recognized by Authority

7.2.1.5. Any reason (s) of public interest

7.2.2. Documentary evidence required

If desk review is considered, the applicant shall be required to submit the following additional documents in order to facilitate thorough/detailed assessments of status of the manufacturing site;

7.2.2.1. Certified Copy of appropriate certificate of compliance to ISO 13485 issued by Stringent Regulatory Authority (SRA)/Notified Body/WHO together with a certified translation attached if not in English

7.2.2.2. A copy of valid of manufacturing license issued by the national regulatory Authority

7.2.2.3. List of all regulatory authorities that carried out onsite quality audit in the last three years.

7.2.2.4. Notarized copy of audit report (s) from the SRA, Notified Body, MDSAP, any other regional harmonization initiatives and/or that from WHO prequalification program carried out within the past three years

7.2.2.5. Annual product quality review reports. For single use devices ideally a report for 25 batches manufactured in the last 36 months or 10 batches manufactured in the last 12 months should be provided.

7.2.2.6. A copy of validation master plan

7.2.2.7. Process validation report for one of the devices intended to be registered in Tanzania

7.2.2.8. A copy of medical devices file for each type and model of the device intended for marketing authorization.

7.2.2.9. Report on validation of sterilization method (where applicable)

7.2.2.10. Report on qualification, maintenance and calibration of critical production and quality control equipment relevant the devices applied for marketing authorization.

7.2.2.11. Device master record and a copy of executed production document of one recent batch of devices applied for registration.

7.2.2.12. Summary report of internal audits for the last three years.

7.2.2.13. Risk management framework of the company.

7.2.2.14. Vendor qualification procedure and reports for critical raw materials used for devices for registration

7.2.2.15. Procedures for handling Out-of-specifications (OOS) including reports of at least three OOS.

8. Grading of Non-Conformances

Non conformances observed during quality audit shall be classified as critical, major and minor.

8.1. Critical non-conformances are failure of the quality system that would result into significant effect on safety and performance of the medical device such that it would have adverse effects to the consumer. (Examples of non-conformances have been attached in Appendix II)

8.2. Major non-conformances are failure of the quality management system with no impact on quality, safety and performance of the medical device and that would result into reduced usability of the medical device without causing harm to the consumer. (Examples of non-conformances have been attached in Appendix II)

8.3. Minor non-conformances which are failure of the quality system that have low probability of affecting the quality or usability of the medical device.

These are examples for guiding purposes and they are not exhaustive. They will be updated from time to time and classification will be based on the site under the audit and products intended to be registered (Examples of non-conformances have been attached in Appendix II)

9. Outcome of the audit

9.1. Facilities observed to have critical non conformances, shall be required to rectify non conformances and apply for re-audit in accordance to established guidelines and procedures.

9.2. Facilities observed to have major non conformances shall be required to rectify the non-conformances and submit compliance report containing corrections made and corrective actions proposed on the outcome of the audit within time specified by the Authority.

9.3. For facilities assessed via desk review procedure and bases on submitted documentation, if critical or major non conformances are speculated, on site audit shall be planned. In case of major or minor non conformances, applicants shall be required to respond to the raised queries by submitting a report on corrections made and corrective actions proposed before conformance of the manufacturing site can be considered.

9.4. Upon fulfilling the quality audit requirements, the authority shall issue a quality audit certificate which shall be valid for three years. The certificate shall be subjected to renewal upon submission of application for renewal in line with the established procedures.

10. Annexes

10.1. Annex I: Format and Contents of Site Master File

10.2. Annex II: Examples of Non-Conformances and Their Classification

The manufacturer shall submit the duly signed information pertaining to Manufacturing premises in the following format. It is expected that the information submitted in the form of hard copy shall also be submitted in the form of electronic copy. The applicant shall submit a succinct document in the Form of "Site Master File" containing specific and factual information about the production and/or control of manufacturing process carried out at manufacturing premises. It shall contain the following information but not limited to:

