ETHIOPIAN FOOD AND DRUG AUTHORITY

Good Manufacturing Practices Guideline for Herbal Medicine

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1 SCOPE

1.1. The objective of the Good Manufacturing Practice (GMP) Guidelines for Herbal Medicinal Products is to ensure that products are consistently manufactured in conformance with quality standard. These guidelines are concerned with all aspects of production and quality control of Herbal Medicinal Products.

1.2. These guidelines are for the manufacture and storage of Herbal Medicinal Products.

1.3. It is necessary to emphasize that, no Herbal Medicinal Product should be manufactured, exported, advertised, sold or distributed in Ethiopia unless it has been registered in accordance with the provisions of the Food and Drug Administration and Control Proclamation 1112/2019 and the accompanying guidelines.

1.4. These guidelines cover the quality aspects of the product, but do not cover safety aspects for the personnel engaged in the plant, nor protection of the environment. Safety and environmental aspects are inherent responsibilities of the company and should be governed by Ethiopian legislation and regulations.

1.5. These guidelines are not applicable to research and development activities of finished Herbal Medicinal Products.

1.6. Good Agricultural and Collection Practice and Good Herbal Processing Practice which is a complement of Good Manufacturing Practice should be practiced in the various processing (primary, secondary or special) of the starting materials through the herbal preparation and/or herbal dosage forms of finished Herbal Medicinal Products and should precede Good Manufacturing Practice.

1.7. The manufacture of Herbal Medicinal Products of sterile origin (infusion, ophthalmic, solution, injectable, implants etc.) is beyond the scope of this guideline.

2 GLOSSARY

For the purposes of this document, the following terms and definitions apply.

Audit: systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable for achieving objectives.

Batch: a quantity of any herbal product produced in a given cycle of manufacture that is uniform in character and quality.

Batch Number: a designation in numbers and/or letters or combination of both that identifies the complete history of the batch, quality control and distribution.

Bulk Product: any processed product, which will have to undergo the packaging operation in order to become a finished product.

Calibration: combination of checking an instrument and adjusting it to bring it within its limits for accuracy according to recognized standards.

Cleaning: all operations that ensure a level of cleanliness and appearance, consisting of separating and eliminating generally visible dirt from a surface by means of the Following combined factors, in variable proportions, such as chemical action, mechanical action, temperature, duration of application.

Complaint: external information claiming a product does not meet defined acceptance criteria.

Contamination: occurrence of any undesirable matter such as chemical, physical and/or microbiological matter in the product.

Contract acceptor: person, company or external organization carrying out an operation on behalf of another person, company or organization.

Contract giver: person, company or external organization that contracts out anoperation to another person, company or organization.

Control: verification that acceptance criteria are met.

Documentation: all written procedures, instructions and records involved in the manufacture and quality control of products.

Finished Herbal Products/Herbal Medicinal Product: a product, containing as active substances exclusively herbal drugs or herbal preparations. They may consistof herbal preparations made from one or more herbs. If more than one herb is used, the term mixed herbal product can also be used. They may contain excipients in addition to the active ingredients. It may contain by tradition, natural organic and inorganic active ingredients, which are not of plant origin (e.g. animal materials and mineral materials). Generally, however finished products or mixed products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered tobe herbal medicinal products.

Guideline: a guideline is a statement by which to determine a course of action. A guideline aims to streamline particular processes according to a set routine or sound practice.

Herbs: a plant that is valued for flavor, scent, or other qualities. Herbs have a variety of uses including culinary and medicinal. General usage differs between culinary herbs and

medicinal herbs. Medicinal herbs include crude materials which could be derived lichen, algae, fungi or higher plants, such leaves, flowers, fruit, fruiting bodies, seeds, stems, wood, bark, root, rhizomes or other parts, which may be entire, fragmented or powdered.

Herbal Preparations: preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed alcoholic beverages and/or honey, or in other materials.

In -Process Control: checks and tests instituted and carried out in the course of the manufacture of a product including checks and tests done on environment and equipment in order to ensure that the end product will comply with its specification.

Internal audit: systematic and independent examination made by competent personnel inside the company, aimed to determine whether activities covered by these guidelines and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable for achieving objectives.

