INSPECTION GUIDELINE, 2018

With additional guide for GPHF-MiniLab™

Inspection Division
Drug Regulatory Authority
Royal Government of Bhutan

1st Edition, 2018

Table of Contents

Background

The inspector has the duty to protect public health by ensuring that all medicinal products in the market comply with the required standards. This compliance is achieved by ensuring that all products circulating in the market have market authorization and that the premises where these medicines are manufactured, stored, distributed, sold and dispensed are operated according to the prescribed standards, rules and regulations.

Law enforcement is the mainstay of the work of an inspector. In accordance with the Section 15 of the Medicines Act of the Kingdom of Bhutan 2003, Chapter XIII of the Bhutan Medicines Rules and Regulation 2012 and Chapter VII of the Blood and Blood Products Regulation 2016, the inspection must be carried out following prescribed standards and procedure. While specific Standard Operating Procedures are to be followed during execution of inspection, this general guideline will help in proper planning and effective utilization of available resources through harmonious approach.

Attributes of an inspector besides their duties, roles and responsibilities are highlighted while general procedures for all types of inspection are detailed in this guideline. An inspector during inspection is expected to discharge their duties diligently and professionally.

Objectives

This guideline should guide inspectors on how to carry out inspection and to determine effectiveness and efficiency of the inspection activities for improving the quality of services.

Scope

This guideline should apply to inspection activities of all the facilities which are involved in manufacture, compounding, import, storage, export, sale, dispensing and distribution of medicinal products.

Definitions

Act refers to the Medicines Act of the Kingdom of Bhutan 2003

Authority refers to the Drug Regulatory Authority

Critical defect refers to a system which has deficiencies that indicates a potential risk and that the product could be harmful to the consumer.

Embargo or seizure memo refers to the memo issued to the licensee at the time of detention or seizure of medicinal products respectively, while enforcing the provisions of the Act. This format is attached as annexure 1 and 2 to this guideline.

Lead Inspector refers to the Inspector identified from the team based on seniority and experience. The Lead Inspector should coordinate and prepare inspection based on SOP.

Major defect refers to a system with deficiencies that may indirectly produce a product which is not in accordance with the market authorization or a deficiency which indicates a potential deviation from the Good Manufacturing Practices.

Manufacturing firms refers to the facilities wherein medicinal products are being manufactured.

Medicinal product refers to all types of medicinal products including biologics, herbal & traditional medicines, raw materials for manufacture of medicines and pharmaceutical formulations. This also includes blood and blood products.

Inspection refers to assessment of medicines and the premises to ensure that it meets prescribed standards, specification and regulatory requirements. Though it is synonymous with the audit, later is used for inspection of pharmaceutical manufacturing facilities.

Inspector refers to inspector appointed by the government under section 15.1 of the Medicines Act of the Kingdom of Bhutan 2003.

Other defect refers to defects which are not classified as either critical or major defects. It refers to feedback or recommendation for improvement to the quality management system or individual procedures.

Sale and distribution premises refers to all the facilities except manufacturing firms which are involved in import, export, sale, storage and distribution of medicinal products. This also includes compounding of formulations which are performed in small scale as part of pharmacy practice within the hospitals and dispensaries.

Premises or facilities refers to the government health and veterinary centers, private retail and wholesale pharmacies, manufacturing firms, projects clinics/ dispensaries, Non-governmental organization and others where medicinal products are handled.

Regulations refers to the Bhutan Medicines Rules and Regulation 2012 and the Blood and Blood Products Regulation of Bhutan 2016.

Acronyms and Abbreviations

CAPA: Corrective Action and Preventive Action
cGMP: current Good Manufacturing Practices
DRA: Drug Regulatory Authority
GMP: Good Manufacturing Practices
GPHF: German Pharma Health Fund-Minilab™
PIC/s: Pharmaceutical Inspection Convention & Pharmaceutical Inspection Co-operation Scheme
Rf: Retardation Factor or ratio-to-front
SMF: Site Master File
SOP: Standard Operating Procedure
SSS: Stock Standard Solution
SSaS: Stock Sample Solution
TAM: Technical Authorization for Manufacture
TLC: Thin Layer Chromatography
UV: Ultra Violet Light
WHO: World Health Organization
WSS: Working Standard Solution
WSaS: Working Sample Solution

Introduction

The main objective of medicinal inspection is to ensure that drugs both locally manufactured and imported meets the set standards of quality, safety and efficacy. It also helps to ensure the safety of the consumers by enforcing medicines regulation related to manufacture, compounding, sale and distribution, importation, exportation, storage, and use of drugs. In doing so, following facilities should be inspected:

- Pharmaceutical manufacturer (those that intends to manufacture (for provisional TAM) and those that are manufacturing medicinal products)
- Ports of entry;
- Retail pharmacies and Wholesale pharmacies;
- Government health and veterinary facilities;
- Project clinics and dispensaries; and
- Any premises or individuals suspected of illegal sale and distribution of medicinal products.

Types of inspection

The planning, organization, method of work and format of the resultant report should always be determined by the precise objective of the inspection. Inspections vary in nature according to the objective.

Routine Inspection

Routine inspections are generally intended for a premise that has applied for a permit to extend its scope of operations or has moved to a new premise/location or has not been inspected in a long time. Routine inspection will be either announced or unannounced as deemed necessary by the Authority. In this type of inspection, the facilities are thoroughly inspected.

Additionally, for pharmaceutical manufacturing firms, routine inspection may be conducted when there are requests for renewal of a license or has introduced new product lines or new products. Further, when significant modifications to manufacturing methods/processes or premises are made, routine inspection may be conducted.

Authorization Inspection
Authorization inspections are undertaken to assess the suitability and adequacy of the new premise before technical authorization is issued. This can be an announced inspection.

Follow-up Inspection
Follow up inspections are normally carried out to ensure that corrective and preventive actions were implemented following recommendations from the previous inspection. Follow-up inspections are planned and conducted depending on the degree of deficiencies or non-compliances. If a time limit was given for applying the corrective measures, the inspection should be unannounced.

Special Inspection
Special inspections are undertaken to deal with specific complaints received about lapses **o**r non-compliances. The inspection should preferably be unannounced.

For GMP, Special Inspections are also made following product recalls. Such type of inspection may be focused on one product, a group of related product or specific manufacturing operations. Special visit may also be made to verify production and product consistency for marketing approval. Additionally, special type of inspection may be made to gather specific information or advise manufacturer on specific requirements.

Cooperation with other agencies

Inspectors are expected to interact and cooperate with other interested parties and relevant law enforcement agencies such as Bhutan Agriculture and Food Regulatory Authority, Department of Revenue and Customs, Bhutan Narcotic Control Authority, Royal Bhutan Police and Bhutan Post.

Organizational aspects

The responsibility, authority and reporting structure of the Inspection Division should be clearly defined and documented supported by written job descriptions for each staff.

