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THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TMDA
Tanzania Medicines & Medical Devices Authority

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

INSPECTOR'S HANDBOOK

THIRD EDITION

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Contents

Acronyms

CC	Column Chromatography
CCC	Counter Current Chromatography
CIF	Cost, IncludingFreight
COA	Certificate of Analysis
CRF	Clean Report of Findings
DQCL	Drug Quality Control Laboratory
FCVR	Final Classification and Valuation Report
FEFO	First Expiring, First Out
FOB	Free on Board
GLC	Gas-Liquid Chromatography
GPHF	Global Pharma Health Fund
HPLC	High-Performance Liquid Chromatography
IP	Import Permit
PC	Paper Chromatography
PI	Pro forma Invoice
PMS	Post Marketing Surveillance
POE	Port of Entry
SOP	Standard Operating Procedure
SPD	Surveillance Program Document
SRF	Sample Receipt Form
SF	Substandard and Falsified
TBS	Tanzania Bureau of Standards
TMDA	Tanzania Medicines and Medical Devices Authority
TLC	Thin-Layer Chromatography
TRA/C&E	Tanzania Revenue Authority/Customs and Excise Department

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Foreword

Inspection is an essential regulatory function in controlling quality, safety and effectiveness of medicines, medical devices, diagnostics and tobacco products. It is the responsibility of TMDA to ensure that those dealing with these products comply with the laid down legal and regulatory standards and requirements in order to protect public health. In view of this TMDA, inspects all activities involved in research, development, manufacture, distribution and supply.

Qualified and experienced Drug Inspectors constitute an indispensable component of an effective inspection system. Drug Inspectors serve as the eyes and ears of the medicines regulatory body and are on the front line in maintaining the identity, quality, purity, and strength of the products manufactured and marketed in any country. In this respect, TMDA Drug Inspectors have an important role in protecting consumers of products regulated by TMDA. Succinctly, the inspector's job is law enforcement.

This Drug Inspector's Handbook, together with other tools, provides guidance on how to conduct inspection of medicines, medical devices, diagnostics and tobacco products. The inspectors shall take immediate action to control and manage any risks which may arise from contravention of the act pending any further action as may be found suitable by the Authority.

Inspectors should perform their duties according to what has been delineated in the handbook. The handbook is intended to serve as a quick reference for Medical Product Inspectors when discharging their inspection duties and responsibilities.

Adam M. Fimbo
Director General
Tanzania Medicines and Medical Devices Authority

Introduction

This handbook has been revised to contain all the products to be inspected according to TMMD Act Cap. 219 namely medicines, medical devices, diagnostics and tobacco products and medical devices which were not covered in the First Edition. It has also been revised for the purpose of removing the products (foods and cosmetics) which are now controlled by TBS following the amendment made by Finance bill of 2018.

The handbook aims at providing guidance to drug inspectors when preparing and performing inspection. It also serves as reference document for inspectors prior and during inspection so that inspection activities are consistently done and thus avoiding bias and double standards. Consistency in conducting inspection activities is very important in ensuring quality assurance of medicines, medical devices, diagnostics and tobacco products by the TMDA.

In order to achieve that goal, inspectors need to be familia with this handbook which contains sufficient working tools needed for observing, investigating and reaching conclusions in a particular inspection.

It is also expected that the handbook shall help inspectors to conduct inspection with integrity and diligence. The code of ethics and conduct of inspectors and the responsibility of inspector have also been outlined with the objective to remind inspectors on their ethical and moral obligations when engaged in inspection activities.

The handbook is applicable for all types of inspections for pharmaceuticals, medical devices diagnostics and tobacco products with exception of GMP inspections.

The document is divided into ten (10) chapters which provide information in regard to:-

a. Introduction to inspection
b. Inspectors
c. Code of conduct of inspectors
d. Port of entry inspection
e. Inspecting distribution points
f. Product surveillance
g. Substandard and Falsified products
h. Monitoring of promotional adverts
i. GPHF Minilab kit for quality control
j. Enforcement

Inspectors are urged to read carefully and use accordingly this handbook together with Tanzania Medicines and Medical Devices Act Cap.219 and Regulations made there under.

Definition of terms

In the context of this handbook the following phrases are defined as follows:

A "break" in a tablet	Separation or dislodging of more than 10 percent of the tablet.
A "break" in a capsule	Fracture in the surface of the capsule.
Adsorbent	Substance that causes passing molecules or ions to adhere to the surface of its particles.
Advertisement	Anything that is aimed or designed to promote the supply, sale or use of a product whether or not for financial gain and it includes a notice, circular, label wrapper or other document, and an announcement made orally or by means of producing or transmitting light or sound.
Analyte/sample	Mixture that is being separated or analyzed.
Caking in suspensions	Settling of the solid material in the suspension to the bottom; the cake does not easily re-disperse on shaking.
Capping or cavitations of tablets	Separation (or tendency toward separation) of a portion of the upper or lower surface of the tablet.
Capsule shapes	Conventional, bullet like, elliptical (oval), oblong, round, tapered ends.
Capsule types	–of hard gelatin shell that consists of two pieces, a base containing the medicine and a cap covering the base. –of soft gelatin shell consisting of two flexible pieces formed into a body that is permanently sealed and that may contain liquids, powders, or semisolids.
Certificate of Analysis	Document supplied by the manufacturer summarizing the physical and analytical data for a particular lot or batch of product that formed the basis for the product batch or lot being released for sale.

Chain of custody	Record of individuals who have accessed sample material from the time of collection by an inspector to its ultimate destruction. The sample and the record, from its time of collection to the time of its destruction, must be kept safely (under key and lock) and under systematic control.
Chipping	Removal of parts of the tablet usually occurring at the edges; caused by low friability.
Chromatogram	Developed TLC plate with substance spots at various positions.
Chromato-plate	TLC plate.
Confiscate/seizure	To officially take away from a vendor or importer, to assume custody of a products consignment stocked in the premises or at the port of entry. The intention is to stop the products' distribution to the public. Usually done for product shown to be counterfeit or of substandard quality or associated with unexpected illness or death.
Retain a consignment	Retention of a consignment pending resolution of outstanding issues by the TMDA. However, if the issues are not resolved to the satisfaction of the TMDA detention status, upon written instruction from the TMDA is converted to rejection.
Detection/Location/ Visualization	Process of locating (making visible) the substances being analyzed on the chromate-plate after development.
Development	Process of separating the sample mixture by the ascending migration of solvent in the adsorbent layer.
Eluent	Solvent (mobile) phase that removes substances from the stationary phase.
Elution	Removal of a compound from a column or stationary phase.
Elution power	Ability to remove compounds from the stationary phase.
Eluotropic series	List of solvents arranged according to their elution power.

Entry Form	Tracking document used by the Tanzania Revenue Authority for all incoming consignments.
Final Classification and Valuation Report	Report prepared at the exporting country port by a third-party contractor to the Tanzania Revenue Authority/Customs and Excise Department. The FCVR confirms the correctness of the imported goods in terms of quality, quantity and value.
First Expiring First Out	Practice intended to keep the product inventory in good rotation to avoid expiring of the shelf life.
Free on Board	Cost of a consignment at the port of export. It does not include the freight charges from the port of export to the destination of import.
GPHF Manual	Manual which include all tests procedures which performed by the Min lab kit.
GPHF Minilab	Stands for Global Pharma Health Fund Minilab, a medicinal product rapid testing kit that has materials for color reaction, thin-layer chromatography, and disintegration testing of essential medicines.
Immediate container	Packing material such as a tin or a bottle that is in direct contact with the medicine; an immediate container is also often referred to as the "primary container".
Import Certificate/ Permit	Document issued by TMDA authorizing the importation of products it regulate into the country.
Liquid or semisolid dosage forms	Dosage forms that can be in clear liquid forms, or suspensions or dry powder for suspensions that must be reconstituted as directed on the label by the manufacturer before use.
Mobile phase	Solvent that flows through the stationary phase by capillary action, dissolving and carrying with it the substances that are being separated or analyzed.
Origin/start	Position about 2 cm from the bottom of a TLC plate, at which sample spots are applied; it may be marked as a line.

Percent (%) of remaining shelf life	This value is equal to— (Expiry Date – Date on Receipt at Port of Entry) × 100 (Expiry Date – Manufacturing Date) Or— (Remaining Shelf Life on Arrival) × 100 (Shelf Life of the Product)
Proforma invoice	Is a quote in an invoice format that may be required by the buyer to apply for an import license, contract for pre-shipment inspection, open a letter of credit or arrange for transfer of hard currency. It is presented to TMDA for approval before a shipment can enter Tanzania. A properly endorsed PI has two signatures from TMDA officials and the TMDA stamp. The signatures and the stamp indicate that the exporter and consignee are both properly licensed and that the drug manufacturer, product, and dosage forms are in compliance with TMDA requirements.
Promotion	Include:- - advertising; - the activities of representatives including detail aids and other printed material used by representative; - the supply of samples; - the provision of inducement to prescribe, dispense, supply, administer, recommend or buy products by the gift, offer or promise of any benefit or bonus, whether in money or in kind; - the provision of hospitality for promotional meetings; - the sponsorship of promotional meetings; - the sponsorship of scientific meetings including payment of travelling and accommodation expenses in connection therewith; - the provision of information to the general public either directly or indirectly; - all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, radio, television, internet, electronic media, interactive data systems and the like. -

Port of entry name	Name of an authorized place of entry for a consignment;
Quarantine	Retention of a consignment until further tests are performed to ascertain its quality.
R_f value	"Retardation factor" or "ratio-to-front" (i.e., a ratio of distance traveled by a substance from the origin to distance traveled by the solvent from the origin.
Sample Receipt Form	Document that an inspector must complete for every sample of product collected.
Secondary container	Packaging material that encloses a number of immediate containers.
Solvent front	Highest position (frontline) reached by the solvent on a chromate-plate after development.
Splitting of a tablet	Partial or complete separation of top or bottom crowns of a tablet from the main body.
Stationary phase	Solid substance coated on glass, plastic, or aluminum plates, which adsorb molecules to be separated.
Post Marketing Surveillance Program	Document that defines which medicinal products are to be collected and tested.
Tablet types	Oral, solution, hypodermic, ophthalmic, buccal, Sublingual, vaginal, pellets, impregnated (including delayed-action, repeat-action, prolonged-action and sustained-action tablets)

Chapter 1

Introduction to inspection

This chapter briefly explains inspection as it relates to medicines, medical devices, diagnostics and tobacco products. It covers the meaning of inspection, objectives of inspection, what needs to be inspected and different types of inspection and levels of inspection.

1.1 Meaning of Inspection

To "inspect" is "to look closely at something, especially to check that everything is in good order." "Inspection" is, therefore, the act of looking closely at something to ensure that it meets certain prescribed or known standards and specifications.

What, then, is product inspection? Based on the definition of "inspection," it is an act of examining or looking closely at all the attributes of medicines, cosmetics and medical devices including the official review of documents, records and conditions of all facilities which deal with storage of the same in order to ensure their conformity to the requirements.

1.2 Objectives of inspection

Inspection is undertaken to ensure:-

- Medicines, medical devices, diagnostics, tobacco products and related supplies either locally manufactured or imported meet the set standards of safety, quality and efficacy in order to protect public health.

- Adherence to the laws and regulations governing manufacturing, distribution, importation, exportation, storage and promotion of medicines, medical devices, diagnostics, and tobacco products.

1.3 What needs to be inspected?

To ensure the use of safe, quality and efficacious medicines, medical devices, diagnostics, and tobacco products entering or circulating in the Tanzanian market, the following are areas to be inspected by the inspector:-

- Ports of entry (POEs),
- Manufacturing facilities,
- Distribution points i.e. importers, pharmacies (retail and wholesale), ADDO shops, health facilities, tobacco product selling outlets, medical device outlets, warehouses and any other establishment or premises where these products may be found, and

- Promotional adverts

1.4 Types of inspections

There are five types of inspections:-

- Routine inspection
- Concise inspection
- Follow-up inspection
- Special or investigative inspection
- Audit inspection.

1.4.1 Routine inspection

Routine inspections entail full review of all aspects and components within a facility. They are generally intended for:-

- A new establishment
- An establishment that has applied for a permit to extend its scope of operations or made important changes in its key personnel or changed to new premises
- An establishment that has not been inspected for a long time
- An establishment with consistent records of non-compliances.

This inspection should be announced except when it has not been conducted for a long time, an unannounced inspection would be the norm.

1.4.2 Concise Inspection

Concise inspection is the evaluation of limited aspects relating to compliance of a facility. A limited number of requirements are selected by the Inspector to serve as indicators of the overall compliance of a facility. The Inspector also has to identify and evaluate any significant changes that could have been introduced by a facility since the last inspection.