Maintenance: any periodic or unplanned support and verification operations designed to keep premises and equipment in proper working condition.

Major equipment: equipment specified in production and laboratory documents which is considered essential to the process.

Manufacture or Manufacturing: the complete set of activities to produce a product, comprising of production and quality control, from acquisition of all raw materials through processing and subsequent packaging and release for distribution of the finished product.

Medicinal Product: any substance or combination of substances presented as having properties for treating or preventing diseases in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medicaldiagnosis.

Medicinal Plant: a wild or cultivated plant used for medicinal purposes**.**

Packaging: the part of production cycle applied to a bulk product to obtain thefinished product.

Packaging Material: any material used in the packaging of a bulk product to obtain the finished product.

Packaging operation: all packaging steps including filling and labelling, which a bulk product has to undergo in order to become a finished product.

Plant: location for production of herbal products.

Premises: physical location, buildings and supporting structures used to conduct receipt, storage, manufacturing, packaging, control and shipment of product, raw materials and packaging materials.

Processing: the part of production cycle starting from weighing of raw materials to obtaining a bulk product.

Production: all operations starting from processing to packaging to obtain a finished product.

Quality Control: all measures taken during manufacturing which are designed to ensure the uniform output of product that will conform to established specifications.

Quarantine: the status of materials or products set apart physically or by system, while awaiting a decision for their rejection or release for processing, packaging or distribution.

Raw Material: any basic ingredient known as unprocessed material or primary commodity that is used to produce a finished herbal medicinal product.

Recall: decision made by a company to call back a product batch that has been put on the market.

Rejected: the status of materials or products which are not permitted to be used for processing, packaging or distribution.

Released: the status of materials or products which are allowed to be used for processing, packaging or distribution.

Returned Product: finished herbal medicinal products sent back to the manufacturer.

Sample: one or more representative elements selected from a set to obtain information about that set.

Sampling: set of operations relating to the taking and preparation of samples.

Sanitation; hygienic control on manufacturing premises, personnel, equipment and material handling.

Specification: a description of a starting material or finished product in terms of its chemical, physical and biological characteristics, if applicable. A specification normally includes descriptive and numerical clauses stating standards and tolerated deviations**.**

Starting Materials: raw materials and packaging materials used in the production of finished herbal **medicinal** products.

Waste: any residue of a production operation, transformation or use, any substance, material, product that its holder intends for disposal.

3 GENERAL CONSIDERATION

3.1. In the manufacture of herbal medicinal products, monitoring is essential in ensuring that products of quality standards are produced.

3.2. Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicines are prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources. As a result, it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products.

3.3. Because of the inherent complexity of naturally grown medicinal plants and the often-variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.

4 PERSONNEL

4.1. General Considerations

4.1.1. There should be sufficient number of personnel with adequate knowledge, experience, training and education relevant to their assigned functions.

4.1.2. The responsibilities placed on any one individual should not be so extensive as to present any risk to the product.

4.1.3. Key personnel i.e., persons responsible for production and quality control, must be employed on full time basis.

4.1.4. Personnel specific duties should be recorded in individual job descriptions and personnel should be given adequate authority to carry out their responsibilities. Duties may however be delegated to designated deputies with satisfactory qualification and practical experience.

4.1.5. All personnel should be responsible for the establishment and maintenance of high-quality standards.

4.1.6. Experts in the different areas of interest in herbal medicine manufacturing may be engaged upon documented confirmation of their education, training or experience in their areas of proficiency.

4.2. Organization, Qualification and Responsibilities

4.2.1. The organizational structure of the company should be such that different persons head the production and quality control sections, neither of which should report to the other. The organizational structure should clearly state the reporting lines for all key personnel.

4.2.2. The head of production should have the requisite training and experience as well as knowledge and understanding of practical problems encountered in the manufacturing of herbal medicinal products.

4.2.3. The head of production should have authority and responsibility to manage production; covering operations, equipment, production personnel, production areas and records.

4.2.4. The head of quality control should have full authority and responsibility for all quality control duties such as establishment, verification and implementation of all quality control procedures. He should have the authority to approve or accept starting materials, intermediates, bulk and finished products that meet specification or to reject those which do not conform or those not manufactured in accordance with approved procedures.