- Inspectors should report either to the Chief of the Division or the Drug Controller right after the completion of inspection activities or in case of such problems requiring interventions during inspection.
- There should be regular meeting of the Inspectors during which experiences from the field are exchanged to promote uniform approach to inspection and enhance their performance.
- Inspectors should strive to collaborate both within and with other divisions.
- Inspectors should work according to the work plan and in line with the Standard Operating Procedures.
- Inspectors stationed at branch office should submit weekly reports of their work to the head office.
- Inspectors should maintain up to date inspection data in the system.
- Inspectors should have a formal statement while recommending for grant or/and maintaining authorizations (licenses).
- The Inspection Division Chief should ensure that all personnel are competent to carry out their assigned duties. They should receive appropriate training that should be documented, and its effectiveness assessed.

Qualification of an inspector

In line with Section 15.1 of the Act, the inspectors should have following prescribed qualification and experience:

- For inspection of sale and distribution premises of pharmaceuticals, the inspector shall have minimum of Diploma in Pharmaceutical Sciences/Pharmacy/Veterinary science OR have a minimum of two years' certificate in Pharmacy with at least five years' experience.
- For inspection of Blood Centers, inspector shall have a minimum qualification of bachelor's degree in relevant field while a minimum of certificate in relevant field is required for inspection of Blood Storage Centers.
- For GMP inspection, the inspector shall have minimum degree in the relevant field. The relevant field shall be determined by the Authority.

In the event, where persons with necessary qualifications but inadequate experience are employed as inspectors, they should work under supervision until substantial experience is accumulated in the field of inspection.

The credibility of the inspection process will depend to a large degree on the technical competency and integrity of the inspectors. Thus, to perform inspections more efficiently, inspectors should have following attributes:

- Competent and possess the required expertise including technical and communication skills to perform the functions that they undertake.
- Appropriate qualifications, training, experience and knowledge of the inspection process.
- Ability to make professional judgment as to the conformity of the inspected party with the requirements of good practices, relevant legislation and be able to make an appropriate risk assessment.
- Willingness to accept the challenges.
- Good skills in determining the genuineness of documents presented for examination.
- Maturity, honesty and integrity.
- Ability to hold discussions with licensee/Competent Person, motivate others and organize their own work with minimum supervision.
- Ability to assess facts quickly and take rational and sound decisions without delay, if necessary.
- Ability to assess character and honesty of persons being interviewed
- Good relations with the licensee/Competent Persons while remaining firm, fair and resolute.

Powers of an Inspector

The Inspector appointed under Section 15.1 of the Medicines Act of the Kingdom of Bhutan 2003 and officials authorized by the Authority may:

- Inspect premises wherein any medicinal product is being manufactured, sold, stocked or offered for sale, dispensed, compounded or distributed.
- Take samples of medicinal product as per the relevant SOPs for testing which is being manufactured, or being sold, dispensed or stocked or offered for sale, or is being distributed.
- Search any person, enter any premises, whenever inspector has reasons to believe that an offence is being, or has been committed
- Carry out duties under the provisions of the Act in accordance with the Civil and Criminal Procedure Code of the Kingdom of Bhutan, 2001.

- Issue the detention/seizure memo attached as Annexure 1 and 2 to the person in possession of the medicinal product in respect of which the offence has been or is being committed.

Duties of an Inspector

The Drug Inspector and the officials authorized under section 15.2 of the Act shall:

- Satisfy himself that the duties and conditions of the licensees and Competent Persons are being observed.
- Satisfy that good practices are followed for manufacture (including compounding, labelling), sale, storage, import, export and distribution of medicinal products.
- Take the sample of the suspected defective product for testing.
- Inspect and verify all records of disposal of pharmaceutical waste in accordance to the Waste Prevention and Management Regulation 2012 and guidelines prescribed thereunder.
- Seize/ embargo the medicinal products by issuing seizure/embargo memo.
- Investigate any compliant made in writing as per the SOPs.
- Maintain record of all inspections made and actions taken in the performance of his/her duties including taking of samples, seizure of stocks and to submit report of such records to the Authority.
- Make such inquiries and inspections as may be necessary to detect sale of medicinal products in contravention of the Act.
- Not disclose any information acquired during official duties without the sanction in writing from the Authority except when required by the court of law and for official business.

Code of Ethics and Conduct for inspectors

The inspectors:

- Should be required to adhere to the established rules, regulations, and SOPs in executing their functions.
- Should not solicit or accept gifts or any other item of monetary value from any individual/organization/manufacturer/entity doing business with or carrying out activities regulated by the Authority or whose interest may be substantially affected by the performance or non-performance of the inspector's duties.

- Should not participate in any matter with an outside individual/organization/manufacturer/entity that will substantially affect their financial interest, performance, or efficiency.
- Should act impartially and not give preferential treatment to any individual/organization/manufacturer/entity.
- Should conserve Authority's property and should not use it for private gain or any activity that is not authorized.
- Should disclose fraud, abuse of power, or corruption to the Authority.
- Should put forth an honest effort to follow established procedures in discharging their duties and in making decisions, if required.
- Should not use the non-public information gained during discharging their duties or from their day-to-day duties for their personal gain, nor allow the improper use of such information to further their private interests.
- Should endeavor to avoid any actions that create the appearance that they are violating the law or ethical standards or not acting impartially.
- Should note that failure to comply with the established rules, regulations, and SOPs is an offence that shall warrant disciplinary action.
- Should make accurate report of the fact observed.
- Should refrain from expressing personal views; such remarks or opinions may be interpreted official.
- Should not neglect anything that may prove useful as an evidence in support of the inspection conducted.
- Should be courteous and demonstrate composure and competence in work. Do not lose temper when abused or accused. Always stay calm.
- Should not be afraid to approach any person or premise.
- Should uphold the honor and dignity of their profession and avoid association with any enterprise of questionable character or apparent conflict of interest (avoid both perceived and potential conflict of interest).
- Should always endeavor to maintain and increase their level of knowledge regarding new developments in the field.
- Should strive to achieve the highest ethical standards for conduct that they are capable of.

Security and Safety of an Inspector

The work of Inspector as law enforcer is certainly associated with risks to their safety. This risk is understandable as during the process of discharging their

duties, inspectors frequently interfere with illegal and deceitful commercial interests. In many instances, the inspection activities cause financial losses to proprietors. In some cases, the inspector may encounter dishonest individuals whose business may have thrived in the unregulated environment and who may resort to any means to maintain their illegal business dealings.

Problems of security for Inspectors cannot be eliminated, but the risks can be reduced if an inspector adhere to the following:

- At the site of inspection, introduce yourself as an inspector and ensure that you have an approval letter from the Authority for inspection of that facility.
- Conduct inspection in a group of at least two because it is easier to threaten an individual than a group of officials.
- Always perform inspections in a courteous but firm manner. Follow the SOPs.
- Inform the other members of the inspection team and the licensee/proprietor of what is expected and of any deficiencies identified during the inspection.

Frequency and duration of Inspection

The frequency of inspection will depend upon the location of the premise, criticality of non-compliances, availability of inspectors and number of complaints received on illegal sale and distribution of medicinal products. Type of inspection, size of the premise to be inspected, purpose of inspection and the number of inspectors is considered while determining the frequency and duration of inspections.

For all in-country pharmaceutical manufacturing firms, inspections should be carried out on a regular schedule, at-least twice a year. However, for new authorization holders, inspection should be more frequent until the inspectors are confident that the licensee and the manufacturers are complying with the relevant national/ international GMP guidelines such as WHO and PIC/s GMP guidelines.