Collectively, the selected indicators and the changes identified indicate facility's attitude toward compliance to requirements. A concise inspection is conducted under the following circumstances:-

- Where premises has a consistent record of compliance with routine inspections in the past.
- Where a sample of aspects can be taken as a good indication of the overall level of compliance with requirements.

However, if the concise inspection uncovers evidence that the level of compliance has fallen, a more comprehensive or full inspection should be performed soon after the concise inspection. These inspections can be announced or unannounced.

1.4.3 Follow-Up Inspection

A follow up inspection is also referred to as a re-inspection or a reassessment of a premise. It is carried out to ensure that corrective measures have been undertaken following advice and notice given during a previous inspection. Depending on the nature of the defects and the work required, the follow-up inspection could be carried out between 7 days and 12 months after the previous inspection. Where a time limit was given to rectify the non-conformance, the inspection should be unannounced.

1.4.4 Special or investigative Inspection

A special inspection is undertaken to do spot checks which could focus on one product, a group of related products, or specific operations e.g. false labeling. This inspection should be unannounced. It is conducted under the following circumstances:-

- When there are complaints about a specific product
- To gather specific information, or to investigate specific operations of a facility.

1.4.5 Audit Inspection

Audit inspections are carried out to guide, support and assist audited part in carrying out inspection activities. The aim of audit inspection is to determine effectiveness, correctness and efficiency of the inspection activities and it covers all areas that inspection activities are carried out. Audit inspection helps to:-

- Ensure uniformity in conducting inspections
- Enhance compliance with legal requirements
- Assist Inspectors in improving their performance
- Identify problems and institute timely interventions
- Maintain and reinforce the administrative and technical links between higher and lower levels
- Make follow up of implementation of previous audit inspection recommendations
- Identify resource needs for inspection activities.

As a minimum requirement, audit inspection shall be conducted annually and is usually announced.

1.5 Inspection and Reporting Levels

There are four recognized levels of inspection of medicines, medical devices and tobacco products:-

- Inspection at Council level
- Inspection at Regional level
- Inspection at Zonal level
- Inspection at Headquarter level.

1.5.1 Inspection at Council level

These are routine inspections conducted at the level of districts, municipals, towns or cities by the inspection team that involves Council Health Management Team (CHMT) as appointed by the respective District/Municipal/Town/City Directors. The inspections are limited to respective districts, municipals, towns or cities.

Reports of these inspections shall be submitted to respective TMDA Zone Offices quarterly and copy submitted to respective Regional Administrative Secretary.

1.5.2 Inspection at Regional level

These are inspections conducted at regional level by the inspection team that involves Regional Health Management Team (RHMT) as appointed by the Regional Medical Officer or any other team under the directive from RAS. They are mainly audit inspection to verify the councils' inspections.

Reports of these inspections shall be submitted to respective TMDA Zone Offices annually and copy submitted to Director General.

1.5.3 Inspection at Zonal level

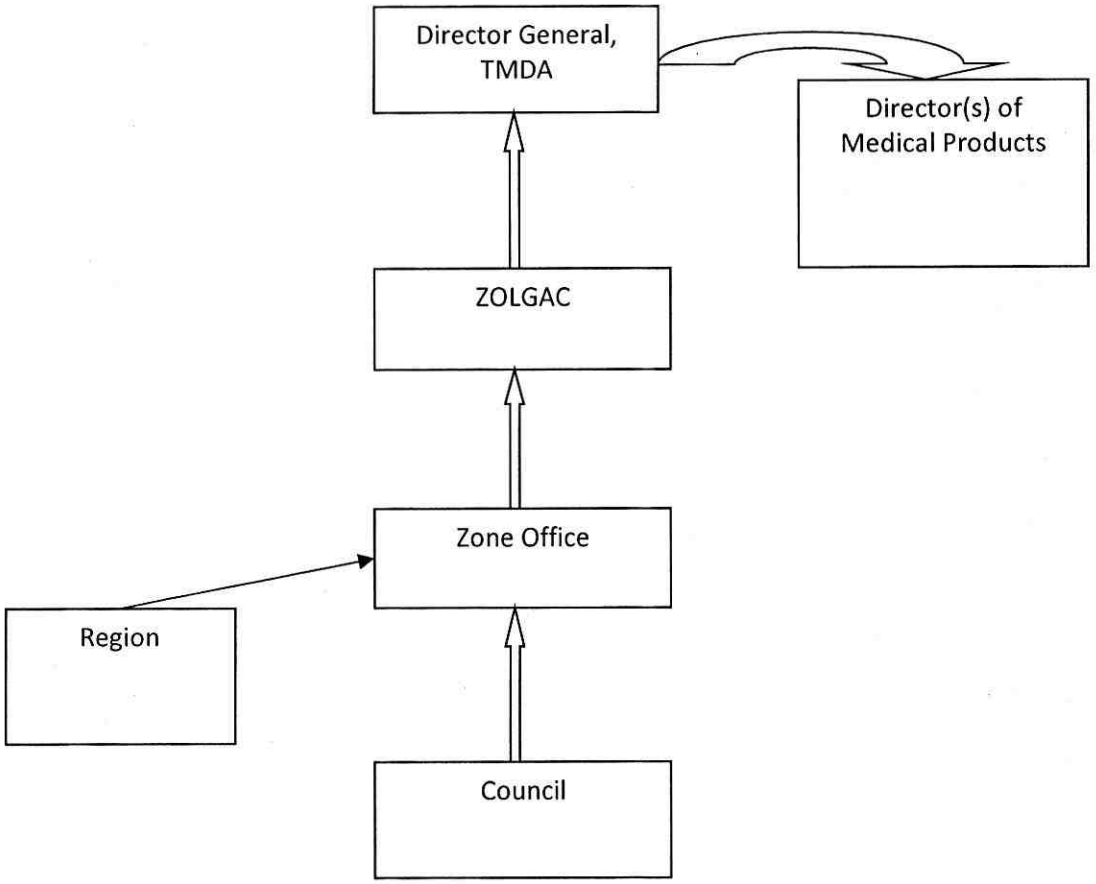
These inspections are conducted by TMDA Zonal Offices to cover all regions within respective zone area. They include routine inspections, concise inspections, follow-up inspections, special or investigative inspections and audit inspections where applicable. Audit inspections are conducted to determine effectiveness, correctness and efficiency of the inspection performed at council and/or region level.

Inspection reports shall be submitted to the Director General on monthly, quarterly, semi annual and annual bases.

1.5.4 Headquarters' inspections

These are normally inspections organized at Headquarter level and conducted jointly with all TMDA zones and other stakeholders. These are special inspections which are conducted at least twice per year.. They are intended to cover large part of the country and specifically aimed to target falsified, substandard, withdrawn or any other illegal products on the market. Inspection reports are submitted to the Director General through Directors responsible for regulation of medical products. Special inspections are also conducted anytime after receiving reports of violations from whistleblowers.

Figure 1: Illustrates medicines, medical devices, diagnostics and tobacco products inspection structure and chain of command/ reporting level



Chapter 2

Drug Inspector

This chapter describes an Inspector, appointment and powers of Inspectors, qualities of Inspector and procedure to be followed by an Inspector once he/she is transferred or ceased to be an Inspector.

2.1 Who is an Inspector?

An inspector is any officer appointed or authorized or recognized as such under section 105 of the Tanzania Medicines and Medical devices Act, Cap 219.

2.2 Qualification of an Inspector

An inspector should have the necessary qualifications in order to effectively take part in inspection activities. The qualifications of the Inspector shall be based on the following:-

- Academic education
- Training
- Experience

2.2.1 Academic education

Inspectors of medicines and medical devices should have atleast a minimum of diploma or degree in pharmacy, veterinary, medical devices or related fields from recognized institutions. Where persons other than the above mentioned professions are employed as Inspectors, they should be adequately experienced in medicines and medical devices control affairs and suitably trained on inspection activities.

2.2.2 Training

In order to be competent to carry out inspections, Inspectors will be required to undergo training in inspection activities. Such trainings would provide them with knowledge and skills needed when planning for, carrying out and reporting inspections.

Apart from basic training, inspectors will also be required to undergo on the-job training conducted by senior Inspectors. Such trainings should involve both theory and practice of inspections and cover inspection techniques, communication and management skills as well as conducting inspections and report writing as trainees.

Continuous training should be provided to Inspectors to keep them abreast with the current knowledge and techniques in carrying out inspections. This would be through attending training programmes, seminars, scientific meetings, conferences and exhibitions organized either by the Authority or other recognised institution.

2.2.3 Experience

Experience as a general concept comprises knowledge or skills in or participation in some activities or events, or knowledge or skills gained through involvement in or exposure to those activities or events.

An Inspector will be deemed experienced when he/she has worked for a minimum three (3) years continously in inspection activities and demonstrate competence in that area. Experienced inspectors are qualified to be Lead Inspectors.

2.3 Appointment of Inspector

The Director General shall appoint Inspectors from TMDA and Local Government Authorities based on qualification and training. Upon appointment Inspectors will be provided with identity cards and their names will be published in the official Government Gazette.

Local Government Inspector's identity card will be valid only in their specific duty stations and not transferable. An Inspector who has changed duty station would be given a new identity card after returning back the previous one to Director General. Any person who is no longer an Inspector would be required to hand over the identity card to the former employer immediately upon cessation of the employment.

2.4 Powers of Inspectors

The appointed Inspectors should have the following powers:-

(i) At all reasonable times enter:-
- Any set of premises which is on the register of premises
- Any premises in which any person whose name is entered in any register under TMMD Act, carries on any business.
- Any premises in respect of which any person is licensed under TMMD Act.

(ii) At any time enter any premises, stall, vehicle, vessel or conveyance or any premises suspected to be dealing with products regulated under this act for the purpose of ensuring compliance.

(iii) Examine or inspect any certificate of registration, license, book, electronic information storage system or other documents in the premises and for that purpose, he may do such other things including the taking of extracts from documents in the possession of the person as may be necessary to effectual the examination or inspection.

(iv) Seize and retain any medicines, medical devices, diagnostics, tobacco products, or articles consisting of, or containing any poison which he has reasonable cause to suspect it is liable to forfeiture under TMMD Act.

(v) Close the premises found to contravene the law and institute criminal proceedings.

(vi) Order the return to the country of origin of any product regulated under TMMD Act imported into the country in contravention of the provisions of the Act.

2.5 Qualities of Inspectors

The Inspector should at least possess the following qualities:-

a) Good knowledge of medicines, medical devices and invitro diagnostics.
b) Good knowledge of the laws and regulations to be enforced
c) Good command of technical terms and excellent communication skills
d) Awareness of the probable methods of using forged or false documents for transactions and skill in determining the genuineness of documents presented for examination
e) Exercise , honesty and integrity
f) Responsible conduct which commands respect
g) Willingness to accept challenges
h) Ability to organize their own work with minimum supervision
i) Ability to assess character and honesty
j) Good public relations image with key personnel or in charge of premises while remaining firm, fair and resolute
k) Ability to hold discussion with company management at completion of inspection.

Chapter 3

Code of Conduct for Inspectors

This chapter enumerates ethical and codes of conduct for Inspectors, responsibilities of Inspectors and requirements for declaration of conflict of interest. It also gives some highlights on Do's and Don'ts for an Inspector and what are expected from the Inspectors.

3.1 Codes of Conduct

The following are the codes of conduct for Inspector:-

a) Strive to achieve the highest ethical and performance standards in carrying out inspection activities;
b) Uphold the honour and dignity of an inspector and avoid association with any enterprise of questionable character or apparent conflict of interest;
c) Protect and promote the interests of the Authority to the best of his/her ability and knowledge, recognizing that the Authority has placed trust and confidence onto him;
d) Strive to acquire new knowledge and skills continuously and use them effectively;
e) Conduct inspection in a manner that will assure independence from outside influence and interest, which would otherwise compromise his ability to render a fair and impartial opinion regarding any inspection conducted;
f) Promptly disclose to the Authority any interest in any business which may affect the quality, or the result of his/her work or remediation;
g) Not use his/her position for personal gain;
h) Make every effort to uphold, maintain and improve the integrity and reputation of the Authority and the Government of Tanzania;
i) Perform duties tactfully, honestly and impartially to avoid circumstances that may lead to conflict of interest;
j) Maintain confidentiality whenever accessing confidential information as a result of inspection;
k) Assess facts quickly and take rational and sound decisions without delay;
l) Not solicit, force or accept bribes from a person whom he/she is serving, already served or will be serving either by doing so in person or by using another person;
m) Not receive presents in form of money, entertainments or any service from a person that may be regarded as geared towards compromising his/her integrity;
n) Disclose fraud or abuse of power and corruption to TMDA;
o) Avoid the use of rude and abusive language;
p) Maintain personal hygiene and dress in respectable attire in accordance with acceptable norms of the office;
q) Make decisions in line with authorized standards and procedures and

r) Report inspection findings truthfully and accurately.
s) Committed to work hard and for long hours.
t) Not without prior approval by TMDA, engage in outside employment or activities and shall not seek or negotiate for employment that will directly conflict with the duties/interests of the TMDA.
u) Conserve TMDA property and shall not use it for private gain.
v) Endeavor to avoid any actions that create an appearance, circumstance that are violating the law or ethical standards as determined by the perspective of a reasonable person with the knowledge of the relevant facts.
w) Adhere to the laid down rules, regulations and standard operating procedures in executing his/her functions.