4.2.5. Where necessary, the quality control activities could be outsourced with an agreement drawn to outline specific roles of concerned parties. (See Section 15).

4.3. Training

4.3.1. All personnel directly involved in manufacturing and quality control activities should be appropriately and continuously trained in manufacturing and quality control operations in accordance with GMP principles.

4.3.2. Records of training should be maintained and effectiveness of trainings should be assessed periodically.

5 PREMISES

5.1. The premises for manufacturing should be suitably located, designed, constructed and maintained to suit the operations to be carried out and facilitate good sanitation and hygiene.

5.2. Effective measures should be taken to avoid any contamination from the surrounding environment and from pests.

5.3. Painted line, flexible barrier in the form of mark or tape may be employed to prevent mix-ups.

5.4. Appropriate change rooms and facilities should be provided. Toilets should be separated from the production areas to prevent product contamination/cross contamination.

5.5. At a minimum, defined areas should be provided for:

5.5.1. Materials receiving bay.

5.5.2. Incoming goods quarantine.

5.5.3. Starting materials storage.

5.5.4. Packaging materials storage

5.5.5. Processing and packaging operations.

5.5.6. Storage of finished products.

5.5.7. Laboratories (where available).

5.5.8. Rejected materials and products.

5.5.9. Returned and recalled products.

5.6. Walls and ceilings should be smooth and easy to maintain. The floor in processing areas should have a smooth surface, easy to clean and disinfect and be made of non-slippery material.

5.7. Drains in processing areas should be of adequate size and should not allow backflow. Open drains outside the processing areas should be avoided, but if required they should facilitate cleaning and disinfection.

5.8. Buildings should be adequately lit and properly ventilated. Lighting points should flush with the ceiling and windows should flush with the walls.

5.9. Pipework, light fittings, ventilation points and other service points in manufacturing areas should be installed in such a way to make for easy cleaning.

5.10. Laboratories (where available) should be separated from the production areas.

5.11. Storage Areas

5.11.1. Storage areas should be of sufficient capacity to allow orderly placement of materials such as starting and packaging materials, bulk and finished products, products in quarantine, released, rejected, returned or recalled products.

5.11.2. Precautions should be taken to prevent herbal materials, preparations and finished products from degradation and infestation with pests as well as biological contamination. Where applicable, special conditions of humidity, temperature and light protection should be provided for storage of plants, extracts, tinctures and other preparations. The premises

should be so constructed as to provide maximum protection for the starting materials, packaging materials and finished herbal products against birds, insects, rodents as well as domestic animals.

5.11.3. Incoming fresh herbal materials should be processed, unless specified otherwise, as soon as possible; or appropriately at the required temperature, humidity or light.

5.11.4. For materials stored in bulk, liability to mould formation or fermentation could arise. Such materials should be stored in aerated rooms or containers using natural or mechanical aeration and ventilation.

5.11.5. Wherever possible, sampling area for starting materials should be provided to prevent contamination.

5.11.6. Receiving and dispatch bays should be separated and should protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned before storage.

5.11.7. Packaging materials storage arrangements should permit separation of different labels and other printed materials to avoid mix-ups.

5.11.8. Herbal materials even when stored in fiber drums, bags or boxes should be stored off the floor and suitably spaced to permit cleaning and inspection.

6 EQUIPMENT

6.1. Construction and Design

6.1.1. Manufacturing equipment should be designed and constructed to suit manufacture of the product.

6.1.2. Equipment and utensils should be kept clean.

6.1.3. Vacuum or wet cleaning methods are preferred. Air and brushes should be used with care and avoided, if possible, as they increase the risk of product contamination.

6.1.4. Non-dedicated equipment should be cleaned between production of different batches and different products to prevent cross-contamination.

6.1.5. Written procedures should be established and followed for cleaning and sanitizing of process equipment and utensils as well as release of the equipment for use in the manufacturing and control of herbal medicinal products.

6.1.6. Responsibility for cleaning of process equipment should be clearly assigned.

6.1.7. Cleaning schedules including complete description of the methods and materials; and dilution of cleaning agents to be used to clean process equipment should be provided.