Inspection Procedure

It is very important to have a written procedure for inspection to institute a uniform and efficient inspection process. Though general principles and

guidelines are same, for clarity, the inspection process is detailed under following two categories:

- GMP audit of Pharmaceutical manufacturer
- Inspection of sale and distribution premises.

General flow of inspection procedure is presented below in figure 1.

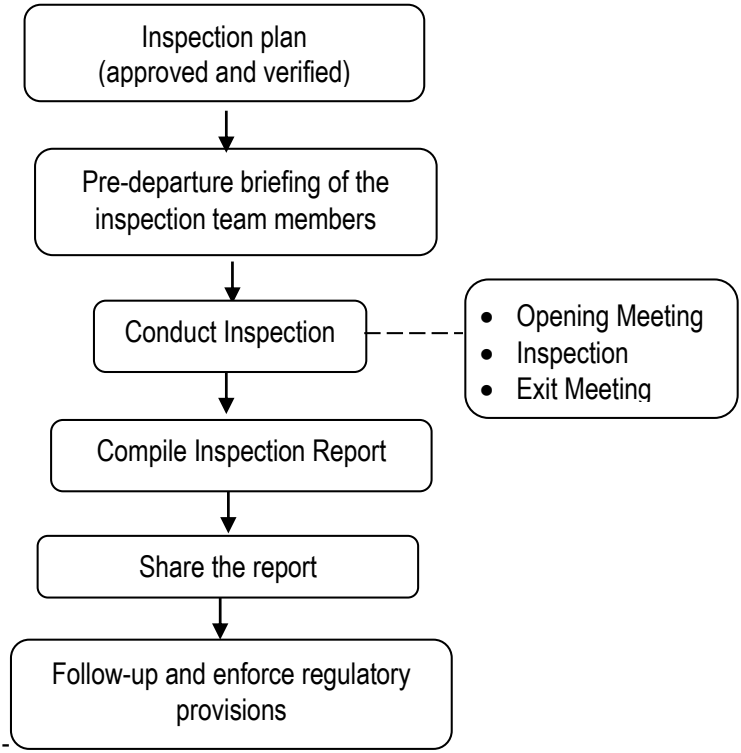

Figure 1: General flow of inspection

GMP Audit of Pharmaceutical Manufacturer

The inspection of pharmaceutical manufacturer is intended to monitor compliance with WHO GMP requirements, PIC/s GMP requirements and other national/ international standards. If serious non-compliances are made, the

manufacturer will not be allowed to manufacture, register the medicines or the registration will be cancelled if the products are already registered. The need for inspection of overseas manufacturing firms will be determined by the Authority using risk-based approach. Availability of budget will be main factor in determining ex-country GMP audit.

Any areas of concern, if any should be identified during pre-inspection documentation review and inspect all areas relevant to the scope of the application for compliance with relevant GMP guidelines.

a. Scope of GMP audit

The scope of GMP audit will vary depending on whether the inspection is carried within or outside the country. When the proponent(s) intents to manufacture medicinal products in the country, the inspection should be conducted to verify suitability of the proposed premise and to verify compliance with the layout plan as submitted in the Site Master File. If the medicines are being manufactured, the inspection will be conducted to verify compliances with standards and cGMP.

The GMP audit will focus on relevant areas such as the facilities, equipment, staff, training materials, production operations, validation and qualification, pest control, complaints, recalls and returns, self-inspection and documentation. However, special inspection may be conducted with a specific purpose as and when required.

b. Preparation for the GMP Audit

The Inspection Division will forecast the annual audit plan for GMP Audit of manufacturing firms considering the frequency of inspection and risk assessment. While planning, the size of the inspection team and inspection duration will depend on types of product manufactured, the complexity of the manufacturing process and the size of the manufacturing facility besides others. For overseas manufacturer, the date for the onsite inspection should be finalized after discussion with the Market Authorization Holder/ the manufacturer.

Inspection begins at the desk of the inspector. A review of documents related to the manufacturer should be made. The document includes TAM, previous inspection reports, and others such as the dossiers submitted at the time of registration, reports of adverse drug reactions, complaints and recall records and the results of regulatory (surveillance) testing, if any. Manufacturer's documents such as the complaints file, and self-inspection/internal audit reports, are valuable sources of information.

c. Formation of GMP Audit team

Audit team should be led by a Lead Inspector and supported by appropriately qualified and experienced inspector(s) and, where required, technical specialists. Some inspections may also be carried out by an individual inspector. However, the team should not consist of members with any real or perceived conflict of interest. An inspector shall not:

- be employed by the manufacturer within three years prior to the date of the inspection.
- have any commercial or financial interest in the manufacturer.
- be a significant shareholder in the manufacturer or the manufacturer's industry.
- be engaged by the manufacturer as a consultant within the last three years.

All the inspectors are required to declare Conflict of Interest using annexure 3 before proceeding for inspection. Before on-site inspection, the inspection team may gather following information of all the manufacturer facilities:

- manufacturing site address and contact details
- list of the items manufactured
- certification from any regulatory agency
- the current SMF or Quality Manual
- details of any significant changes made since the last inspection
- electronic copies of records or other documents, such as SOPs, validation plans, any regulatory actions taken (recalls or product alerts)
- any other information the inspector deems relevant

d. Onsite GMP audit

The onsite GMP audit should be conducted in accordance with the relevant SOPs and must include following process:

i. Opening meeting

The visit usually begins with a meeting between the inspector(s), representatives of the manufacturer or plant management, and those responsible for the production or areas to be inspected. At the opening meeting, inspector or inspection team should:

- introduce themselves
- clearly describe the inspection objectives and scope
- explain the inspection process and how inspection findings and report will be shared
- provide with an inspection plan
- record attendance
- Presentation from the manufacturer pertaining to the objectives of the inspection, if available will also be included in this meeting.

To escort the inspection, the manufacturing firm may appoint at-least one representative. It is advantageous to have the escort who is familiar with the quality systems of the manufacturer and who are involved in the self-inspection/ internal audit program.

ii. Conducting the inspection

Some basic rules for conducting the inspection are as follows:

- Inspection should follow the original plan as far as possible; items that are specific to certain areas of the facility, such as in-process testing and working documents, may need to be checked at the point of operation.
- It is advisable to follow production flow from reception of the starting materials till the dispatch of the finished products. The frequency of recalls and return of goods should be carefully noted.
- Documents such as master formulae, test specifications, SOPs, batch records, and documents relating to the control of printed materials and labelling operations should be closely verified.
- Besides verifying documents, it is essential that the inspection be based largely on observation and cover the total working hours of the manufacturer. It is recommended that the inspector start the plant tour as soon as possible after arrival.
- Inspectors can use a checklist to ensure that all areas of operations have been investigated. However, rigid adherence to a too-detailed checklist can

lead to possible overlooking of vulnerable areas of a quality assurance system specific to the manufacturer/plant under investigation.