3.2 Responsibilities of Inspectors

a) To conduct inspections according to the relevant guidelines
b) To collect samples and submit them to laboratory for analysis
c) To prepare and submit inspection reports according to SOPs
d) To process applications for registration of premises, licenses, imports and export permits of medicines, medical devices, diagnostics and tobacco products.
e) To supervise destruction of unfit products and prepare disposal certificates.
f) To prepare status reports on license permits, import and exports of medicines , medical devices, diagnostics and tobacco products.
g) To monitor promotion advertisements as per TMMD Act, Regulations and guidelines.

3.3 What is expected from Inspector?

During inspection, the Inspector should always remember the following:-

a) Contact the person in charge of the establishment by approaching him or her in a dignified, non-arrogant, and cordial manner. Avoid being arrogant.
b) Present credentials (e.g., your identity card) and explain the purpose of your visit.
c) Use diplomacy, tact, and persuasiveness to acquire the necessary information and all necessary inspection details. Use respective standard operating procedures (SOPs)/Inspection Checklist to achieve this.
d) In case of refusal to undergo inspection, explain that refusing is a criminal offense and courteously discuss the matter with the owner or responsible person on the premises
e) Upon completion of inspection, meet the owner or person in charge to discuss the findings. Adopt a courteous attitude in calling attention to the practices or conditions observed at the time of inspection; make suggestions for minor corrections to be made as you perform the inspection.
f) If any samples have been taken for testing, enquire a receipt/ invoice or sign the sample collection form with the person from whom samples are taken.

3.4 Do's & Don'ts for Inspectors

a) Exercise confidentiality: do not reveal to a third party findings/observations regarding your work
b) Make accurate reports of the facts observed.
c) Be courteous and demonstrate poise and competence in your work.
d) Refrain from expressing personal views; such remarks or opinions may be interpreted as official.
e) Do not lose temper when abused or accused.
f) Do not miss a single object, correspondence, record, accounts book, chit, rough book, or other relevant papers, which may prove to be material evidence in establishing conduct, transactions and circumstances, and so on of the establishment being inspected.
g) Do not fail to mention or record all items seized. Full details and descriptions of the incriminating articles or circumstances for which a charge will be opened (in case of intention to institute legal charges) should be recorded with witnesses present and signatures of responsible persons should be on the seizure document.

3.5 Declaration of conflict of interest

When appointing or authorizing Inspectors, Director General shall take into account not to appoint or authorize an Inspector who has interest in the manufacture, importation or sale of any product regulated under TMMD Act Cap.219. In view of that Inspector shall be required to declare their business interest by filling in Conflict of Interest Declaration Form .

Chapter 4

Ports of Entry Inspection

Section 73 of the Tanzania Medicines and Medical devices Act, Cap 219 gives the Authority mandate to regulate importation and exportation of medicines, medical devices, diagnostics and tobacco products. After receiving import authorization, imported consignments are subjected to inspection at the POEs before they are allowed to enter into the country. This chapter therefore explains how inspection of the product is carried out at the POEs.

4.1 Authorized Ports of Entry

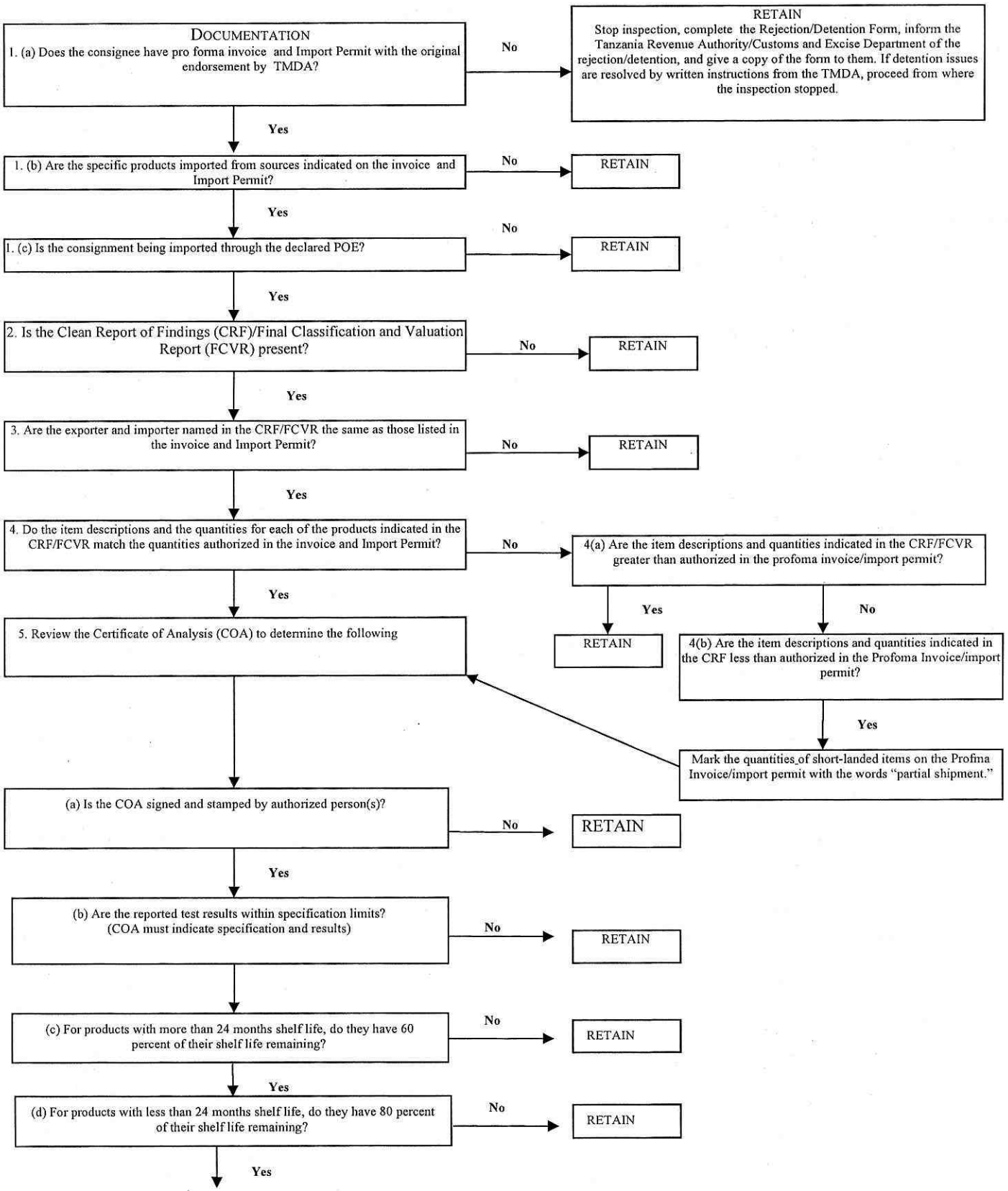
In order to have effective control of imports and exports, the following POEs have been identified as official entry and exit points for the regulated products:-

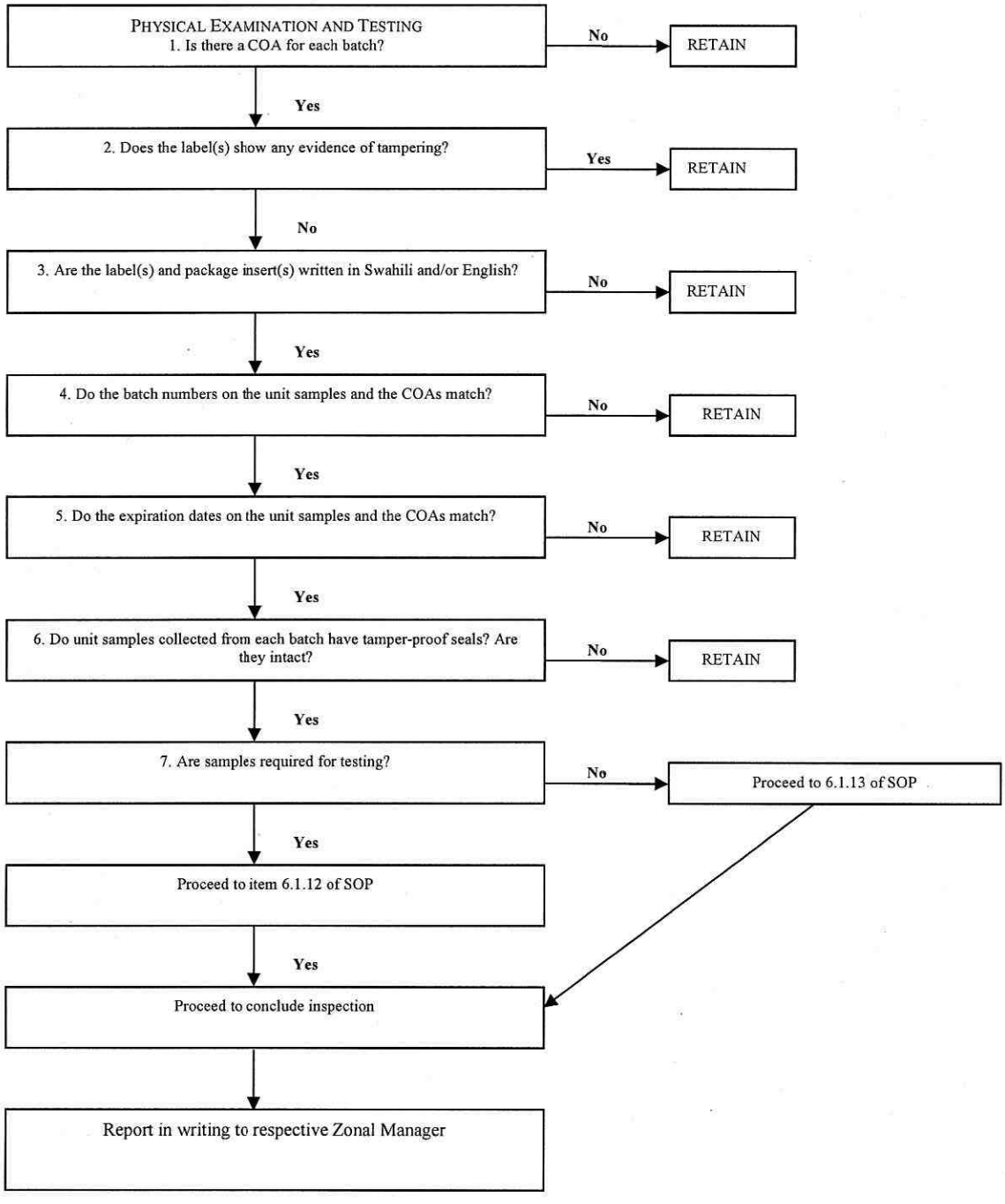
- *Dar es Salaam International Airport*
- *Dar es Salaam Sea Port*
- *Kilimanjaro International Airport*
- *Horohoro*
- *Holili*
- *Namanga*
- *Sirari*
- *Mwanza Lake Port*
- *Mwanza Airport*
- *Tanga Sea Port*
- *Tunduma*
- *Mtukula*
- *Rusumo*
- *Kabanga*
- *Kasumulu*

4.2 Step-wise procedure for inspecting imported consignments

The following flowchart which is self-explanatory summarizes step-by-step actions and decisions that Inspectors at the POE must adhere to when inspecting consignments entering the country.

Guidance Checklist for conducting physical/visual examination of medicines, medical devices, diagnostics and tobacco products is provided as **Annex 1**.