S/N	Requirements	Information
A	**GENERAL INFORMATION**	
I	**Brief information on the site (including name and address), relation to other sites**	In not more than 250 words, outline the company's activities, other sites (if any)
II	**Manufacturing activities**	1. Indicate whether the site has been approved by National Authority, or any foreign Competent Authority 2. Quote the relevant document (license) as issued by the Competent Authority. State the period of validity of license/certificate document (if the validity of the document is given in the country concerned). Any conditions and/or restrictions should be stated.
III	**Any other operations carried out on the site**	This covers both medical device related and non-medical device (including medicinal products) related activities.
IV	**Name and exact address of the site, including telephone, fax numbers, web site and e-mail**	1. Name of company, site address and mailing address (if different from site address) 2. Telephone, fax nos. and email address of

<table>
<tr><th>S/N</th><th>Requirements</th><th>Information</th></tr>
<tr><td></td><td>address</td><td>contact person</td></tr>
<tr><td>V</td><td>Type of medical devices handled on the site and information about specifically toxic or hazardous substances handled, mentioning the way they are handled and precautions taken</td><td>1. Quote the type of medical devices handled, specifying if the medical device is handled under a contractual agreement with a contract giver.

2. Note any toxic, hazardous, highly sensitizing substances handled e.g. antibiotics, hormones, cytostatics. Note whether special precautions were taken for such medical devices. (List the appropriate license numbers where applicable)</td></tr>
<tr><td>VI</td><td>Short description of the site (size, location and immediate environment and other activities on the site)</td><td>1. Provide a map indicating the location of the site(s) and the surrounding area. Mark the site(s).

2. Other activities on the site.</td></tr>
<tr><td>VII</td><td>Number of employees engaged in Production, Quality Control, warehousing, and distribution</td><td>
<table>
<tr><th>Area of Operation</th><th>No of Permanent/ regular employees</th><th>No of Contractual employees</th></tr>
<tr><td>Production</td><td></td><td></td></tr>
<tr><td>Quality Control</td><td></td><td></td></tr>
<tr><td>Warehousing</td><td></td><td></td></tr>
<tr><td>Storage</td><td></td><td></td></tr>
<tr><td>Distribution</td><td></td><td></td></tr>
<tr><td>Technical &Engineering Support Services</td><td></td><td></td></tr>
<tr><td>Total</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

S/N	Requirements	Information
VIII	**Use of outside scientific, analytical or other technical assistance in relation to the design, manufacture and testing**	For each work process outsourced or sub-contracted (Including contract delivery companies), give: - 1. Name, address, telephone no. and fax. no. of contractor 2. Brief outline of the activity being undertaken in not more than 250words.
IX	**Short description of the quality management system of the company**	(Not more than 750 words). 1. State the company's Quality Policy. 2. Define the responsibility of the Quality Assurance function. 3. Describe the elements of the QA system e.g. organizational structure, responsibilities, procedures, processes. 4. Describe the audit programme (self-inspection or audits by external organizations undertaken). 5. Describe how results are reviewed to demonstrate the adequacy of the quality system in relation to the objective i.e., quality, efficacy and safety of the product. 6. Describe vendors' qualification/validation policy. When suppliers of critical starting materials and packaging materials - actives, excipient, containers, closures and printed packaging materials are assessed, give details of how this is done. 7. Record if the company has been certified to industry standards (e.g.ISO9000, ISO13485:2016).

S/N	Requirements	Information
		8. Describe the release for sale procedure for finished products
X	**Devices details registered with foreign countries**	State name of the devices along with the name of the countries where the device is approved/ registered.
B	**PERSONNEL**	
I	**Organization chart showing the arrangements for key personnel**	Organizing chart/ organogram listing key personnel (Management Representative, Quality Assurance, Production, and Quality Control) has to be constructed. Record Senior Managers and Supervisors only.
II	**Qualification, experience and responsibilities of key personnel**	1. Brief details of qualifications and years of relevant experience since qualifying. 2. Job descriptions for the key personnel
III	**Personnel training**	Give brief details of the training programme and include induction and continuous training, as follows: - 1. Describe how training needs are identified and by whom. 2. Give details of training relative to quality assurance of the products. 3. State the form of training e.g. in-house, external, and how practical experience is gained and which staff are involved. 4. Explain training evaluation procedures. 5. Explain how retraining needs are identified. 6. Give brief details of training records keeping.
IV	**Health requirements for personnel engaged in**	Give brief details of the following:

S/N	Requirements	Information
	production	1. Who is responsible for checking health of employees? 2. Is there a mandatory medical examination during recruitment? 3. Are employees routinely checked from time to time depending on the nature of their work? 4. Is there a system for reporting sickness or contact with sick people before working in a critical area? 5. Is there a system of reporting back after illness? 6. Are those who work in clean areas (Grade A-D) subject to additional monitoring?
V	**Personnel hygiene requirements, including clothing**	Give brief details of the following: 1. Is there suitable washing, changing and rest areas? 2. Is the clothing suitable for the activity undertaken? 3. Briefly describe the clothing 4. Are there clear instructions on how protective clothing should be used and when it should be changed? 5. Is in-house or external laundry used?
C	**PREMISES**	
I	**Plan/layout of the manufacturing area**	Give Schematic diagrams of the manufacturing areas
II	**Nature of Construction and finishes**	
III	**Heat, Ventilation & Air Conditioning System**	

S/N	Requirements	Information
	[HVAC]:	
IV	**Electric system:**	
V	**Compressed air**	
VI	**Water System**	
VII	**Firefighting system**	
VIII	**Maintenance**	
D	**EQUIPMENT**	
I	**Production Equipment**	
II	**Quality Control Equipment**	
III	**Maintenance**	
IV	**Qualification and Calibration**	
V	**Sanitation**	
E	**DOCUMENTATION**	
I	**Preparation, Revision and Distribution of Documents**	
F	**PRODUCTION**	
I	**Master Production Documents**	
II	**Handling of materials**	
III	**Handling of Rejected Materials and products**	
IV	**Process Validation**	
G	**QUALITY CONTROL**	
I	Quality Control System	
H	**CONTRACT MANUFACTURING AND ANALYSIS (if any)**	
I		
I	**DISTRIBUTION, COMPLAINTS AND PRODUCT RECALLS**	
I	**Distribution**	
II	**Records of Distribution**	

S/N	Requirements	Information
III	**Complaints**	
IV	**Product recall**	
J	**SELF – INSPECTION**	
I	**Self – inspection System**	
K	**APPENDIX**	
I	**Factory organization chart**	
II	**Site plan**	
III	**Plant layout**	

EXAMPLES OF NON-CONFORMANCES AND THEIR CLASSIFICATION

Annex II

Classification	Examples
Critical non-conformances	a. Evidence of cross contamination; b. Absence of acceptable air supply system; c. Absence of qualification records, maintenance and monitoring records; d. Absence of key personnel to include management representative; e. Key personnel not meeting the prescribed qualifications; f. Lack of proper controls in handling of starting materials, in process bulks materials and materials in quarantine or rejected areas; g. Improper documentation; h. Poor cleaning procedures of the manufacturing equipment and premises to include absence or poor cleaning validation, lack of cleaning procedures and lack of cleaning monitoring records; i. No or inappropriate status labeling and identification of material in process; j. Line clearance not properly done, where applicable; k. Frequent occurrence of major non-compliances that shows a trend; l. Failure by the auditee to take a corrective action within a given limit to a major non-conformance; m. Poor quality control methods to include unvalidated analytical methods for starting and finished products; n. Key equipment for analysis are not qualified; o. Unethical practices to include use of unqualified personnel in key areas; p. Release of products without proper authorization; q. Evidence of cheating or data falsification; r. Absence of design history file for class c and d devices; s. Inappropriate storage of raw materials and finished products;
Major non-conformances	a. Wrong reconciliation of starting and packaging materials; b. Absence of document control system, standard operating

EXAMPLES OF NON-CONFORMANCES AND THEIR CLASSIFICATION

Annex II

Classification	Examples
	procedures (sops) and records; c. Incorrect storage of reagents; d. Building material not fit for the industry; e. Failure to conduct management review; f. No or inappropriate equipment status labeling, where applicable; g. Failure to conduct temperature mapping where applicable; h. Absence of quality policy; i. Failure to conduct customer surveys.
Minor non-conformances	a. Overwriting without signatures; b. Some signatures missing in the batch record; c. Evidence of use of obsolete standard operating procedures;

EXAMPLES OF NON-CONFORMANCES AND THEIR CLASSIFICATION

Annex II