- Significant changes in facilities, equipment, products, and key personnel since the last inspection should be noted. The principle here is that changes represent possible areas of weakness or causes of non-compliance with GMP. For example, new equipment may require changes to be made in procedures; new product lines may require new product master files; and departures of key personnel such as the quality control manager may result in behavioral or procedural changes.
- During inspection, the inspector would require access to other premises, documents, or information on the manufacturer which are required for inspection, and the inspectors are authorized as per the provisions of the Medicines Act and the regulation. The photographs or videos taken during the visit may be excellent illustrative material for the report.

If the inspection is conducted over few days, at the end of each day debriefing meeting to discuss issues that arose during the day should be convened. Additional information may be sought during this process to address any issues raised.

The Inspectors during the visit may take samples for testing. Samples are usually taken from released products (e.g., from the finished-goods warehouse) but may also be taken from stocks of raw materials or in-process material.

iii. Closing meeting

A closing meeting should be convened at the end of the inspection between the inspection team and senior management and any other staff nominated by the manufacturer. At this meeting:

- summarize the findings and present any potential deficiencies
- discuss any divergence of opinion between the manufacturer and the inspectors
- discuss the conditions likely to be applied to the license or certificate
- record attendance

A written closing meeting summary listing all potential deficiencies should be given to the manufacturer following SOP. This would ensure that the manufacturer is aware of the content of the post-inspection letter. This would also allow the manufacturer to start remedying any deficiencies immediately.

e. Inspection Report

The Lead Inspector should spearhead and compile the inspection report following the SOP. A copy of the complete written report, after approval by the Drug Controller, should be provided to the management of the manufacturer attested with covering letter. Inspection reports are confidential documents. However, based on international agreements, reports may be shared with other drug regulatory authorities.

Changes and improvements following previous inspection should be noted by inspectors. Positive observations should take form of a description of the processes that the manufacturer is carrying out particularly well.

The inspection report may contain following information:

i. Inspector's information

This includes:

- Date of inspection(s) and name(s) of inspector(s).
- Brief report of inspection activities undertaken. Samples taken, and results obtained.
- Assessment of the SMF.
- GMP-related recalls from the market of any product in the last two years.

ii. Summary and conclusions

This should include:

- The inspector's general impression of the manufacturer and his/her assessment of the acceptability of its GMP status for the range of products concerned.
- Failures to comply with the standards and guidelines such as the WHO and PIC/s Guide to Good Manufacturing Practice (in order of importance) and with the time limits set for them to be corrected by the manufacturer.

iii. General information about the manufacturer

This may include:

- Brief information on the manufacturer (including name and address including contact details), relation to other sites, and, any information relevant to understanding the manufacturing operations.
- Pharmaceutical manufacturing activities as authorized by the Authority.

- Any other manufacturing activities carried out on the site.
- Type of products manufactured on the site, and information about any specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
- Brief description of the site (size, location, and immediate environment and other manufacturing activities on the site).
- Number of employees engaged in production, quality control, storage, and distribution.
- Use of outside scientific, analytical, or other technical assistance in relation to manufacture and analysis.
- Brief description of the quality management system of the manufacturer responsible for manufacture.

iv. **Personnel**

This may include:

- Organizational chart showing the arrangements for quality assurance, including production and quality control.
- Qualifications, experience, and responsibilities of key personnel.
- Outline of arrangements for basic and in-service training and how records are maintained.
- Requirements and assessment of health conditions of personnel engaged in production.
- Personnel hygiene requirements such as clothing.

v. **Premises and equipment**

This may include:

- Nature of construction and finishes.
- Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination. Classification of the rooms used for the manufacture of sterile products should be mentioned.
    - Specific areas for handling of highly toxic, hazardous, and sensitizing materials.
    - Brief description of water systems including sanitation.
    - Description of scheduled preventive maintenance programs for premises and equipment

- Brief description of critical equipment used in production and control laboratories
- Qualification and calibration of equipment and their recording system.
- Arrangements for computerized system validation.
- Availability of written specifications and procedures for cleaning manufacturing areas and equipment**.**

vi. **Documentation**

This may include:

- Arrangements for preparation, revision, and distribution of necessary documentation for manufacture.
- Any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls on air and water).

vii. Production

This may include:

- Brief description of production operations, wherever possible, flow sheets and charts specifying important parameters may be incorporated.
- Arrangements for the handling of starting materials, packaging materials, and finished products, including sampling, quarantine, release, and storage.
- Arrangements for the handling of rejected materials and products.
- Brief description of process validation.

viii. **Quality control**

This may include:

- Description of the quality control system and activities of the quality control department.
- Procedures for the release of finished products.

ix. **Contract manufacture and analysis (in any)**

Description of assessment of GMP compliance of the contract accepter.

x. **Distribution, complaints, and product recall**

This may include:

- Arrangements and recording system for distribution of finished product.

- Arrangements for handling of complaints and product recalls.

xi. **Internal Audit/ Self-inspection**

Brief description of the self-inspection system.

f. Classification of Deficiencies:

Deficiencies (non-compliance with GMP requirements) should distinguish whether the defect lies in the system itself or in a failure to comply with the system. For instance, when cleaning is found to be suboptimal, it is important to know whether the SOPs are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

The deficiencies are primarily classified into Critical, Major and Others. However, when major deficiency is repeated, it will be marked as critical deficiency and necessary actions shall be taken as per the Act and the Regulations.

Each deficiency in the inspection report should be clear, concise, accurate and factual with apparent evidences without causing any ambiguity.

ii. Follow up on CAPA

If any observation is drawn upon inspection, the auditee must submit CAPA plan using prescribed form to the Authority. The Lead Inspector and responsible audit team members must review the CAPA plan and assign responsible inspector to follow-up. Follow-up audit may be planned, if necessary.

g. Regulatory actions

The manufacturer will be asked to furnish CAPA plan and to rectify the non-conformances accordingly. If observations are serious such as suspected quality defects or manufactured under conditions that do not comply with cGMP requirements, the Authority may prevent manufacture of such products. The TAM will be suspended and revoked as per the Act and the regulation. In extreme cases, the closing down of operations may be required.

Inspection Procedure for Inspection of sale & distribution of medicines

To harmonize and standardize the inspection procedure for an efficient inspection, it is imperative to have a written procedure for Inspection. This procedure applies to inspection of all premises engaged in medicine except for manufacturing facilities. The inspection should be conducted in the following manner:

a. Preparation of Inspection Plan

The Inspection Division is responsible for forecasting the annual inspection plan for inspection of sale and distribution premises, considering the frequency of inspection and risk assessment.

The In-Charge of sales and distribution unit in consultation with the Chief of Inspection Division should propose appropriate date for inspection and form inspection team. The identified Inspector(s) should declare any potential or perceived conflict of interest. The Lead Inspector should be identified based on seniority and experience who should coordinate and prepare inspection based on SOP.

Upon approval of the plan, the inspection team should convene pre-departure briefing and review documents such as relevant guidelines and previous inspection report, if any.

b. Inspection Process On-site

When the inspection team is at the site of the inspection, they should follow following processes:

i. Opening Meeting:

Upon reaching the site of inspection, an opening meeting is to be conducted by the Lead Inspector involving the head of the agencies/premises and/or Competent Person or licensees. Credentials such as official identification card or an office order should be presented. Opening meeting provides avenue to share objective(s), scope of inspection and inspection agenda to the auditee. It also encompasses the inspection process and process of sharing the inspection report.

ii. Conduct of Inspection:

The inspection may be conducted as a team or the inspection team may be divided according to the size of the premise and scope of inspection. Inspection must be conducted using checklist designed for the purpose, but it should not be restricted to the specified checklist only. Do not assume anything during the inspection.