DOCUMENTATION
1. (a) Does the consignee have pro forma invoice and Import Permit with the original endorsement by TMDA?
No
RETAIN
Stop inspection, complete the Rejection/Detention Form, inform the Tanzania Revenue Authority/Customs and Excise Department of the rejection/detention, and give a copy of the form to them. If detention issues are resolved by written instructions from the TMDA, proceed from where the inspection stopped.
Yes
1. (b) Are the specific products imported from sources indicated on the invoice and Import Permit?
No
RETAIN
Yes
1. (c) Is the consignment being imported through the declared POE?
No
RETAIN
Yes
2. Is the Clean Report of Findings (CRF)/Final Classification and Valuation Report (FCVR) present?
No
RETAIN
Yes
3. Are the exporter and importer named in the CRF/FCVR the same as those listed in the invoice and Import Permit?
No
RETAIN
Yes
4. Do the item descriptions and the quantities for each of the products indicated in the CRF/FCVR match the quantities authorized in the invoice and Import Permit?
No
4(a) Are the item descriptions and quantities indicated in the CRF/FCVR greater than authorized in the profoma invoice/import permit?
Yes
RETAIN
No
4(b) Are the item descriptions and quantities indicated in the CRF less than authorized in the Profoma Invoice/import permit?
Yes
Mark the quantities of short-landed items on the Profma Invoice/import permit with the words "partial shipment."
Yes
5. Review the Certificate of Analysis (COA) to determine the following
(a) Is the COA signed and stamped by authorized person(s)?
No
RETAIN
Yes
(b) Are the reported test results within specification limits? (COA must indicate specification and results)
No
RETAIN
(c) For products with more than 24 months shelf life, do they have 60 percent of their shelf life remaining?
No
RETAIN
Yes
(d) For products with less than 24 months shelf life, do they have 80 percent of their shelf life remaining?
No
RETAIN
Yes


PHYSICAL EXAMINATION AND TESTING
1. Is there a COA for each batch?
No
RETAIN
Yes
2. Does the label(s) show any evidence of tampering?
Yes
RETAIN
No
3. Are the label(s) and package insert(s) written in Swahili and/or English?
No
RETAIN
Yes
4. Do the batch numbers on the unit samples and the COAs match?
No
RETAIN
Yes
5. Do the expiration dates on the unit samples and the COAs match?
No
RETAIN
Yes
6. Do unit samples collected from each batch have tamper-proof seals? Are they intact?
No
RETAIN
Yes
7. Are samples required for testing?
No
Proceed to 6.1.13 of SOP
Yes
Proceed to item 6.1.12 of SOP
Yes
Proceed to conclude inspection
Report in writing to respective Zonal Manager

Chapter 5

Inspecting Distribution Points

This chapter elaborates on how inspection should be conducted for the new and operating establishments. Overall objective is to verify compliance to laws, regulations and guidelines.

5.1 Distribution points

In the distribution chain several kinds of establishments can be distinguished:-

- Manufacturing facilities
- Importers
- Pharmacies (retail and wholesale)
- ADDO shops
- Pharmacies and Pharmaceutical Storage facilities at Hospitals, Health Centers and Dispensaries
- Tobacco product Outlets
- Medical Device Outlets
- Warehouses
- Any other facility or premises where these products are found

5.2 Stages of conducting inspection

Inspection of the distribution points involves the following stages:-

- Planning for inspection
- Carrying out inspection
- Report writing

5.2.1 Planning for inspection

Planning include:-

- Preparation of inspection schedule and budget
- Preparation of inspection tools

5.2.1.1 Preparation of inspection schedule and budget

When preparing inspection schedule and budget, the following should be considered:-

- Selecting premises to be inspected based on associated risk.
- Grouping together establishments from the same location so that single trip can be organized. Preferably a minimum of two (2) establishments shall be

inspected in each day per team. However, the number shall depend on the type of business and quantity of products within the establishment.

- Travelling logistics
- Communication with other regulatory stakeholders/regulators based on the type of inspection
- Availability of funds

The schedule shall include names and physical addresses of an establishment, type of inspection, date of inspection and names of inspectors including the Lead Inspector. For each establishment inspection must be carried out by a minimum of two (2) Inspectors.

5.2.1.2 Preparation of inspection tools

Inspectors must prepare themselves for the inspection by collecting all the necessary tools needed to carry out inspection judiciously and thoroughly such as appropriate checklists, Acts, Regulations, Guidelines, SOPs and List of registered products and/or premises. Preparation also should include appointment of the Lead Inspector and review of previous inspection report, schedule and logistics such as communication and transport.

5.2.2 Carrying out inspection

When carrying out the inspection, Inspectors should follow the following steps:-

- Introduction to the government representative at respective area
- Introduction to Person in-charge of the establishment
- Perform inspection
- Briefing of the inspection outcome

5.2.2.1 Introduction to Government Representative within respective area

Upon reaching at respective area, where the inspection is to take place, the inspection team should report to the LGA's representative at that specific area (Regional and District level). Inspector(s) must present their credentials; explain the purpose of the inspection and request for an officer to accompany the inspectors during the inspection if necessary.

5.2.2.2 Introduction to Person in-charge of the establishment

Upon reaching the establishment where the inspection is to take place, the inspection must begin with the introduction of the Inspector(s) to the person in-charge or responsible for the establishment. Inspector(s) must present their credentials; explain the purpose of the inspection to the individual in-charge and request for an officer to accompany the inspectors during the inspection.

5.2.2.3 Perform inspection

When conducting inspection, Inspectors should observe and comment in the inspection checklist the following parameters:-

- General conditions of the establishment
- Physical examination of product
- Storage conditions
- Records keeping and documentation,
- Security
- Any other observation

Inspection of general conditions of establishments shall be applicable to human pharmaceutical importers, veterinary medicine outlets, medical device importer, cosmetic outlets and warehouses.

Inspectors should perform inspection systematically using appropriate inspection checklist and forms as follows:

- Guidance Checklist for conducting physical/visual examination of medicines, medical devices, diagnostics and tobacco products
- Checklist for inspecting new establishment no. TMDA/DMC/MCIE/C/001
- Confiscation forms of products, Form No.: TMDA/DMC/MCIE/F/010
- Inspection observation form and registered premises inspection checklists no. TMDA/DMC/MCIE/F/050 & TMDA/DMC/MCIE/C/004

5.2.2.4 Briefing of the inspection outcome

Inspector should convey inspection findings and observations in brief to the inspectee. Both positive and negative findings should be reported. Any suggestions for improvements may also be communicated. The findings should be filled in the inspection memorandum form of the respective inspection checklist which shall be signed in duplicate by both parties (i.e inspectors and inspectee) to indicate the non conformances, suggested corrective measures and time frame. One copy should remain with inspectee.

5.2.3 Report writing

Inspectors should prepare a final inspection report to incorporate all findings and observations where necessary for each establishment inspected. Inspection report should be written and submitted to Supervisors not more than fourteen (14) days on completion of inspection or as stipulated. Sufficient details should be provided to enable an independent assessment, comprehension and easy decision making. The format for an inspection report which Inspector should follow is attached as **Annex 1.**

Chapter 6

Product Surveillance

This chapter explains how to monitor quality of registered medicines, medical devices, diagnostics and tobacco products (Post Marketing Surveillance). Quality monitoring is one component of product surveillance whose overall objective is to ensure continued quality, safety and efficacy of products after they have been placed on the market.

6.1 Approaches for quality monitoring

Principally, there are five (5) approaches undertaken to monitor quality of products on the market:-

- Product inspection and testing at POEs
- Product inspection and testing at distribution points
- Structured Post Marketing Surveillance Programme
- Handling customer complaints
- Special operations

Effective undertaking of these approaches helps an Inspector to detect not only unregistered products, but also falsified, substandard and other illegal products on the market.

6.1.1 Product inspection and testing at POEs

During inspection of consignments at POE, Inspectors should collect samples of medicines, medical devices, diagnostics and tobacco products whenever necessary for testing as follows:-

- Samples of medicines for routine testing using Minilab Kit.
- Any suspicious sample of medicines, medical devices, diagnostics and tobacco products

6.1.1.1 Samples of medicines for routine testing

Samples of medicines for routine testing should be collected at the port of entry (as indicated in the flowchart for inspecting imported consignments in Chapter 4) and screened using the Global Pharma Health Fund (GPHF) Minilab Kit methods. Sampling should be done as per current SOP for sampling and sample collection form TMDA/DMC/MCIE/F/003 should be filled whenever sample is collected. Test methods are elaborated in details in Chapter 7 of this handbook.

Samples that will fail screening test and samples with doubtful screening results should be sent to TMDA laboratory for confirmatory/ full testing.

6.1.1.2 Suspicious samples of medicines, medical devices, diagnostics and tobacco products at POE

When conducting physical/ visual examination of the products at POEs and find products that do not meet physical quality specifications are identified, an Inspector should collect sample and send to the TMDA laboratory for confirmatory testing

6.1.2 Product inspection and testing at distribution points

When inspecting products at distribution points, Inspectors should collect samples of medicines, medical devices, diagnostics and tobacco products for testing as follows:-

- Samples of medicines for routine testing using Minilab Kit
- Any suspicious samples of medicines, medical devices, diagnostics and tobacco products.

6.1.2.1 Samples of medicines for routine testing

These samples are mainly collected from importers, health facilities and domestic manufacturers. As for POEs, samples should be collected following procedures outlined in the current SOP for sampling and by using sample collection form (**Annex 10**) and screened using the Global Pharma Health Fund (GPHF) Minilab Kit methods.

6.1.2.2 Suspicious samples of medicines, medical devices, diagnostics and tobacco products at distribution points

When conducting physical/ visual examination of the products during the routine inspection of the distribution point and products that do not meet physical quality specifications are discovered, an Inspector should collect samples by following the same sampling SOP and send to the TMDA laboratory for confirmatory testing.

6.1.3 Structured Post Marketing Surveillance Programme

Samples of products which are under Post Marketing Surveillance Programme (PMS) should be collected as per the current established programme and SOP for collecting samples for PMS.

6.1.4 Handling customer complaints

Inspection is initiated after receiving customer complaints regarding the quality, safety and efficacy of medicines, medical devices, diagnostics and tobacco products. The

customers or patients report their complaints by filling in online customer complaints Form or the Green form - Patients Adverse event reporting form..

On receipt of complaints the following steps should be executed:-

a) Acknowledge receipt of the complaint
b) Conduct thorough investigation
c) Collect sample for testing (remember to collect exhibit samples)
d) Take necessary regulatory action
e) Give feedback

6.1.5 Special operations

A special operation is conducted by focusing on one product, a group of related products, or specific operations e.g. false labeling. This inspection is unannounced and is conducted when there are complaints about a specific product or in order to gather specific information, or to investigate specific operations of a facility.

Chapter 7

Falsified Products

7.1 What is a falsified product ?

Falsified products have been defined as those products which deliberately or fraudulently misrepresent their identity, composition or source.

According to the TMMD Act, Cap. 219 (Section 76), a falsified product (referred as counterfeit product in TMDA Act) is defined as a product:-

a) manufactured under a name which belongs to another product
b) Which is an imitation of, or substitute for another product, resembles another product likely to deceive or bears upon its label or container the name of another product unless it is plainly and conspicuously marked so as to reveal its true character and its lack of identity with such other product
c) Whose label or container bears the name of an individual or company purporting to be a manufacturer of the product; which individual or company is fictitious or does not exist.
d) Which has been substitute wholly or in part by another substance;
e) Purports to be a product of manufacturer of whom it is not truly product.

Falsified can apply to both branded and generic products, and falsified products may include products whith correct ingredieints or with wrong ingredients, without active ingredient, with insufficient active ingredient or with fake packaging.

7.2 What is a substandard product?

Substandard products also called "**out of specification products"** are defined as products that fail to meet either quality standards or specifications, or both i.e. products whose composition and ingredient do not meet the correct specifications, as result they are ineffective and often dangerous to patient. Substandard products may occur as a result of negligence, human error, insufficient human and financial resources or counterfeiting.