6.1.8. The equipment surfaces in contact with starting material, in-process material and finished product should not react with or adsorb the materials being processed.

6.1.9. Equipment should not adversely affect the product through leaking valves, lubricant drips and inappropriate modifications or adaptations.

6.1.10. Equipment should permit effective cleaning, avoid dust or dirt build up and any adverse effect on the quality of products.

6.1.11. Equipment should be closed or contained for intended usage. Where open equipment is to be used, precautions should be taken to prevent the risk of contamination.

6.1.12. Non-wooden equipment should be used unless tradition demands the use of wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.), these should be dedicated per product/material unless otherwise justified.

6.2. Installation and Location

6.2.1. Equipment should be located to avoid congestion and permit free movement of man and material.

6.2.2. Equipment should be properly identified using identification numbers to assure that products do not become admixed or confused with one another.

6.2.3. Measures to assure protection of personnel, products and environment should be put in place.

6.3. Maintenance of Equipment

6.3.1. Weighing, measuring, testing and recording equipment should be checked and calibrated regularly and all records of such activities should be maintained.

6.3.2. Where applicable, calibration of equipment should be performed using standards traceable to certified standards and a calibration label affixed to such equipment.

6.3.3. Measuring instrument that do not meet calibration criteria or whose calibration date has expired should not be used but labelled “not permitted for use”.

6.3.4. All forms of calibration should be done according to written in-house procedures or done externally by certified/authorized personnel.

7 SANITATION AND HYGIENE

7.1.1. Sanitation and hygiene should be practiced to avoid contamination of products. It should cover personnel, premises, equipment, production materials and containers.

7.2. Personnel

7.2.1. Personnel engaged in the manufacture, processing, packaging, or holding of herbal medicinal products should wear clean clothing appropriate for assigned duties. Protective apparel, such as head, face, nose, hand, feet and arm coverings, should be worn to ensure personnel safety and protection of herbal medicinal products from contamination.

7.2.2. Personnel should be healthy to perform their assigned duties. Regular medical examination should be conducted once a year for all personnel that come in contact with materials and products and records of these medical examinations should be retained and updated.

7.2.3. Personnel must practice good personal hygiene and sanitation.

7.2.4. Factory wears should not be worn out of the area they are meant for.

7.2.5. Any personnel shown at any time to be ill or have open lesions that may adversely affect the quality of products should not be allowed to handle raw materials, packaging materials, in-process materials, and finished products.

7.2.6. Smoking, eating and drinking are not permitted in production, laboratory, storage or other areas where they might adversely affect product quality.

7.3. Premises

7.3.1. Adequate washing and well-ventilated toilet facilities should be provided for employees and these should be separated from the production area.

7.3.2. Suitable locker facilities should be provided at appropriate locations for the storage of employees' clothing and personal belongings.

7.3.3. Waste material should be regularly collected in suitable receptacles for removal to collection points outside the production area.

7.3.4. Rodenticides, insecticides, fumigating agents and sanitizing materials must not contaminate equipment, raw materials, packaging materials, in-process materials or finished products.

8 MATERIALS MANAGEMENT

8.1. Standard operating procedures on the sourcing, receipt, identification, storage, handling, sampling, testing, and approval or rejection of materials should be established and followed.

8.2. Materials should always be handled and stored under appropriate conditions of temperature and humidity in a manner that prevent degradation and contamination.

8.3. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion following the first expire, first out (FEFO) or

first in, first out (FIFO) principle.

8.4. Upon receipt, each incoming delivery should be checked against the relevant documentation and physically verified by label description, type and quantity.

8.5. The consignment should be carefully inspected for defects and damage; records should be retained for each delivery.

8.6. Records should be maintained showing all receipts and issues of products.

8.7. All labels and containers of materials should not be altered, tampered or changed.

8.8. There should be a supplier selection and approval process, which will define minimum acceptable conditions for approval of suppliers. Agents and suppliers in the supply chain should be identifiable and their activities should be adequately controlled not to jeopardize the identity, performance or quality of the material.

8.9. Starting materials should be purchased only from approved suppliers and where possible directly from the producer against an agreed specification.