Inspector can gather data and evidences through observation, asking, interviewing and reviewing documents and process. The photographs or videos taken during the visit may be excellent illustrative material for the report.

During inspection, the Inspector may take sample(s) for analysis following SOPs when there is doubt on the quality of medicinal products. After on-site inspection, the inspection team should discuss and classify deficiencies either as Critical, Major or Others.

iii. Exit / Closing Meeting:

Upon completion of the inspection, a closing meeting must be conducted where all the personnel involved in inspection are acknowledged. The summary of the inspection findings should be presented to the auditee team emphasizing both strength and deficiencies.

Closing meeting provides platform to confirm the deficiencies and opportunity to auditee to justify and substantiate their stand in case of any debatable deficiencies. The instant inspection report should be prepared and shared to the auditee team upon finalization of the inspection findings.

iv. Sharing of Inspection Report

Upon reaching the office, the Lead Inspector should coordinate and compile the inspection report following the SOP without any manipulation. The inspection report compiled post inspection must contain following details:

- Name and address of the premise inspected
- Date of Inspection
- Date of previous inspection conducted (if any)
- Inspection ID
- Technical Authorization number

- Name of Competent Person along with the registration number
- Scope of inspection
- Classified observations or deficiencies
- Name & signature of the inspectors

The inspection report which is verified by the Chief of the Inspection Division and approved by the Drug Controller should be officially shared with the auditee and necessary actions should be taken as per the provisions of the Act and the Regulations.

Based on the observation/ non-conformances shared, the auditee must be asked to submit CAPA plan using prescribed form to the Authority. This will be reviewed by responsible inspector and follow-up inspection may be planned, if necessary.

General regulatory requirements:

a. Guidance on premise requirements

Any person must not operate sale, distribution, compounding and manufacture of medicinal products from unauthorized premises. The name and certificate of registration of the registered Competent Person and technical authorization in case of private pharmacies must be conspicuously displayed at the premise in which the business is carried on.

For any changes related to the name of the pharmacy, location, Competent Person and the Licensee, the Authority should be notified.

b. External Premises Requirements

This includes:

- The pharmacy premise should be easily identifiable as a healthcare facility and must reflect the professional nature of the pharmacy.
- All areas of external pharmacy including windows, doors and ceilings must be appropriate, intact and in a good state of repair.
- Guttering and paintworks must be clean and in good order and surfaces must be non-shedding. Both external and internal premises must be free from leaks and exposed wirings.

- Effective pest control measures should be adopted to prevent the entry of rodents and other pests.
- The signage dedicated for the premise must be clear and legible as per the specification prescribed by the Authority. The signage must incorporate the name of the premise and business hour. It should be displayed at a conspicuous place and illuminated.

c. Internal Premises Requirements:

This general guidance applies to all the relevant areas within the pharmacy, including the dispensary, patient consultation area and other areas where professional pharmacy services are accessed.

- The areas of pharmacy should be separated from residential areas.
- Patients entering the pharmacy should be readily able to identify where they can access the competent person and where prescriptions are dispensed.
- The layout and fittings in respect of the storage of medicinal products must facilitate their proper storage and supervision of sale or distribution.
- Adequate lighting, ventilation or air conditioning should be provided to ensure correct storage and safe dispensing of medicinal products within the pharmacy.
- The temperature within the pharmacy must be within the range specified by the Authority and temperature monitoring system should be conducted at least twice in a day to ensure quality storage of medicinal products.
- All the floors within the registered premise should be intact with even surface. Flooring should be of cleanable material and should be maintained clean always.
- All areas of the pharmacy should be kept clean and a regular cleaning schedule should be in place for all areas of the pharmacy including dispensary and storage areas and such records maintained for inspection.
- Appropriate pest control measures should be adopted to prevent infestation of rodents and other pests.

d. Dispensary

- The dispensary size and layout must facilitate an uninterrupted, safe and efficient workflow and effective storage of all medicines.

- Appropriate shelving must be in place so that no medicines are stored on the floor, on stairs or passageways.
- The shelves must be appropriately labelled, and the medicinal products should be arranged and segregated as per the label.
- Schedule C or Controlled Drugs should be kept in a separate room, cabinet or safety box under lock and key and it should be dispensed only upon presentation of prescription.
- The dispensary area should be well-lit with adequate ventilation and must be maintained hygienically and be free from all sources of contamination.
- The dispensary must have arrangements for the proper storage and disposal of all types of waste materials.

e. Storage areas within Authorized premises

- Sufficient storage space should be allocated to allow orderly management of stock and effective stock rotation.
- For new establishments, the design of walls and ceilings of the storage area should facilitate ease of cleaning and maintenance.
- Pellets or elevations shall be furnished to prevent direct contact of medicinal products with the floor.
- Adequate number of appropriate shelves and racks should be placed in the storage area to facilitate orderly and correct storage of products.
- The area should be well-lit with adequate ventilation or air conditioning to ensure good storage of products.
- The temperature of the storage area should not exceed the temperature specified by the Authority (28°C) and a thermometer must be placed in the area to monitor the temperature.
- The medicines must be stored at a temperature recommended by the manufacturer.
- Pellets or elevations should be used to prevent medicinal products coming into direct contact with floor.
- Medicines should be protected from direct sunlight and they should be stored away from the wall to facilitate ease of cleaning and appropriate ventilation.
- Medicines must be arranged alphabetically or according to their therapeutic groups and the medicines should be segregated and arranged on shelves as per the label.

- Expired or damaged medicines should be quantified, recorded, quarantined and labelled with the statement "Expired / Damaged Medicines".

f. Guidance on Dispensing

i. Good Dispensing Practice:

The competent person should ensure that:

- No damaged, counterfeit, substandard, or expired medicines are dispensed.
- Medicines dispensed are authorized by the Authority.
- Prescription medicines are dispensed only against valid prescription.
- The prescription should bear sign and seal of the concerned pharmacy.
- The patient is dispensed and directed to complete the full course of treatment.
- Every drug is dispensed according to the principles of good dispensing practices.

ii. Counseling Patients:

The competent person should ensure that the patient understands the dosing instructions and drug information before leaving the premise.

iii. Labeling Dispensed Medicines:

- Every dispensed medicine should be labeled appropriately using appropriate language or pictographs.
- Labeling of the dispensed medicine must be clear and legible.
- The label must indicate:
  a. Name of the medicine (if dispensed in loose)
  b. Strength, dosage and total quantity of the medicine dispensed
  c. Direction of use and
  d. Expiry date

iv. Record Keeping and Documentation

- A record of medicines dispensed should be maintained
- For each prescription medicine dispensed, a record should be maintained as follows:
  a. Serial number of entry
  b. Date of dispensing

c. Name / BMHC ID and address of the prescriber
d. Name of the patient
e. Name and quantity of the prescription medicine dispensed

- A file must be maintained for all the correspondences and inspection reports received from the Authority including proforma invoice.
- A copy of regulatory forms such as adverse drug reactions form and defective complaint form should be maintained.