7.3 How to identify a falsified product

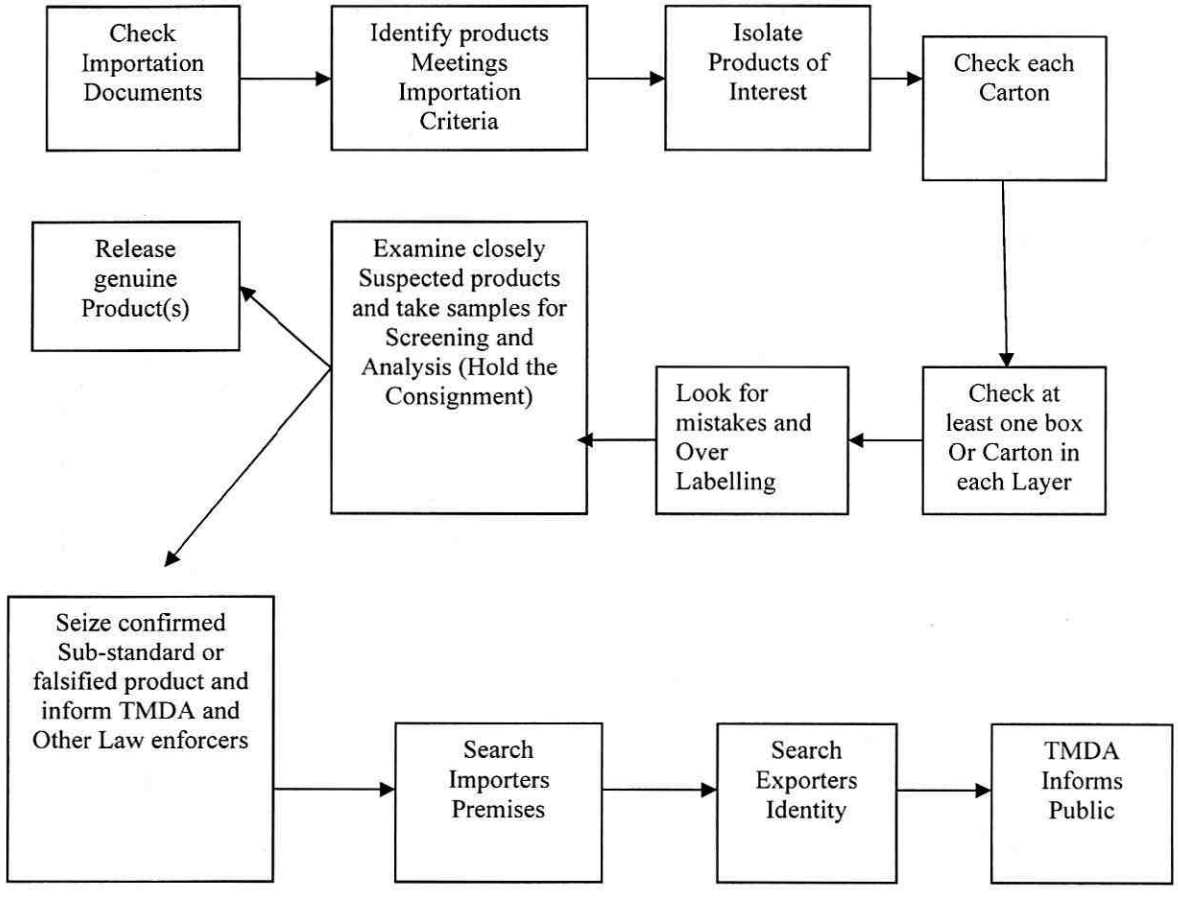
A perfect falsified product (i.e. that is well made and well labeled) is very difficult to detect.

However the following guide can help an Inspector to detect falsfied products.

What to check when examining a product:-

- Examine packaging, external and internal differences
- State of primary container if it is secure and intact
- The label of the product – its appearance, color, language, spelling and other details; is there over labeling?
- Trade name / brand name of the product – is it a registered product?
- Active Pharmaceutical Ingredient (API) name & Manufacturer's name and address – are they correct?
- Strength of the product
- Pharmaceutical dosage form and number of units
- Batch No, Manufacturing and Expiry dates – are they well printed on the label or can be easily erased
- Physical appearance of tablets/capsules/vials - uniform colour and appearances?
- Security features - compare with registered product.

Process flow diagram on how to identify falsified product:



7.4 Handling and reporting of SF medical products

SF denotes Substandard/ Falsified/ medical products.

The following questions helps a Drug Inspector to establish fact on handling SF medical product incident.

Where:

- Where is the suspect product located now?
- Where is it supplied?, and is it in the regulated chain (e.g. hospitals, clinics, pharmacies) ? or unregulated supply chain (e.g. street markets, illegal internet pharmacies)?
- Where does the product represent a risk , only in your Country or are other countries at risk?
- Where are any adverse reactions taking place?

When:

- When was the suspect product first discovered?
- When was the SF product first made available to the public or to the location/source first identified?
- When was the SF product purchased/sold?
- When did any adverse reactions take place?

Who:

- Who is the source?
- Who does it belong to?
- Who has possession of it?
- Who supplied it?
- Who else is/was involved in the transaction (Importers, brokers, Agents, wholesalers)?
- Who was it supplied to (forwarded onto) or exported to?
- Who is at risk (patient profile).?

What:

- What is the product(s)?
- What is the batch number(s). Is it authentic and for which market?
- What is/are the expiry dates?
- What condition is the product designed to treat?
- What packaging is it in (country specific, language)?
- What is the product licence/ registration number – is it authentic for the market?
- What are the severity of adverse reactions?

How:

- How far has the regulated supply chain been penetrated, has it reached patients?
- How do we get a sample (need six samples if possible)?
- How do we test (regulator's laboratory, manufacturer, where is a reference sample for testing)?
- How much of the product is available?
- How much does it cost (falsified and authentic)?
- How big is the national market for the authentic product and/or internationally?
- How many patients are at risk and how many adverse reactions are reported?

Drug Inspector should consider risk to public health by asking him/herself the following questions.

- Have any adverse reactions been reported
- Conduct enquiries with Pharmacovigilance Centres
- Who is at risk
- What is medical assessment
- Has suspect product reached consumers through pharmacies, the internet or other means (Has product entered the regulated supply chain)
- Is the product and packaging designed to deceive a Pharmacist that it is genuine
- Consult manufacturer of the genuine product
- Is the batch number and expiry date authentic, if so when was the authentic batch released
- How quickly would a batch be sold to patients
- Has the manufacturer received any complaints about that batch or product.

Chapter 8

Monitoring of Promotional Activities

Among the responsibilities of an Inspector is to monitor promotion of medicines, medical devices and cosmetics on the market. The aim is to ensure that public and health care professionals receive the correct information about the products to help them make an informed decision on the choice and rational use of products. It also includes protecting from false, misleading or deceptive promotions that would create erroneous impression regarding products they consume. This chapter provide guidance to Inspectors on how promotional activities related to medical devices and cosmetics can be monitored.

8.1 Promotion activities to be monitored

Promotional activities to be monitored are in the form of:-

- Still pictures
- Sound
- Light and Sound
- Web based
- Sales promotion
- Medical representatives and other promotion personnel
- Promotional samples
- Promotional meetings
- Public health programmes/ campaigns

8.1.1 Still pictures

These include promotional adverts in print media such as magazines, newspapers, journals, diaries, calenders, flyers, brochures, billboards, posters, branding on vehicles, buildings, benches and any other printed publication or promotion material.

8.1.2 Sound

These are promotional adverts with sound effect such as broadcast over radio, radio cassettes or any audio.

8.1.3 Light and Sound

These are promotional adverts which have light and sound effects together such as television, cinema advertisements and videos.

8.1.4 Web based

These are promotional adverts on the websites, internet or blogs.

8.1.5 Sales promotion

This is any activity with the purpose of introducing, publicising or promoting the sale of a product such as price-off and banded offers. It also includes giving discounts and banding of different pack sizes of the same product within the same range, with or without a discount distribution of samples.

8.1.6 Medical representatives and other promotion personnel

Medical representatives or any other persons involved in promotion of regulated products should have sufficient scientific knowledge about products they promote to enable them provide as precise and complete information as possible

8.1.7 Promotional samples

a) There should be no sale or supply of samples of medicines or medical devices to any member of the public for promotional purposes.

b) Samples of medicines (except for traditional medicines) and medical devices may only be supplied as free samples to qualified prescribers or pharmacists for the purpose of promotion.

c) The free samples provided by medical representatives should be labelled "Physician Sample not for Sale".

d) There are no restrictions applicable to cosmetics with regard to provision of this section.

8.1.8 Promotion meetings

a) All meetings including workshops, conferences, seminars symposia and exhibitions that are organized or sponsored by any company or under its control targeting the healthcare professionals, or any other person for the purpose of promoting medicines, medical devices or cosmetics or its launching should first obtain approval from the Authority.

8.1.9 Public health programmes/ campaigns

a) Campaigns relating to medicines, medical devices or cosmetics that are directed to the general public with a view of providing information, promoting awareness or education about a particular condition or disease are encouraged. But, care must be taken to ensure that the information provided is correct as per this handbook. Public health programme such as government controlled programme (vaccination & malaria campaigns etc) that have been

approved by the responsible Ministry are required to obtain an approval letter from the Authority

8.2 Inspectors roles

When inspecting promotional material Inspectors should make sure that;

a) Promoted products have been registered or authorized by the Authority.

b) Language used on promotional adverts are either English or Swahili or both, simple-to-understand, easily comprehensible and should not bring fear or distress to the public.

c) Promotion of products has been designed in such a way that it is clear and that the material or message are in line with the product being advertised.

d) Promotion must present information which is factually correct and those facts should not be exaggerated in any way.

e) Promotion materials are consistent with the approved product information with regards to the conditions or illness for which it has been registered.

f) Promotions are provided as per the approved adverts and it should not contain changes without approval of the Authority.

g) Public information about planned or ongoing trials in unauthorized indications/uses is not acceptable.

h) Promotion must encourage the correct and proper use of relevant products.

i) Promotional claims are presented based on study findings

j) Promotion does not refer to the Act or contain any statement which expressly or implicitly suggests that the use of the product is endorsed by the Authority.

k) Promotion of products are not conducted to the public in open markets, bus stands and moving vehicles unless approved by the Authority.

l) No posters are displayed for a specific product in a public place such as hospitals, clinics, shops.

Chapter 9

GPHF Minilab Kit for Quality Control

2.3 The GPHF Minilab

Minilab kit is simple and relatively easy technique for quality screening of essential medicinal products under importation and those already on the market. The GPHF Minilab kit can perform three tests namely:

- Thin Layer Chromatography
- Disintegration
- Colour reaction.

a. Thin layer chromatography (TLC)

TLC method is used for qualitative determination of active ingredients, related substances and impurities present on the dosage form. The method employs the principle of comparing spots obtained between test and reference solutions. The principal spot obtained with the test solution must correspond with the chromatographic runs of the lower and higher standard solutions in terms of colour, shape, size, intensity and retardation factor (R_f) value.

b. Disintegration

Simple disintegration test is used to test the possibility of solid dosage forms (e.g. tablets) to break into small particles to indicate that the product can dissolve and undergo dissolution to release the active ingredient. This is simply done using a 100ml wide neck glass bottle filled with water heated to 37°C. The tablet should be shaken occasionally for about 30 minutes, if it does not disintegrate within 30 minutes then it is an indication that it might have dissolution problem; necessitating confirmatory testing. This method is applicable to non-coated tablets. In case of coated tablets, these must be sent to TMDA laboratory for testing.

c. Colour reaction

The colour reaction is the third weapon to use if all the above tests appear to be positive. The Minilab colour reaction is easy to use and is the perfect tool for primary screening of spurious medicinal products on the spot. This method should be performed if a monograph is available e.g. Quinine.

9.1.1 Thin Layer Chromatography

9.1.1.1 Introduction to Chromatography

Chromatography is a physicochemical technique that is used primarily for the separation of components of a given sample, in which the individual components are distributed between two different phases, one of which is stationary while the other moves (is mobile). The stationary phase may be a solid or liquid supported on a solid or gel, and may be packed in a column, spread as a layer, or distributed as a film. Thus, a chromatographic system basically consists of three components: a stationary phase, a mobile phase and an inert support or matrix.

Thin Layer Chromatography is a liquid-solid planar chromatographic technique in which the stationary phase consists of a finely divided polar adsorbent material in the form of a uniform thin layer bonded onto a plate. After a mixture of drugs in the form of a solution is applied onto the plate, the plate is placed in a developing chamber, and, in the mobile phase, the drugs will move across the plate because the solvent moves up the plate by capillary action. The separation of the drugs is dependent on their solubility and the affinity between the two phases. The substances being separated/ analyzed are eventually detected on the chromatogram by UV light and chemical reactions.

TLC is primarily a separation technique, but under controlled conditions it can be useful as an analytical tool for identification and quantification of drug substances, detection of impurities, degradation products and prohibited ingredients in cosmetics products, and monitoring chemical reactions.

i. Stationary Phase

A stationary phase consists of a thin layer of appropriate adsorbent bonded onto a suitable support, which may be a glass, plastic, or aluminum plate. Binding to the plate is assured by mixing the adsorbent with a binding agent, such as calcium sulfate. Plates may be prepared in the laboratory or purchased from a reliable supplier. Pre-coated silica gel TLC plates with a binder and fluorescent indicator (silica gel GF254) are used.

ii. Mobile Phase

The mobile phase is the transport medium, the choice of which will depend on the substances to be separated and the adsorbent to be used. The mobile phase has two functions:—

(a) First, it must displace the solute (Active Ingredient/substance) from the adsorbent, so as to make it able to migrate across the TLC plate. Thus, it must have elution power. In normal-phase TLC, elution power increases with the increasing polarity of the mobile phase.

(b) Secondly, it must help to separate a mixture of products, excipients, impurities and prohibited ingredients so that they can be deposited at different positions on the chromate-plate and have different R_f values.

The solvent may be composed of one component or a mixture of two or more solvents (i.e. a solvent system). The solvents to be used in this course are able to perform the two functions for the specified products being analyzed.

iii. ***Separation Chamber***

The separation chamber is a container, usually made of glass, into which the mobile phase and a loaded TLC plate are placed in order to effect separation or analysis. A glass jar, which closes tightly, can prevent the loss of mobile phase and, hence, poor results.