8.10. Changes in materials or the source of supply of starting materials should be handled through the formal change control system of the manufacturer to evaluate the effect of the change on the finished herbal medicinal product quality.

8.11. Only permitted substances should be used for fumigation, cleaning, lubrication of equipment and pest control.

8.12. Verification of materials

8.12.1. All deliveries of starting materials and packaging materials should be checked and verified for conformity to specifications and should be traceable to the product.

8.12.2. Samples of raw materials should be physically checked for conformity to specifications prior to release for use. The raw materials should be clearly labeled.

8.12.3. All finished Herbal Medicinal Products must be clean and checked for appropriate protective packing to ensure no leakage, perforation or exposure.

8.13. Rejected materials

8.13.1. Deliveries of raw materials that do not comply with specification should be segregated and disposed according to standard operating procedures.

8.14. Returned Products

8.14.1. Returned products should be identified and stored separately in allocated areas.

8.14.2. All returned products should be tested, if necessary, in addition to physical evaluation before being released for distribution.

8.14.3. Returned products, which do not comply with the original specifications should be

rejected.

8.14.4. Rejected products should be disposed according to appropriate procedures.

8.14.5. Records of returned products must be maintained.

9 PRODUCTION

9.1. Water

9.1.1. Special attention should be paid to water, since it is an important starting material. Water production equipment and water systems should supply water of required quality. Water systems should be sanitized according to well-established procedures.

9.1.2. The chemical and microbiological quality of water used in production should be monitored periodically, according to written procedures and any anomaly should be documented and followed up by appropriate corrective action.

9.1.3. The standard for water intended for use in production should not be below the quality of potable water.

9.1.4. The choice of water purification method should be determined by the product requirements including the storage as well as delivery system with proper maintenance.

9.2. Weighing and Measurement

9.2.1. Weighing should be carried out using calibrated equipment.

9.2.2. All weighing and measurement carried out should be recorded and checked by Quality Control personnel.

9.3. Production and Processing Instructions

9.3.1. All starting materials used should be approved according to specifications.

9.3.2. All manufacturing procedures should be carried out according to written procedures. The instructions for all processes should be clearly written and adequately documented describing the different operations to be performed on the plant material, such as drying, crushing, milling and sifting.

9.3.3. All required in-process controls should be carried out and recorded.

9.3.4. Bulk products should be properly labelled until approved by the Quality Control personnel.

9.3.5. Particular attention should be paid to problem of cross-contamination in all stages of production**.**

9.3.6. The time and temperatures required in the drying process, and the methods should be documented.

9.3.7. The methods to be used to control fragment or particle size and instruction on removing

other unwanted materials should also be stated.

9.3.8. The drying conditions chosen should be appropriate to the type of plant material processed, which depends on both the character of the active ingredients (e.g. essential oils) and the type of plant part collected (e.g. root, leaf, flower).

9.3.9. Drying by direct exposure to sunlight, if not specifically contraindicated, is possible, however drying on the ground should be avoided.

9.3.10. For the production of processed extracts, the instructions should specify details of any vehicle or solvent that may be used, the durations and temperatures needed for extraction, and any concentration stages and methods that may be required.

9.3.11. The permissible environmental conditions e.g. temperatures, humidity and standard of cleanliness, should be stated.

9.3.12. The rules that apply to the disposal of spent herbal material after processing should also be described.

9.4. Batch Numbering System

9.4.1. Every finished product should bear a production identification number, which enables the history of the product to be traced.

9.4.2. A batch numbering system should be specific for the product and a particular batchnumber should not be repeated for the same product in order to avoid confusion.

9.4.3. Whenever possible, the batch number should be printed on the immediate and outer container of the product.

9.4.4. Records of batch numbers should be maintained.

9.5. Dry Products

9.5.1. Handling of dry materials and products should be given special attention. Where possible, dust-containing production system or other suitable methods should be employed.

9.6. Wet Products

9.6.1. Wet products should be produced in such a way as to protect the product from microbial and other contamination.

9.6.2. The use of closed systems of production and transfer is recommended.

9.6.3. Where pipe-lines are used for delivery of ingredients or bulk products, care should be taken to ensure that the pipe-line systems are free from contamination.