Search Warrant

Search warrant is required for search of any individual or any premise to avoid unexpected obstruction to the Inspectors. This would also ensure efficient investigation and the safety of the Inspector. The requirement of a search warrant can be decided by the Authority and must be obtained in accordance with the Civil and Criminal Procedure Code of Bhutan 2001.

Sampling of medicinal products

Sampling comprises the operations designed to select a portion of pharmaceuticals products for a defined purpose. The sampling procedure should be appropriate to the purpose of sampling, to the type of controls intended to be applied to the samples and to the materials to be sampled.

All operations related to sampling should be performed with care using proper equipment and tools. Any contamination of the sample by the dust or other foreign materials is liable to jeopardize the validity of the subsequent analysis.

Sampling of any medicinal product should follow proper sampling procedure and the premise from where sample was taken must be acknowledged. Proper record should be maintained for the sampled products.

Port of entry consignment inspection

Any medicinal products imported into the country are inspected for their compliance to the marketing authorization at the port of entry before it is released for distribution or use. Details of the consignment to be inspected should be obtained from the clients and recorded as per SOP.

Inspector must verify the Import Authorization and Pro-forma invoice of the consignment. The received consignment must also be cross verified with the inspection kit, if registered. In case of disparities, it must be further verified using the dossier submitted for registration. If required, registered samples from the Registration Division should also be obtained.

Embargo and seizure of medicinal products

The Inspectors can embargo the medicines if any of the following conditions are observed:

a. Lack of Import Authorization;
b. Unregistered products or imported registered products not conforming to the sample medicinal products or packaging specifications as per the registered product; or
c. Any breach of provisions of the Act and the Regulations.

The medicinal products would be seized if any of the following conditions are observed:

1. Unauthorized personal or premises;
2. Found banned products;
3. Counterfeit/Fraudulent products;
4. Breach of conditions under the Regulations;
5. Tampering of embargoed products; or
6. If the Competent Person/ Licensee voluntary surrenders the embargoed product

The Inspector should explain the reasons for the embargo or seizure of the medicines and list using the embargo or seizure memo attached as annexures. This memo should be signed by the Inspector(s) and countersigned by the Competent Person/Licensee. The memo should be shared.

The embargoed products should be packed and sealed with an embargo cello tape while cautioning not to disturb or tamper the embargoed products until further directives from the Authority.

The Drug Inspector should record following information for the medicines which are embargoed/ seized:

- Name of the product
- Name of the manufacturer
- Batch number
- Manufacturing and Expiry date
- Quantity; and
- Maximum Retail Price per unit, if available.

The Inspector should ensure that necessary actions are taken for embargoed or seized medicines. This may include handing over of seized medicines to the focal person in the Division, handing over of unregistered medicine to the Post Marketing Control Division and auctioning of the seized registered medicinal products following standard procedures.

Documentations and Records

The documentation system should ensure that any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents. All records should be safely stored for an adequate period and held under conditions that guarantee their security and confidentiality, unless otherwise legally required.

All instructions, standards or written procedures, worksheets, checklists and reference data relevant to the work of the inspection should be kept up to date and be readily available to staff.

Regulatory actions

All regulatory actions such as warnings, fines and penalties should be enforced as per the act and the regulations.

Internal audit and periodic review within the Inspection Division

The Inspection Division should implement a system of planned and documented internal audits and periodic reviews of its compliance with the criteria of these guidelines and SOPs. The internal audits must be conducted by competent staff to ensure that all formulated procedures are adhered to. Based on the results of these audits, the Chief of the Division must ensure that the inspection system remains effective. There should be procedures for corrective and preventive action.

The Inspectors should be evaluated before being allowed to perform inspections. Periodic reviews should also be undertaken to examine the performance of individual inspectors to ensure consistency.

A record of all audits and reviews should be kept and should include the findings, conclusions, recommendations and follow-up action. These records should be retained for at least 3 years.

Use of German Pharma Health Fund-Minilab™ for Verification of Identity and Content of Drugs

General Introduction

Quality assurance of pharmaceutical products, whether locally manufactured or imported, is of prime importance in any health care system. Lack of quality assurance endangers the lives of citizens. Many developing countries, like Bhutan, rely mostly on imported drugs. As we are at the risk of being supplied with substandard products. Thus, affordable but reliable methods for quality assurance are urgently required to ensure that imported products meet the prescribed standards and are safe for human use.

This document is designed to guide inspector to test the product using the German Pharma Health Fund Minilab kit (GPHF Minilab). Visual analysis, disintegration, TLC and color reactions are the test parameters for testing medicinal products.

Medicinal products from particularly cheap sources; with defective dosage forms or packaging; and drug products with incomplete, damaged, or missing labels or with labels written in a foreign language should be subjected to these tests. The test may be repeated with two other samples to eliminate anomalous results. If products do not pass all tests, recommend for testing at national or other Drug Testing Laboratory. Keep some retained samples in a safe place for future investigations.

It is recommended to put on protective clothing—for example, an apron, hand gloves and safety spectacles always to avoid accidental contact with potentially hazardous test solutions.

Visual Inspection

Inspection of Packaging Material

Medicinal product must be sampled in accordance with the SOP. At the time of sampling, the container should be properly sealed, labelled and be without defects and damage while the seals must be intact.

A strong smell when the container is opened often indicates drug degradation. Excessive powder or pieces of tablets at the bottom of the container indicates the presence of abraded and broken tablets or crushed and opened capsules. Another deleterious effect, excessive moisture uptake, is indicated by fused tablets and capsules or by recrystallized drug substance on the solid formulation itself or on the container.

Inspection of Labels

Both the immediate/primary container and the carton should have a durable label fixed on them. Labels may be replaced by printed handwriting, but it must be legible and indelible. At a minimum, the label should provide:

- Name of the drug and its strength,
- Number of unit doses in the container
- Manufacturer's name and address,
- Batch or lot number,
- Expiry date, and
- Storage conditions required for the drug

Inspection of Dosage Forms

Tablets and capsules should show no signs of physical defects and blemishes such as dirty marks or spots, mottling or discoloration and hardening and softening, fusion or swelling, abrasion or erosion, or any other defects such as cracks or chips, dents or punctures, lose powder, crystallization or strange smell.

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 so that the drug is available to the body. Poor drug processing or wrong storage may cause tablets and capsules to harden and fail

the disintegration test. The test determines whether tablets and capsules disintegrate in water within 30 minutes.

All uncoated tablets and capsules and all soluble, dispersible, effervescent, and film-coated tablets (i.e., all quick-release formulations) must 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 can deviate from this time of complete disintegration. These tablets and capsules should be labelled as such and not be subjected to this test. These products require a more sophisticated disintegration test.

Simple counterfeit 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 vial, while 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 to the bottom of the container.

Procedure for Disintegration Test

Place one tablet or capsule into a 100 mL wide-neck bottle containing 100 mL of water. The temperature of the water should be close to body temperature (37ºC). Stir or shake the liquid every few minutes, continuing for 30 minutes. You may stop earlier if the tablet or capsule has already disintegrated.