9.1.1.2 TLC methods

The TLC technique involves the following procedures;

- Preparation of plates
- Preparation of mobile phase
- Application of samples and standards
- Development (running the chromatogram)
- Detection of analytes (Active Ingredient)

i. Preparation of Plates

Plates may be prepared in the laboratory or purchased. For this course and the analytical work you will be performing at your stations using the GPHF Minilab kit, pre-coated plates have been supplied. The plates provided are of analytical standard with a layer thickness of 250 cm and a size of 5 ´ 10 cm.

ii. Preparation of Mobile Phase

The specified mobile phase has to be thoroughly mixed and placed in the development chamber at a depth of about 5 to 10 mm. For reproducible results, the chamber must be saturated with the mobile phase by lining it with a filter paper before running the chromatogram. Pre-saturation prevents evaporation of the mobile phase, which would otherwise adversely affect the separation and position and shape of spots. When developing the chromate-plate, a concave solvent front indicates that the chamber is not well saturated. This must be avoided.

iii. Application of Samples and Standards

(a) Samples and standards must be dissolved in a suitable solvent, preferably a volatile solvent with low polarity, to reduce diffusion of sample. Polar solvents are strongly adsorbed to the layer, leading to marked irregularities and distortion of spots, as the mobile phase passes up the thin layer.

(b) The starting line (origin) is drawn lightly with a pencil, not a pen. The latter has organic ink, which would be taken up with the solvent when the chromate-plate is being developed. The pencil should be soft to avoid scratching the plate, which would distort the separation of substances. The starting line is drawn parallel to and about 1.5 cm from the bottom of the plate; this distance ensures that the line does not touch the solvent in the developing chamber. If the line touches the solvent, the applied substances would be washed down into the mobile phase, and a reliable chromatogram would not be obtained.

(c) On the line, spotting positions may be marked lightly with a pencil about 1 cm apart. Since the plate may run more than one sample, each spot must be properly labeled with the pencil.

(d) Samples may be applied (spotted) by using a micropipette, capillary tube, or calibrated micro syringe. For this course, 2 µL capillary tubes will be used for the purpose. Usually about 1 to 10 µL of each sample is spotted on the starting line, but in this course only 2 µL of each sample and standard will be spotted.

(e) The spotting device must be extremely small in order to obtain small spots not more than 4 mm in diameter. When large spots are applied, poor resolution results, and hence spots will be too close to each other.

(f) Only a small amount of sample should be applied (about10 µg), since overloading also leads to spreading of spots with possible tailing and other effects, resulting in erratic R_f values.

(g) Where the necessary sample may be loaded in portions, a little is applied, allowed to dry, then more is applied again, so that eventually you end up with small spots.

(h) Much care must be taken when spotting samples. The micro capillary should just touch the TLC plate, so as to avoid making a hole on the thin layer. A hole obstructs solvent flow, thus the moving spots are distorted, which may lead to poor resolution by preventing separation of substances with close R_f values.

(i) After applying all spots, they should be allowed to dry completely before the plate is placed in the developing jar. This is because the presence of sample solvent, especially water and other polar solvents will drastically alter chromatographic properties, leading to unreliable results.

iv. Development (Running the Chromatogram)

A loaded TLC plate must be in contact with the mobile phase in order for separation to be effected. The plate is placed in a vertical position in the developing chamber saturated with the solvent, with the lower edge being immersed in the mobile phase. A pair of tweezers (forceps) may be used to hold the plate to avoid contamination of the plate with hand oils.

The TLC plate may be developed with one or multiple solvents and on one or two dimensions, perpendicular to each other. In this course, one-dimensional, ascending development will be applied. Development occurs when the mobile phase moves up the plate by capillary action. It is allowed to proceed until the solvent front is close to the top edge of the plate (i.e., about three quarters the height of the plate). Spots are separated depending on how strongly they are adsorbed to the stationary phase and their distribution coefficients in the mobile phase. Polar molecules are strongly adsorbed to the stationary phase, will move slowly, and will be at lower positions on the plate. Non-polar molecules are more soluble in the relatively less polar mobile phase; they will move faster and their spots will be at a higher position on the chromatogram.

v. Detection of Analytes

After development, the plate is taken out of the jar and dried prior to detection of the separated substances. Spots on the developed chromatogram may be located by using various methods. Colored components are visible in daylight and may be detected as such. However, most organic substances are colorless and need other means of detection, some of which are nondestructive, while others are destructive. Such detection methods include the following.

9.1.1.3 Non-destructive Methods

- On examination of a plate containing a fluorescent indicator under short-wave UV light (254 nm), absorbing compounds appear as dark spots on a green background.
- Examination of the plate under long-wave UV (365 nm) will reveal naturally fluorescent compounds.
- Any spots visualized under UV should be marked lightly with a pencil.
- Detection of substances that cannot be detected by UV is achieved by using chemical reagents, which produce various colors with the substances. The reagents are used in the form of sprays or vapors. A good hood is necessary when sprays are used. Exposure to iodine vapor is one of the nondestructive ways of detection with chemical reagents.

9.1.1.4 Destructive Detection Methods

Such methods change the substances being analyzed. For example, the use of concentrated sulfuric acid is very useful for locating various substances. Plates are sprayed or dipped in the reagent, followed by heating at about 120°C. Separated substances are charred and appear as dark or dark-brown spots.

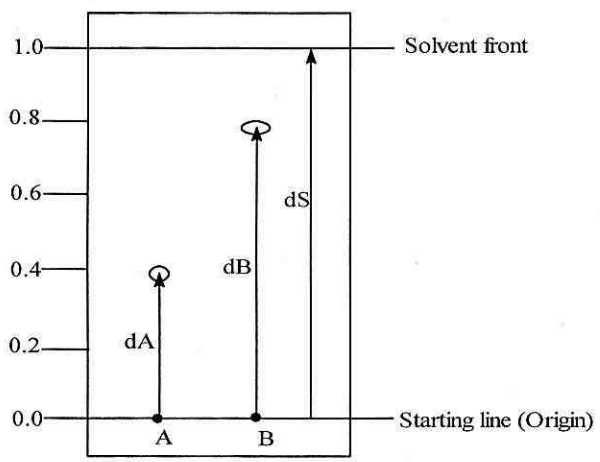
In this phase of this course, antimalarials, anti TB and ARV will be analyzed. Examination of chromatograms with UV light (254 nm and 365 nm) will be applied for all substances. In addition, the plates will be exposed to iodine vapor. Substances being analyzed appear as brown spots. The spots disappear quickly when exposed to the atmosphere; hence, they have to be traced with a pencil immediately after exposure to iodine. In the case of Artesunate combination products, plates will also be exposed to dilute sulfuric acid in methanol then place on the hotplate for some times then the spot will appear, since Artesunate and Ethambutol Hydrochloride analytes are not visible under UV and may not be visible in iodine vapor.

9.1.1.5 Evaluation

Evaluation of chromatograms is done by determination of R_f values and visual examination of spots.

i. Determination of R_f Values

R_f value, a "retardation factor" or "ratio-to-front," is determined by measuring the distances moved by the spot and the solvent. R_f value is calculated by the formula shown below:



R_f = Distance of spot center from start/Distance of solvent front from start

Thus, for substances A and B in the above figure,

R_f values are calculated as;
$R_fA = dA/dS$

$R_fB = dB/dS$

R_f values range between 0.00 and 1.00. To avoid the use of decimal points, R_f values are multiplied by 100. The values become hR_f values and range between 0 and 100.

Note the following;
(a) R_f values serve just as a guideline, since they vary depending on a number of factors.
(b) When a drug sample is run alongside a reference standard, the R_f value will be the same if both products contain the same compound.

ii. Visual Evaluation

Visual evaluation is important both qualitatively and quantitatively. Thus, for a given drug to be accepted as being of good quality and as being the same drug contained in a given dosage unit, it must correspond to the standards provided in terms of travel distances, color, and sizes of the spots on the chromatogram. Therefore, it is important to carefully;

(a) Compare the spot sizes (quantitative ratios). The spot size (area) is proportional to the amount of substance being analyzed. If the spot of a given drug being analyzed is smaller than that of the standard applied at the same concentration, then the given drug will be of poor quality, containing less of the active ingredient than expected. When a suitable color reaction is carried out on the chromatogram, spot density can be determined with a densitometer. Spot density is also proportional to the amount of substance applied. For the purpose of our training and practical field work, the densitometer will not be utilized, but spots will be evaluated in terms of spot sizes and visual color intensity.
(b) Compare the distances moved by various components. This will give the Rf values, which are especially useful qualitatively for identification purposes. By comparison of distances traveled or Rf values, one can tell whether or not the drug being analyzed is the same as the given reference standard.
(c) Compare various properties (e.g., fluorescence or fluorescence quenching). This is also important qualitatively. For a given drug to be the same as the reference standard, its spot must appear similar to that of the reference when examined under UV light.
(d) Compare colors after exposing to a chemical reagent and after heating, where this is indicated. This is useful both qualitatively and quantitatively.

iii. Documentation

TLC chromatograms may be traced on paper and colored according to the color of spots. Photocopy and Photographs of chromatograms may also be taken.

Examples of TLC testing method for minilab kit testing of some antiretrovirals, antituberclosis and some antimalarials are provided below;

(a) TLC method for Dolutegravir, Lamivudine and Tenofovir DF (50mg/300/300mg) tablets

Method: In-house Methods

Requirement:

Stationary Phase:	Silica Gel 60 with UV indicator (at 254nm)	
Mobile Phase:	Dichloromethane	12ml
	Ethanol	3ml
	Formic acid	5ml

Preparation:

Standard Stock solution: Dolutegravir/Lamivudine/Tenofovir DF (50/300/300mg/tablet) standard, powder and dissolve in 40mls of Methanol R

Std working 100%: 1ml of std stock solution + 2ml of methanol (0.41 mg/ml Dolutegravir)

Std working 80% 1ml of std stock solution + 3ml of methanol (0.31mg/ml Dolutegravir)

Sample Stock solution: Dolutegravir/Lamivudine/Tenofovir DF (50/300/300mg/tablet) standard, powder and dissolve in 40mls of Methanol R

Sample working 100%: 1ml of std stock solution + 2ml of methanol (0.41mg/ml Dolutegravir)

Plate preparation and Development:

- Heat the Aluminium back of the TLC Silica gel 60 plate using either spirit lamp for 3-5 minutes or place the plate on dry iron for 30mins. Allow to cool
- Spot **5µl** each of the standard and sample working solutions on the marked TLC plate and dry plate using dry iron provided for 1min. Proceed for development in the chamber.
- Allow the mobile phase in the chamber to saturate for 1hour before developing the TLC plate.
- Develop the TLC plate until it reaches ¾th level on the plate, remove and allow it to dry in current of air.

Detection:
Examine your chromatogram under UV light 254nm

(a) Rifampicin, Isoniazid, Pyrazinamide and Ethambutol hydrochloride 275mg tablet

Challenge:_Detection of Ethambutol Hydrochloride

Preparation of Standard Solutions

- Crush Rifampicin/**Isoniazid**/Pyrazinamide/**Ethambutol** reference tablet wrapped in aluminium foil to a fine powder using pestle.
- Empty the foil into 50ml glass bottle and wash down the residue as described below.

Reference standard solutions
Reference tablet + 30ml Methanol ► close & shake 3 minutes = Stock Standard Solution
1 ml Stock STD Solution + 5 ml of Methanol ► close and Shake = 100% Working Standard Solution
1 ml Stock STD Solution + 7 ml of Methanol ► close and Shake = 80% Working Standard Solution

Preparation of Sample Solutions

- Crush one whole tablet in aluminium foil to a fine powder using pestle.
- Empty the foil into 50ml glass bottle and wash down the residue as described below.

Sample solutions *(is prepared in comparison to 275mg of Ethambutol Hydrochloride/tab)*

Sample tablet + 30ml Methanol ► close & shake 3 minutes = Stock Sample Solution
1 ml Stock Sample Solution + 7 ml of Methanol ► close and Shake = 100% Working Sample Solution

Mobile Phase

Methanol	12ml
Toluene	10ml
Concentrated Ammonia solution	0.5 ml

Spotting: Mark your TLC plate 1.5cm from bottom
Apply 2ul of each 100% Wstd Solution, 100% Wsample solution and 80% of working standard Solution

Detection

1. After drying of the plate, observe plate under UV light of 254nm (Circle the observed spots) (for Rifam/Isoni/Pyrazi)
2. Dip the chromatoplate in the Petri dish containing acidified methanolic ninhydrin solution (for Ethambutol)
3. Measure the Rf of the principal spots

NB: Acidified methanolic ninhydrin solution - 0.3g or a well filled spatula of ninhydrin in 15ml acidified methanol)
Acidified methanol – add 3ml of glacial acetic acid in 15ml of methanol

(b) Artemether 20mg/Lumefantrine 120mg in fixed dose combination tablet

Challenge: 1. Detection of Artemether

Preparation of Standard Solutions

- Crush Artemether/Lumefantrine reference tablet 20/120mg wrapped in aluminium foil to a fine powder using pestle.