9.7. Labeling and Packaging

9.7.1. Packaging line should be inspected for clearance prior to operation. Equipment should be clean and functional. All materials and products from previous packaging operation

should have been removed.

9.7.2. Samples should be taken and checked at random during labeling and packaging operations.

9.7.3. Each labeling and packaging line should be clearly identified to avoid mix-up.

9.7.4. Excess labels and packaging materials should be returned to the store and recorded.

9.7.5. Any rejected packaging materials should be disposed of accordingly and reconciliation made and recorded.

9.8. Finished Products

9.8.1. Finished Products should be quarantined until QC reports are received and if satisfactory, the products are transferred to the finished products store. The batch manufacturing record should be archived for up to one year after expiry of the batch.

9.8.2. All finished products should be approved by Quality Control prior to release.

10 QUALITY CONTROL

10.1. Introduction

10.1.1. Quality control is an essential part of GMP. It provides assurance that products will be of consistent quality appropriate to intended use.

10.1.2. A quality control system should be established to ensure that products contain the correct materials of specified quality and quantity and are manufactured under proper conditions according to standard operating procedures.

10.1.3. Quality control involves sampling, inspecting and testing of starting materials, in-process, intermediate, bulk, and finished products. It also includes environmental monitoring programs, review of batch documentation, sample retention program, stability studies and maintaining correct specifications of materials and products.

10.1.4. Adequate laboratory facilities for the testing and approval or rejection of materials and herbal medicinal products should be available in-house to the quality control unit where possible. Where these services are outsourced, the quality control unit should have facilities to conduct analyses of minimal parameters critical to the quality of the product.

10.2. Specifications

10.2.1. All specifications should be approved by the Quality Control personnel.

10.2.2. Raw and packaging material specifications should include:

10.2.2.1. Name of material

10.2.2.2. Description of the material

10.2.2.3. Testing parameters and acceptance limits

10.2.2.4. Storage and safety conditions.

10.2.2.5. Bulk and finished product specifications should include:

10.2.2.6. Name of product

10.2.2.7. Description of product

10.2.2.8. Physical properties of the product

10.2.2.9. Chemical assay and/or microbiological assays and their acceptance limits

10.2.2.10. Storage conditions and safety precautions.

11 DOCUMENTATION

11.1. General

11.1.1. Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP.

11.1.2. The documentation system should include the complete history of each batch, from starting materials to finished products. The system should record executed activities for maintenance, storage, quality control, primary distribution and other specific matters related to GMP.

11.1.3. Documents should be approved, signed and dated by the appropriate responsible persons.

11.1.4. No document should be changed without authorization and approval.

11.1.5. There should be a system for preventing the use of superseded documents.

11.1.6. If an error is made or detected on a record, it should be corrected in such a manner that the original entry is not lost and correction is made close to the original entry, initialed (or append signature) and dated.

11.1.7. Where documents bear instructions, they should be clearly written in a step-by-step manner.

11.1.8. Documents should be dated and authorized.

11.1.9. Documents should be readily available to relevant parties.

11.2. Standard Operating Procedures (SOPs)

11.2.1. Standard Operating Procedures (SOPs) give directions for performing certain operations.

11.2.2. SOPs and associated records of actions taken should be available for, but not limited to the following activities:

11.2.2.1. Facility and equipment cleaning

11.2.2.2. Personnel matters

11.2.2.3. Materials management activities

11.2.2.4. Production activities

11.2.2.5. Quality control activities

11.2.2.6. Pest control

11.2.2.7. Product complaints

11.2.2.8. Product recalls

11.2.2.9. Self-Inspection

11.3. Master Formula

11.3.1. The Master formula should be available for each product. This document should contain the following information:

11.3.1.1. Product name

11.3.1.2. Intended packaging materials, and storage conditions

11.3.1.3. List of raw materials used

11.3.1.4. List of equipment used.

11.3.1.5. Description of the manufacturing process

11.3.1.6. In-process controls with their limits in processing and packaging.

11.4. Batch Manufacturing Record (BMR)

11.4.1. Batch Manufacturing Records should include production and processing instructions and be prepared for each batch of product.