The tablet or capsule passes the test if no residue remains in the liquid, or if any remaining residue consists of fragments of coating or is a soft mass with no palpable core. Repeat the test on five more tablets or capsules. The batch passes the test if all six tablets or capsules disintegrate. Repeat the entire test cycle if one tablet or capsule fails to disintegrate. Test the batch a third time if another tablet or capsule fails in the second run.

Color Reactions

Introduction

Both visual and disintegration tests will allow identification of rough counterfeits for timely rejection. Color reaction will be third phase to use if a product passes the previous tests. In general, all potentially counterfeit samples should be subjected to a TLC assay as described in the GPHF Minilab or referred to a fully equipped laboratory for further investigations prior to taking legal action.

Individual monograph must be followed while performing the test as reagents and apparatus required are indicated on the monograph concerned. While deionized or distilled water is the most commonly used solvent, clear tap water or rainwater will also serve the purpose. All test solutions have been shown to be stable for at least three months under tropical climate conditions.

Test performance

A pestle and circular filter paper (instead of a mortar) is needed for grinding tablets or granules to fine powder. Using filter paper avoids the risk of cross-contamination between different batches during routine work because each sample will need a fresh filter paper. If no filter paper is available, it may be replaced with any other sort of paper, such as newsprint.

Grinding should be done away from fans, as fan will blow the sample off the work surface. This may be of potential hazard to the inspector if the substance is inhaled or comes in contact with eyes or skin and may trigger an allergic reaction to penicillin or other related compounds.

For sachets and hard gelatin capsules, they are opened, and their contents poured straight onto the filter paper. Division of the powder should be done according to the instructions given in an individual monograph, using a spatula. Soft gelatin capsules are opened by cutting them into an appropriate number of pieces using a pair of scissors, a blade, or a scalpel. Then the appropriate amount of powdered sample or the appropriate number of pieces is transferred into a graduated test tube using either the spatula or a micro-spoon as directed in the individual monographs.

The test tube should be held using a test tube clamp. Add the required volume of the test sample and then shake the tube during which a characteristic color for identification purposes is produced. Vigorous shaking of the test tube is often required to achieve the necessary color reaction.

Use of wet test-tube and poor shaking of the reaction mix will give poor test results. Shake but do not swing, the test tube; swinging may lead to anomalous test results. You might want to place the test tube for a moment into the tube rack. Sometimes a hot water bath is required to get the color reaction started. Fill a 100 mL wide-neck bottle with about 50 mL of water and heat it on a hotplate. Then insert the test tube containing the test sample into the water, making sure that the reaction mix in the test tube is just below the water surface. A color that didn't appear in the cold will now be gradually produced in the heat.

A travel iron can serve as a hotplate when placed upside down. Avoid direct contact with any hotplate. Sometimes even a hot water bath doesn't produce enough heat to get a color reaction started; then an alcohol lamp containing methylated spirits is used to produce a flame sufficiently hot to cause the color reaction. Just hold the test tube containing the test sample into the flame using a clamp and frequently shake the tube. Gradually, a color is produced that would not emerge in the cold.

Thin-Layer Chromatography

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

Standard TLC Conditions

a. Stationary Phase

The stationary phase consists of a thin layer of appropriate adsorbent bonded onto a suitable support, which may be a glass, plastic, or aluminium plate. Binding to the plate is assured by mixing the adsorbent with a binding agent, such as Calciumsulfate. Plates may be prepared in the laboratory or purchased from a reliable supplier.

Adsorbents are porous materials of a different chemical nature that are made into finely divided particles so that they provide a large surface area for effective separation. Commonly used adsorbents include silica gel and alumina. Silica gel is hydrated silicic acid with polar functional groups on the surface, which adsorbs polar molecules. It is the most widely used adsorbent for TLC.

b. 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:

- ✓ First, it must displace the solute (drug) from the adsorbent to make it able to migrate across the TLC plate. Thus, it must have elution power.
- ✓ Second, it must help to separate a mixture of drugs, excipients, and impurities so that they can be deposited at various positions on the chromatoplate and have different Rf values.

The solvent may be made up of one component or a mixture of two or more solvents (i.e., a solvent system). The solvents to be used in this course can perform the two functions for the specified drugs being analyzed, and most are mixtures.

c. Separation/Development Chamber

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

d. Preparation of the Stock Standard Solution (SSS)

The preparation of SSS requires a whole ***reference tablet*** containing a stated amount of drug, which is crushed prior to extraction following procedure below:

- ✓ Wrap a tablet in aluminium foil and crush it to a fine powder using a pestle.
- ✓ Empty the contents of the aluminium foil over a laboratory glass bottle of appropriate capacity and wash down all residual solid material with an appropriate volume of solvent using a straight pipette.

- ✓ Close the bottle and shake it for about three minutes until most of the solids are dissolved.
- ✓ Allow the solution to stand for another five minutes until the undissolved residue settles below the clear supernatant liquid.

This solution should be labelled as "Stock Standard Solution (SSS)"; it contains a known concentration of the drug per milliliter. Freshly prepare the standard solution for each test.

e. Preparation of the Working Standard Solution (WSS 100%) 100 Percent (Upper Working Limit)

Using a pipette, add a stated volume of the clear stock standard solution (SSS) into an appropriate vial and add a stated volume of diluting solvent. Close and shake the vial. The solution obtained should be labelled as "Working Standard Solution 100% (WSS100%)" and contain a known amount of the drug per milliliter. This higher working standard solution represents a drug product of excellent quality containing 100 percent of the drug.

f. Preparation of the Working Standard Solution (WSS 80%) 80 Percent (Lower Working Limit)

Pipette a given volume of the stock standard solution (SSS) into an appropriate vial and add a stated volume of a specified solvent. Close and shake the vial. The solution obtained should be labelled as "Working Standard Solution 80% (WSS 80%)" and contain a known amount of drug per milliliter. This is more dilute than the 100 percent working standard solution and thus represents a drug product of inferior quality containing just 80 percent of the amount of drug stated on the product's label. In the current investigation, this drug level represents the lower acceptable limit for a given product.

g. Preparation of the Stock Sample Solution (SSaS) from a Drug Product Claiming a Stated Potency per Unit

The preparation of a stock sample solution requires a whole tablet or capsule from an appropriate drug product sampled in the field. The drug is extracted completely from the sample using the same procedure as for the authentic reference standard: a tablet is wrapped in aluminium foil and crushed to a fine powder prior to transfer into a laboratory glass bottle of a specified capacity. Powder obtained from a capsule should be transferred directly into the

laboratory glass bottle, finally putting the empty cap and body shells into the bottle as well. Add a specified volume of appropriate solvent using a straight pipette, close the bottle, and shake it for about three minutes until most of the solids are dissolved. Allow the solution to stand for another five minutes until the undissolved residue settles below the clear supernatant liquid. This solution should be labelled as "Stock Sample Solution (SSaS)"; it contains a known amount of total drug per milliliter. Freshly prepare the sample solution for each test.

h. Preparation of the Working Sample Solution (WSaS)

Pipette a specified volume of the stock sample solution (SSaS) into an appropriate vial and add a given volume of solvent. Close and shake the vial. The solution obtained should be labelled as "Working Sample Solution (WSaS)." The expected concentrations of both drug compounds in the working sample solution should match the concentration of drug of the higher working standard solution produced previously.