- Empty the foil into 25ml glass bottle and wash down the residue as described below.

Reference standard solutions

Ref tab 20/120mg + 10ml of Acetone ► close & shake 3 minutes = 2.0mg of Artemether/ml = Stock Std Sol = 100% Working Std Sol
4 ml Stock Standard Solution + 1 ml of Acetone ► close and Shake = 1.6 mg of Artemether /ml = 80% Working Standard Solution

Preparation of Sample Solutions (20/120mg Artemether/Lumefantrine)

- Crush one whole tablet in aluminum foil to a fine powder using pestle.

- Empty the foil into 25ml glass bottle and wash down the residue as described below.

Sample solutions

20/120mg Sample + 10ml of acetone ► close & shake 3 minutes = 2.0mg of Artemether /ml = Stock Spl Sol =100% Working Sample Solution

Mobile Phase

Toluene	:	18ml
Ethyl acetate	:	4ml
Glacial Acetic Acid	:	2ml

Detection

1. Observe under UV light of 254nm (for Lumefantrine)
2. Staining with Methanolic Sulfuric acid solution 5% (mix 19ml of Methanol + 1ml of 96% Sulfuric acid) (for Artemether)

(c) Ritonavir 100mg tablets

Method: GPHF-Minilab (*Review and Extension 2020*)

Requirement: Stationary Phase: Silica Gel 60 with UV indicator (at 254nm)

Mobile Phase:	Toluene	15 ml
	Ethyl acetate	3 ml
	Methanol	1 ml
	Glacial acetic acid 96%	1 ml

Preparation:

Standard Stock solution:	Ritonavir (100mg/tablet) standard powder and dissolve in 10mls of Methanol R.
Standard working 100%:	1ml of std stock solution + 1ml of methanol (5mg/ml Ritonavir)
Sample Stock solution:	Ritonavir (100mg/tablet) standard powder and dissolve in 10mls of Methanol R.
Sample working solution:	1ml of sample stock solution + 1ml of methanol (5mg/ml Ritonavir)

Development:

- Allow the chamber to saturate.
- Apply 2µl of your standard 100% and sample working solution onto a TLC plate & allow to dry.
- Develop the plate until ¾ of the plate and remove, allow it to dry in current of air.

Detection:
Examine your chromatogram under UV light 254nm

Results:

The principal spots obtained with sample solution should correspond in position, appearance and intensity with that obtained with standard solution.

(d) Lamivudine, Nevirapine & Stavudine tablet

Challenge:

Preparation of Standard Solutions

- Crush Lamivudine/Stavudine/Nevirapine reference tablet wrapped in aluminium foil to a fine powder using pestle.
- Empty the foil into 50ml glass bottle and wash down the residue as described below.

Reference standard solutions

Reference tablet + 40ml Water + 3drops of Conc. Hcl ► close & shake 3 minutes = Stock Standard Solution
1 ml Stock STD Solution + 3 ml of Methanol ► close and Shake = 100% Working Standard Solution
1 ml Stock STD Solution + 4 ml of Methanol ► close and Shake = 80% Working Standard Solution

Preparation of Sample Solutions

- Crush one whole tablet in aluminium foil to a fine powder using pestle.
- Empty the foil into 50ml glass bottle and wash down the residue as described below.

Sample solutions (is prepared in comparison to 200mg of Nevirapine/tab)

Sample tablet + 40ml Water + 3drops of Conc Hcl ► close & shake 3 minutes = Stock Sample Solution
1 ml Stock Spl Solution + 3 ml of Methanol ► close and Shake = 100% Working Sample Solution

Mobile Phase

Ethyl acetate	:	11ml
Methanol	:	5ml
Toluene	:	4 ml

Spotting: Mark your TLC plate 1.5cm from bottom
Apply 2ul of each 100% Wstd Solution, 100% Wsample solution and 80% of Wstandard Solution

Detection

1. After drying of the plate, observe plate with UV of 254nm and 366nm (Circle the observed spots)

2. Expose the plate on Iodine vapor

3. Measure the Rf of the principal spots

(e) Rifampicin, Isoniazid 75mg, Pyrazinamide and Ethambutol Hydrochloride tablet - edited

Challenge:_Detection of Ethambutol Hydrochloride

Preparation of Standard Solutions

- Crush Rifampicin/Isoniazid/Pyrazinamide/Ethambutol reference tablet wrapped in aluminium foil to a fine powder using pestle.
- Empty the foil into 25ml glass bottle and wash down the residue as described below.

Reference standard solutions

Reference tablet + 15ml Methanol ► close & shake 3 minutes = Stock Standard Solution
2 ml Stock STD Solution + 8 ml of Methanol ► close and Shake = 100% Working Standard Solution
4 ml 100% STD Solution + 1 ml of Methanol ► close and Shake = 80% Working Standard Solution

Preparation of Sample Solutions

- Crush one whole tablet in aluminium foil to a fine powder using pestle.
- Empty the foil into 50ml glass bottle and wash down the residue as described below.

Sample solutions (is prepared in comparison to 75mg of Isoniazid/tab)

Sample tablet + 30ml Methanol ► close & shake 3 minutes = Stock Sample Solution
1 ml Stock Sample Solution + 7 ml of Methanol ► close and Shake = 100% Working Sample Solution

Mobile Phase

Methanol	12ml
Toluene	10ml
Concentrated Ammonia solution	0.5 ml

Spotting: Mark your TLC plate 1.5cm from bottom

Apply 2ul of each 100% Wstd Solution, 100% Wsample solution and 80% of working standard Solution

Detection

3. After drying of the plate, observe plate under UV light of 254nm (Circle the observed spots) (for Rifam/Isoni/Pyrazi)
4. Dip the chromatoplate in the Petri dish containing acidified methanolic ninhydrin solution (for Ethambutol)
5. Measure the Rf of the principal spots

NB: Acidified methanolic ninhydrin solution - 0.3g or a well filled spatula of ninhydrin in 15ml acidified methanol)
Acidified methanol – add 3ml of glacial acetic acid in 15ml of methanol

9.1.2 Disintegration Test

Tablets should be sufficiently hard to withstand handling without crumbling or breaking but they should also be sufficiently soft for easy disintegration in the stomach or intestine in order to make the drug available to the body. Due to poor drug processing or wrong storage, tablets and capsules may harden and fail the disintegration test. The test determines whether tablets or capsules disintegrate in water within 30 minutes.

All uncoated tablets and capsules and all soluble, dispersible, effervescent, and film-coated tablets—hence, all quick-release formulations—have to comply with this time of complete disintegration. Sugar-coated tablets may meet this specification, but it is not a requirement. Only modified-release and enteric-coated tablets and capsules are allowed to deviate from this time of complete disintegration. These tablets and capsules should be labeled as such and not be subjected to this test. These products require a more sophisticated disintegration test.

Simple falsified preparations such as capsules containing just sand or ground ceramics, or tablets made only of meat flour, are easily spotted by their disintegration behavior. Ground ceramics or sand settles straight to the bottom of the flask, whereas the supernatant liquid stays clear or almost clear. Tablets and capsules containing only meat flour never really disintegrate. They just soak up water and form a sticky mass or disintegrate into a couple of sticky lumps that slowly settle at the bottom of a beaker. State-of-the-art tablets and capsules containing modern disintegrants behave completely differently. For example, uncoated tablets of good quality will normally completely disintegrate in water at 37°C within 15 minutes.

Disintegration is defined as that state in which no residue of the tablets and capsules, except fragments of undissolved coating, remains in the test solution. It is a major defect if a drug product doesn't pass this test. The product can be rejected at this stage already. No further TLC assay or any other tests are required. This will save organic solvent and reference samples.

Below are disintegration test method of some products;

(a) Artemether/Lumefantrine tablets

Medium: Water (37 °C)
Time: 30 minutes
Procedure:
Measure 100ml water
Heat water to the temperature
Set timer 30min & Drop tablet & close the bottle
Tilt up & down in moderate speed until the whole tablet breaks into small pieces
Record the time taken to break.

(b) Rifampicin/Isoniazid/Pyrazinamide/Ethambutol TABLETS

Medium: Water (37 °C)
Time: 30 minutes
Procedure:
Measure 100ml water
Heat water to the temperature
Set timer 30min & Drop tablet & close the bottle
Tilt up & down in moderate speed until the whole tablet breaks into small pieces
Record the time taken to break.

(c) Lamivudine/Stavudine/Nevirapine tablets

Medium: Water (37 °C)
Time: 30 minutes
Procedure:
Measure 100ml water
Heat water to the temperature
Set timer 30min & Drop tablet & close the bottle
Tilt up & down in moderate speed until the whole tablet breaks into small pieces
Record the time taken to break.

9.1.3 Colour reactions

Visual inspection of labels, packaging materials, multi-unit dose containers, single-unit dose containers, folding cartons, tablets, and description aids for visual inspection of capsules as well as disintegration test allow the identification of rough counterfeits for timely rejection prior to employing color reactions for further examination. Therefore, color reaction will be our third weapon to use if all the above tests appear to be positive.

We have discussed a number of color reactions in the previous sections. If you have done color reactions by using the monographs described above, you will know that most of the color reactions involved are not only tedious but also time consuming, and you need some special training to be able to do them precisely. In contrast, the color reactions discussed next are not only cheap but also requiring little training.

The Minilab color reaction is easy to use and is the perfect tool for primary screening of spurious drug products on the spot. Many national and international pharmacopeias have been screened for the selection of color reactions on pharmaceutical preparations.

All methods selected have been tested and are sufficiently rugged, accurate, and sensitive to verify the identity of drug product on routine basis. A time-consuming extraction of the drug will not be necessarily required. All the tests are well described in the manual that is provided with our Minilab kits. The tests described in the manual are only intended to verify the identity of pharmaceutical preparations. They should not be used to replace pharmacopeia monographs.

All samples, which are potentially counterfeit, should be subjected to a TLC assay as described in the second volume of the manual or referred to a full-equipped laboratory for further investigations prior to taking legal action. For good and reliable analytical results, only reagents and solvents of high purity should be used. The concentrations, which are commonly expressed in normalities or molarities, have been converted into percentages for easier understanding.

Reagents and test solutions are dispensed via volume. Tablets or capsules containing a fixed amount of drug substance are dispensed by just dividing them into equal parts as directed in the individual monograph. A balance will not be required.

Deionized or distilled water is the most common solvent to be used. In places where this grade of quality is not easily accessible, clear tap or rainwater might be used. (There are provisions made that are indicated on the individual monograph concerned.)

2.4 Health and Safety

It is recommended to use protective gears - for example, an apron, gloves and safety spectacles - before starting work especially on a colour reaction. Spectacles must be worn at all times to avoid accidental contact with potentially hazardous test solutions and subsequent eye injuries.

2.5 Screening report

To conclude the Minilab test, the inspector shall fill in Screening report form F02/TMDA/DLS/SOP/011

Chapter 10

Enforcement

Inspection of regulated products shall be carried out by Inspectors in the appropriate manner as provided for in the Act and this handbook. Inspectors shall take immediate action to control and manage any risks which may arise from contravention of the Act pending any further action as may be found just by the Authority.