11.4.2. Each BMR should include the following:

11.4.2.1. Name of product

11.4.2.2. Batch number (See section 9.4)

11.4.2.3. Batch formula (as contained in the Master Formula) and records of weighing of` materials and samples of packaging materials.

11.4.2.4. Evidence of line clearance before commencement of each batch processing.

11.4.2.5. Manufacturing process and records of completion of each step

11.4.2.6. Date of the start and finish of processing and packaging

11.4.2.7. Identity of individual major equipment and lines or location used

11.4.2.8. Records of cleaning of equipment used for processing as appropriate

11.4.2.9. In-process control and laboratory results, such as pH and temperature test records, etc.

11.4.2.10. Packaging line clearance inspection record

11.4.2.11. Any sampling record(s) performed during various steps of processing

11.4.2.12. Any investigation of specific failure or discrepancies

11.4.2.13. Results of examination and testing of packed and labelled products.

11.5. Quality Control Records

11.5.1. Records for each testing and release or rejection of starting materials, intermediates, bulk and finished product should be maintained and records may include but not limited to:

11.5.1.1. Date of test

11.5.1.2. Identification of the material

11.5.1.3. Supplier name

11.5.1.4. Date of receipt

11.5.1.5. Original batch number if any

11.5.1.6. Batch number

11.5.1.7. Quality control number (where available)

11.5.1.8. Quantity received

11.5.1.9. Date of sampling

11.5.1.10. Quality control results.

12 SELF-INSPECTION

12.1. Self-Inspection consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it.

12.2. Designated, competent personnel are selected as a team from the company to conduct this audit for the purpose of detecting any shortcomings in the implementation of GMP and to recommend the necessary corrective action.

12.3. There should be an SOP for conducting self-inspection and a report should be written on completion of each self-inspection.

12.4. All observations made during the self-inspection should be evaluated and shared appropriately with management.

12.5. A follow-up should confirm the satisfactory completion or implementation of corrective actions.

12.6. Self-inspections should be performed routinely and in addition, may be performed on special occasions e.g. in the case of product recalls or repeated rejections, or when an inspection by the Agency is announced.

13 PRODUCT COMPLAINTS

13.1. A person should be designated to handle complaints and decide on measures to be taken.

13.2. There should be written procedures describing the action to be taken, including the needto consider a recall, in the case of a complaint involving a possible product defect.

13.3. Complaints involving product defects should be recorded with all the original details and investigated.

13.4. If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected.

13.5. Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

13.6. All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

13.7. Complaint records should be regularly reviewed for an indication of specific or recurring problems that require attention and which might justify the recall of marketed products.

13.8. EFDA should be informed if a manufacturer is considering action following possiblefaulty manufacture and product deterioration, which may lead to serious safety issues.

14 PRODUCT RECALLS

14.1. There should be a system of recall from the market of products known or suspected to be defective.

14.2. A person responsible for the execution and co-ordination of recalls should be designated.

14.3. Written procedures for recall should be established and regularly reviewed. Recall operations should be capable of being initiated promptly.

14.4. The primary distribution records should be readily available to the person(s) responsible for recalls, and they should contain sufficient information of distributors.

14.5. The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

14.6. The effectiveness of the arrangements for recalls should be evaluated from time to time (mock recall).

14.7. A written instruction should be established to ensure recalled products are stored securely in a segregated area while awaiting decision.

15 CONTRACT MANUFACTURING AND ANALYSIS

15.1. The conditions of contract manufacturing and analysis should be clearly defined, agreed, and controlled so as to avoid misunderstandings, which could result in a product or work of unsatisfactory quality.

15.2. All aspects of contracted work should be specified to obtain a quality product conforming to the agreed standards.

15.3. There should be a written contract between the contract giver and the contract acceptor to clearly establish the duties and responsibilities of each party.

15.4. In case of contract analysis, the scope of the contract should permit inspection of the contract facilities and activities of the contract acceptor by the Agency.

16 REFERENCES

- National Good Manufacturing Practice for Pharmaceutical Products, Third Edition, 2023Good Manufacturing Practices for Pharmaceutical Products, World Health Organization (WHO) Technical Report Series No. 986; 2014.

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