Methodology

The TLC technique involves the following procedures:

a. Preparation of Mobile Phase/Development Chamber:

The specified mobile phase must be thoroughly mixed and placed in the development chamber. 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 adversely affect the separation and position and shape of spots. When developing the chromatoplate, a concave solvent front indicates that the chamber is not well saturated. This must be properly balanced.

b. Application of Standard Sample and Working Sample

Standards sample and working sample must be crushed and 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.

c. Spotting

Mark an origin line parallel to and about 1 cm from the bottom edge and 1 cm from the top of the edge of the chromatoplate and apply 2 µL of each test and standard solution using the microcapillary pipettes supplied. Up to four spots can be placed on a TLC plate. Check the uniformity of all spots using UV light of 254 nm. All spots should be circular in shape and equally spaced across the origin line.

Although their intensity may differ, *their diameter never should*. Different intensities are due to residual amounts of tablet and capsule excipients or different drug concentrations in the sample solutions. A difference in spot size, however, is due to poor spotting. Repeat this step if homogeneous spotting is not achieved the first time.

d. Development (Running the Chromatogram)

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

Development occurs when the mobile phase moves up the plate. It can proceed until the solvent front is close to the top edge of the plate (which is marked with the pencil or 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 constant distribution in the mobile phase.

Development

Using a pipette, add a given volume of mobile phase into the jar being used as the TLC developing chamber. Close the chamber and mix thoroughly. Line the chamber's wall with filter paper and wait for about 15 minutes to ensure saturation of the chamber with solvent vapor. Carefully place the loaded TLC plate into the jar. Close the jar and develop the chromatoplate for about 15 minutes, or until the solvent front has moved about three-quarters of the length or to the top marks of the plate. Remove the plate from the chamber, mark the

solvent front, and allow any excess solvent to evaporate, using a hotplate if necessary.

Detection

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 detected by using short-wave UV light or Iodine staining (or as per directives of manual). Any spots visualized under UV should be marked lightly with a pencil.

Examination of chromatograms with UV light (254 nm and 365 nm) should be done for all substances. In addition, all 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 must be traced with a pencil immediately after exposure to iodine. In some case, where spots may not be detected in the plates either by UV light or Iodine staining further detection is conducted as given in the manual.

Evaluation

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

a. Determination of Rf Values

Rf value, a “retardation factor” or “ratio-to-front,” is determined by measuring the distances moved by the spot and the solvent. The Rf value is equal to the distance of the spot center from the start divided by the distance of the solvent front from the start.

Rf values serve as a guideline only, since they vary depending on several factors. When a drug sample is run alongside a reference standard, the Rf value will be the same if both products contain the same compound.

b. Visual Evaluation

Visual evaluation is important both qualitatively and quantitatively. Thus, for a given drug to be accepted as being of excellent 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 and sizes of the spots on the chromatogram. Therefore, it is important to carefully:

- 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 is of inferior quality, containing less of the active ingredient than expected. 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 travelled or Rf values, you can tell whether the drug being analyzed is the same as the given reference standard.

- Compare various properties. This is also important qualitatively. For a given drug to be the same as the reference standard, its spot must appear similar to the reference spot when examined under UV light.

TLC chromatograms may be traced on paper or work sheet. Photographs of chromatograms may also be taken. However, proper documentation should be maintained.

Cleaning and Storing the Minilab After Use

The test tubes should be thoroughly cleaned after use, and the reagents and test solutions properly stored or disposed of. Disposal of used reagents and test solutions should be done following standard procedures. After disposal of test mixtures, rinse the empty test tubes with tap water. Use the test tube brush for test tube cleaning. If stains persist, soak the tubes in a mixture of water and detergent overnight. Do not use a spatula or anything similar to scrape off resistant stains. This will destroy the test tube.

Finally, rinse and return all the test tubes upside down to the test tube rack. All items should be put back into the protective case after being properly cleaned and dried.

Annexure 1: Seizure Memo

Form: **III- SM**
Regulation Section: **20(d)**

SEIZURE MEMO

Inspection ref. no……

To,
……
……

Under clause 169 of the Regulation, your products are hereby seized due to reasons below: (Tick the appropriate reason/s)

a. Unauthorised personnel or premises
b. Banned products
c. Counterfeit/Fraudulent products, or
d. Breach of conditions under the Regulation.

Details of product or packages: (Name of the product, batch, manufacturer)

……
……
……
……

(*Use additional sheet if required*)

Name and signature of Inspector……

Date: ……

Annexure 2: Embargo Memo

Form: **IV-EM**
Regulation Section: **20(e)**

EMBARGO MEMO

Inspection ref. no……

To,
……

……

Under clause 171 of the Regulation, your products are hereby embargoed due to reasons below: (Tick the appropriate reason/s)

a. Lack of Import Authorization
b. Unregistered products. or
c. Imported Registered products not conforming to the sample medicinal products or packaging specifications submitted at the time of product registration.

Details of product or packages: (Name of the product, batch, manufacturer, expiry date)

……..
……
……
……

(*Use additional sheet if required*)

Name and signature of Inspector……
Date: ……

Annexure 3: Conflict of Interest form

FORM 3/2

ROYAL CIVIL SERVICE COMMISSION
ROYAL GOVERNMENT OF BHUTAN

DECLARATION OF CONFLICT OF INTEREST

I, ……(name), bearing CID/EID No……....., (Position Title) …….. (Agency) ……..…… as per the provisions of Section 3.3.25 of Chapter 3 of the BCSR 2018, I declare that in serving as a member of ……(Committee) in.....….(Agency):

- I do not have or anticipate any Conflict of Interest. I shall notify the Agency concerned immediately in the event such interests arise in the course of or before discharging my duty; OR

- I do have Conflict of Interest in view of the following reason(s):
  - Family Member: …….
  - Close Relative: ……
  - Close Friend: ……
  - In-Laws: ……
  - Enemy: ……
  - Others: ……

I hereby confirm that the above information is true to the best of my knowledge. In the event the above declaration is found to be incorrect, I shall be liable for administrative/legal action.

Date:

Place:

Signature

References

a. Audit and Licensing of Pharmaceutical Manufacturers, HSA Regulatory Guidance, 2014
b. Bhutan Medicines Rules and Regulation 2012
c. Civil and Criminal Procedure Code of Bhutan 2001
d. GMP Conformity Assessment of an Overseas Manufacturer, HSA Regulatory Guidance, 2016
e. Guidance Notes on Good Distribution Practice, HSA Regulatory Guidance, 2015
f. Inspection of Drug distribution channel, WHO TRS 885, 1999
g. Inspection Guideline, TFDA
h. Inspectors Handbook, 2nd Edition 2005, TFDA
i. Medicines Act of the Kingdom of Bhutan 2003

Vision:
The most dynamic, reliable and client-centric model regulatory organization.

Mission
Promoting availability of quality, safe, and efficacious medicinal products for consumers

Contact Details:

Inspection Division, Drug Regulatory Authority
Royal Government of Bhutan
Thimphu: Bhutan
EPABX: +975-02- 337074/5
Fax: +975-02-335803
www.dra.gov.bt