In exercising their powers for ensuring compliance to the Act and for proper administration of inspections; inspectors shall take immediate actions on the following scenarios which contravenes the Act or Regulations or Rules made therein:-

S/N	OFFENCE	SECTION	PENALTY	COMPUTED PENALTY
1.	Manufacture for sale, sell, supply or store products regulated under the Act in premises that are not registered	Section 18(4)	Fine of not exceeding 5,000,000 or to imprisonment for a term not exceeding two years or both such fine and imprisonment	Offence of unregistered Premises cannot be compounded. However, because most businesses are willing to comply, the following measures should be taken; • Order to close premises until permit has been obtained. • For un-renewed business permit give 14 days for permit renewal and penalty after 3 months. • Unregistered importers will most likely have other offences like lack of import permit and having unregistered medicines. Actions will be taken accordingly.
2.	Manufacture, import or wholesale	Section 22(3)	Fine not exceeding 5,000,000 or	This offence can be compounded for wholesale and importers

	products regulated under this Act that are not registered c/s 22(2)(a) and (b)		imprisonment for a term not exceeding two years or both	because it was created for Manufacturers and Importers of unregistered products. However, since most of the offenders are just retailers, Inspectors may use the general fine under S.123(1) which is 1,000,000 shillings or imprisonment for 6 months. If repeated the offence can be charged with 12 months imprisonment. Computation of formular under fees and charges Regulations 2022: 1) **When medical products will not be subjected for disposal:** • Offender can be charged 2% FOB, + 15% of 2% FOB for paying special permit out of time 2) **Incase of Products for disposal,** the cost of 25% shall be imposed plus 2/3 of 1000000. **NB**: The 25% Disposal Cost is not a must to apply until when the products are found unfit for use. Take note that, when the Special permits has been retrospectively charged/

				granted together with 15% fine. The Products may be allowed to be sold under the Special permits because is not always true that all unregistered products are condemned for disposal (Read section 57 of the Act)
3.	Restriction for sale of products regulated under this Act c/s 22(2)(c) and (d) [Registered, appropriate or against license conditions]	Section 22(4)	Fine not exceeding 500,000 or imprisonment not exceeding tree months or both	Offence can be compounded if committed by retailers dealing with unregistered medical products. 3) **When medical products will not be subjected for disposal:** • Offender can be charged 2% FOB, + 15% of 2% FOB for paying special permit out of time 4) **Incase of Products for disposal,** the cost of 25% shall be imposed plus 2/3 of 500000. **NB**: The computation above may apply for the offences of dealing with medical products without appropriate permits or against license conditions.
4.	Manufacture, sale and distribution of undesirable drugs, medical	Section 60(2)	Fine not less than one million shillings or imprisonment for a term of not	The offence cannot be compounded **NB**: The prohibited medical product referred

	drugs or herbal drugs contrary to Section 60(1)		less than six months or both	must have been published in the government gazette (GN number)
5.	Violating the conditions for conducting clinical trails	Section 71	Fine of not less than ten million shillings or to imprisonment for a term of not less than five years or both	The offence cannot be compounded **NB**: The offence does not relate to the fees and charges so the matter may be taken to court for legal action.
6.	Importing and exporting of drugs, medical devices, herbal drugs or poisons into Mainland Tanzania without license or permit in accordance to Section 73(1)	Section 73(6)	Fine of not less than one million shillings or to imprisonment for a term of not less than six months or to both fine and imprisonment	Computation of formular under fees and charges Regulations 2022: • 2% FOB, + 15% of 2% FOB for Pay out of time without condemning the medical products; and • Incase of Products for disposal the 25% shall be charged plus the 2/3 of 1000000/=.
7.	Sale of adulterated or unfit drugs, medical devices and herbal drugs (including expired drugs, medical devices and herbal drugs) C/S 75(1)-(3) &(6)	Section 75(1)-(3)&(6)	Fine of not less than five hundred shillings for an individual and not less than three millions for a body cooperate	Compounding of offence is permitted. Computation of formular under fees and charges Regulations 2022: Disposal fees of 25% shall be charged plus the 2/3 of 500,000/= for an individual and 2/3 of 3,000,000/= for a body corporate.
8.	Manufacture, import, supply, possess or offer for sale any counterfeit drug, herbal drug or	Section 76(1), (2)	Fine of not less than five million shillings or to imprisonment for term of not less than two	1. If the product has been previously identified and analysis conducted and public notice issued, preference first should be taken to court, in the

	medical device c/s 76(1),(2)		years or both	alternative computation of formular under fees and charges Regulations 2022: • 2/3 of 5,000,000/= + 25% disposal cost 2. If the product is only suspected to be counterfeit (not officially identified), institute trial by way of Preliminary Enquiry (PE). Take samples for laboratory analysis as per section 101 of TMDA Act that requires to divide samples into three. Once results are out and confirmed to be counterfeit, institute legal proceedings. In case samples taken did not meet the legal requirements of dividing into three, after laboratory analysis consider compounding of offence.
9.	Dealing in any prohibited drugs without permit issued by the Authority in accordance to Section 82(1)	Section 82(2)	Imprisonment for a term of not less than five years and where the convicted person satisfies the court on special circumstances, liable to a fine of not less than five million shillings or to imprisonment	If disposal is required, 25% shall be paid plus 2/3 of 5,000,000.

			for a term not less than one year or to both fine and imprisonment.	
10.	Selling or supplying or have in possession for purposes of selling or supplying any product regulated by the Act in a container or package which is not labelled c/s 92(1)	Section 92(3)	If is an individual, fine of not less than five hundred thousand shillings or to imprisonment for a term of not less than three months or both fine and imprisonment.	If disposal is required, 25% shall be paid plus a fine of 2/3 of the 500,000/=
11.	Advertising drugs, medical devices or herbal drugs in a manner that is false, misleading or deceptive or likely to create erroneous impression c/s 98(1),(2) and (4)	Section 98(4)	If is an individual, fine of not less than one hundred thousand shillings or to imprisonment for a term of not less than two weeks or both fine and imprisonment If is a body corporate or association, fine of not less than one million shillings.	If is an individual, fine of 2/3 of TZS 100,000/= may be imposed or for a body corporate a fine of 2/3 of TZS 1,000,000/=. If disposal is required, 25% shall be paid
12.	Removes, alters or obliterates the mark, seal or other designation with intent to deceive any	Section 101(4)	Fine of not less than one hundred thousand shillings or to imprisonment	If disposal is required, 25% shall be paid plus 2/3 of 100000

	person		for a term of not less than two weeks or to both such fine and imprisonment.	
13.	Refuses or fails without reasonable excuse, to give any information which he is lawfully required to give. -Gives any information which is false in a material particular or which he reasonably believes to be untrue -Refuses or fails without reasonable excuse, to give any information which he is lawfully required to give.	Section 106(3)	Fine of not less than five hundred thousand shillings or to imprisonment for a term of not less than three months or to both	Offense cannot be compounded. **Rationale**: It is not related to Fees and charges.
14.	Discloses any particulars or information or fails to comply with the requirements set under Section 107(1) – (3) *	Section 107(4) & (5)	General Penalty S.123	Offense cannot be compounded. Reason: It is not related to Fees and charges.

15.	Usage of certificate of analysis obtained under Section 108(1) for the purpose of advertisement	Section 108(3)	Fine of not more than one hundred thousand shillings or to imprisonment for a term of not less than two weeks or both	Offense cannot be compounded. **Rationale**: It is not related to Fees and charges.
16.	Offense relating to warranties or certificate of analysis	Section 113	Fine of not less than three hundred thousand shillings or to imprisonment for a term of not less than one month or both such fine and imprisonment.	Offense cannot be compounded. **Rationale**: It is not related to Fees and charges.
17.	Forfeiture	Section 115(1)	General penalty S.123	Offence cannot be compounded. **Rationale**: It is not related to Fees and charges. It is only by court order or other large remedies under the Act.
18.	Operating a product manufacturing facility without key technical personnel,	General Section of Act and Regulation No.16, GMP Regulations, 2018	Fine under general S.123(1) which is 1,000,000 shillings or imprisonment for 6 months. If repeated the offence can be charged with 12 months imprisonment.	Offence can be compounded. Issues a stop order of production for a period that will be specified in the Memorandum agreed and signed by inspectors and facility representatives after which the service of the key personnel will have been secured.

19.	Lack of quality control laboratory in a Manufacturing facility and any other critical deficiency contrary to provision of the Act	General Section 123 of the Act and Regulation No.11, GMP Regulations,2018	Fine under general S.123(1) which is 1,000,000 shillings or imprisonment for 6 months. If repeated the offence can be charged with 12 months imprisonment.	Offence can be compounded. Issues a stop order of production for a period that will be specified in the Memorandum agreed and signed by inspectors and facility representatives after which the deficiencies shall have been corrected.
20.	Falsification of importation documents	Section No.335 of the penal code	Imprisonment for seven years	Detain the consignment and institute legal procedures
21.	Premises operating without a superintendent e.g. pharmacist, veterinarian contrary to Regulation No.5 of premises registration Regulations, 2021	General Section 123 of the Act	Fine under General S.123(1) which is 1,000,000 shillings or imprisonment for 6 months. If repeated the offence can be charged with 12 months imprisonment.	May be compounded. For importers, issue three month notice to seek the services of another superintendent. Failure to do so close the premises. For other premises, liaise with Pharmacy council or Veterinary council of Tanzania
22.	Registered premises found under improper conditions eg. Not clean, storage temperature and humidity exceed limits, and leakage of the roof contrary to Regulation No.9 of the GSDP Regulations, 2021	General Section 123 of TMDA Act, Cap.219	Fine under general S.123(1) which is 1,000,000 shillings or imprisonment for 6 months. If repeated the offence can be charged with 12 months imprisonment.	Order to immediately clean the premises. Also order to put in place AC system, and renovating roof as appropriate within 14 days.

23.	Lack of proper documentation and no record-keeping Contrary to Regulation No.34 of the GSDP Regulations, 2021	General Section 123 of TMDA Act, Cap.219	Fine under general S.123(1) which is 1,000,000 shillings or imprisonment for 6 months. If repeated the offence can be charged with 12 months imprisonment.	• If no purchase documents, compound the offence. • Lack of other documents (e.g Job descriptions, procedures, quality manual), order to put in place a documentation and record system within 14 days.
24.	Manufacture, Sell or use any controlled drug for medicinal or scientific purpose C/S 78 (1)-(4) example failure to retain prescriptions,	Section 78 (1)-(4)	Fine not less than Fifty thousand shillings or to imprisonment for a term not exceeding six months or both	Order for justification. If not satisfactory issue warning letter or based on extent of violation institute legal proceedings
25.	Sell, Supply, import any product by way of wholesale dealing or retail without permit granted by the Authority for that purpose (eg. *Found in possession of products belonging to Government*)	Section 22(2)(c)	• Fine of not less than five million shillings or to imprisonment for a term not exceeding two years or to both for manufacturers, importers and wholesalers. • Fine not exceeding	No compounding of offence, Seize the products and institute legal proceedings

			five hundred shillings or to imprisonment for a term not exceeding three months or to both for retails	
26.\	Willfully delaying or obstructing an inspector C/S 106 (3) (a)	Section 106 (3)(a)	• Fine not less than five hundred thousand shillings or imprisonment for a term not less than three months or both	No compounding of offence. Institute legal proceedings.

Notwithstanding measures instituted by the Authority or Inspectors, the Authority shall be at liberty to institute any criminal proceedings before a competent court of law.

ANNEXES
Annex 1:

Guidance Checklist for conducting physical/visual examination of medicines, cosmetics and medical devices

SN	Name of Products	Batch No.

A: Test Results and Observations: Tablets/Capsules

	Parameter	Specification(s)	Status		Results/Other Observations
			Pass	Fail	
1	Uniformity of Size (visual inspection)	Uniform in size			
2	Uniformity of Shape	Uniform in shape			
3	Uniformity of color	Uniform in color			
4	Presence of open or broken capsules	Free of open or broken capsules			
5	Stickiness	Non-stick			
6	State of primary container	Should not show any evidence of cracks, breaks, tears, or leakage.			

B: Test Results and Observations: Solution and Suspension Dosage Forms

	Parameter	Specification(s)	Status		Results/Other Observations
			Pass	Fail	
1.	(a) Particulate matter	Liquids (syrups and solutions) should be entirely free of foreign particles			
	(b) Clarity	The liquid/solution should be clear and free of turbidity			
2	Liquid/solution and parenteral dosage forms	Easily dispersed to obtain a homogeneous suspension upon moderate shaking for 20 seconds			
		Remain homogeneous for at least three minutes			
3	State of primary container	Should not show any evidence of cracks, breaks, tears, or leakage.			

C: **Labelling requirements**

s/n	Instructions	Result /Decision		
1	Are there COAs for each batch?	Y	N	
2	Do the labels show any evidence of tampering?	Y	N	
3	Is the language written on the label and package insert Swahili and/or English?	Y	N	
4	Do the batch numbers on the unit samples and the COAs match?	Y	N	
5	Do the expiration dates on the unit samples and the COAs match?	Y	N	
6	Do unit samples collected from each batch have tamper-proof seals? Are the seals intact?	Y	N	
7	Are samples required for testing? If yes, proceed to SOP # TFDA/DMC/MI&E/SOP/010	Y	N	If no, proceed below to conclude the inspection.

Annex 2

Inspection Report Format

This format provides guidance on writing inspection report by inspectors

(i) Cover page
- Name of institution
- Title of the report
- Name of inspectors
- Date

(ii) Acknowledgement
An appreciation of the contribution and participation of groups of people, stakeholders and individuals involved in one way or another during inspection

(iii) Acronyms
List of abbreviations commonly used in the report

(iv) Table of contents
List of topics and pages to be located

(v) Introduction
- General overview
- Scope of inspection
- Purpose/ objectives of inspection
- Methodology

(vi) Main body of the report
- Observations/ findings
- Conclusion

(vii) Recommendation

(viii) Name of inspectors and signature
Name and signatures of inspectors participated in that inspection

(ix) Appendices
- List of inspected establishments
  To indicate name and address of the establishment, observation found and action taken

- List of tools and checklist used