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Review Article

A Review Article on Good Manufacture of Practice

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ABSTRACT

provides a concise summary of the principles, regulations, and guidelines designed to ensure that products are consistently produced and controlled according to quality standards. GMP applies to manufacturing processes for pharmaceuticals, food, cosmetics, and other products where safety and quality are paramount. The goal of GMP is to minimize risks involved in production, such as contamination, errors, and deviations, through stringent controls on equipment, environment, personnel, and processes. The abstract typically highlights the key aspects of GMP, such as.

INTRODUCTION

This document is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (API s) under an appropriate system for managing quality. It is also intended to help ensure that API s meet the quality and purity characteristics that they purport, or are represented, to possess· In this guidance, the term manufacturing is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of API s and the related controls. In this guidance, the term should identifier recommendations that, when followed, will ensure compliance with C GMP s. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes. For the purposes of this guidance, the terms current good manufacturing practices and good manufacturing practices are equivalent. The guidance as a whole does not cover safety aspects for the personnel engaged in manufacturing, nor aspects related to protecting the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

Definition:

GMP is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by the marketing authorization. Good Manufacturing

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Practices (GMP s) are regulations that describe the methods, equipment, facilities, and controls required for producing:

- Human and veterinary products
- Medical devices
- Processed food

Scope

This guidance applies to the manufacture of API s for use in human drug (medicinal) products. It applies to the manufacture of sterile API s only up to the point immediately prior to the API s being rendered sterile. The sterilization and aseptic processing of sterile API s is not covered by this guidance, but should be performed in accordance with GMP guidelines for drug (Medi guidelines for drug (medicinal) primal) products as defined by local authorities. This guidance conducts as defined by local authorities. This guidance covers API s that are manufactured by chemical synthesis, extraction, cell culture/fermentation, recovery from natural sources, or any combination of these processes. ed activities should be defined and documented. There should be a quality unit(s) that is independent of production and that full fills both quality assurance (QA) and quality control (QC)Specific guidance for API s manufactured by cell culture/fermentation is described in Section XVIII (18). This guidance excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractional), and gene therapy API s. However, it does include API s that are produced using blood or plasma as raw Materials Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guidance. In addition, the guidance does not apply to medical gases, bulk-packaged drug (medicinal) products (e.g., tablets or capsules in bulk containers), or radio pharmaceuticals. Section XIX (19) contains guidance that only applies to the manufacture of API s used in the production of drug (medicinal) products specifically for clinical trials (investigation medicinal products). An API starting material is a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material.[1]

[2] Principle

Quality should be the responsibility of all persons involved in manufacturing. Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel. The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related responsibilities. The quality unit can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization. The persons authorized to release intermediates and API s should be specified. All quality-related activities should be recorded at the time they are performed. Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented. No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in Section X (10) or the use of raw materials or intermediates pending completion of evaluation). Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious.

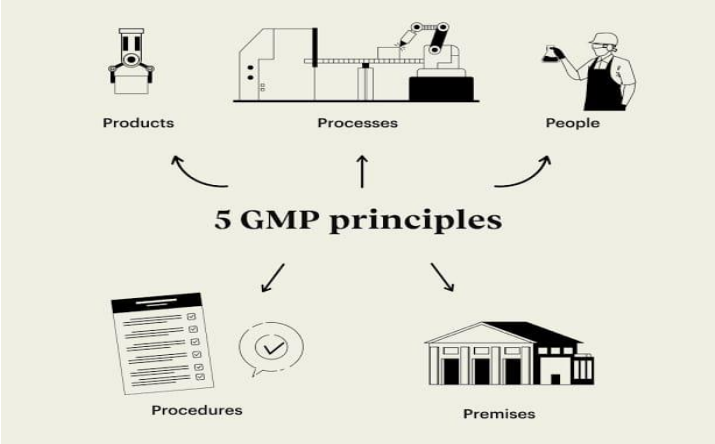

Figure:1 Principles of GMP

GMP deficiencies, product defects and related actions (e.g., quality-related complaints, recalls, and regulatory actions).

Personnel:

A. Personnel Qualifications: There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and API s. The responsibilities of all personnel engaged in the manufacture of intermediates and API s should be specified in writing. Training should be regularly conducted by qualified individuals and should cover, at a minimum, the operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

B. Personnel Hygiene: Personnel should practice good sanitation and health habits. Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved, and this clothing should be changed, when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn, when necessary, to protect intermediates and API s from contamination. Personnel should avoid direct contact with intermediates or API s. Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas. Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of API s. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the API s until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the API s. Contains Nonbinding Recommendations.

C. Consultants: Consultants advising on the manufacture and control of intermediates or API s should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

Buildings And Facilities

A. Design and Construction: Buildings and facilities used in the manufacture of intermediates and API s should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed

to minimize potential contamination. Were microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants, as appropriate. Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. Where equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors. The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination. There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejections
- Quarantine before release or rejection of intermediates and API s
- of intermediates and Sampling API s
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
- Storage of released materials
- Production operations
- Packaging and labeling operations
- Laboratory operations

It Contains Nonbinding Recommendations 10 Adequate and clean washing and toilet facilities should be provided for personnel. These facilities should be equipped with hot and cold water, as appropriate, soap or detergent, air dryers, or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate. Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process, intermediate, or API.

B. Utilities: All utilities that could affect product quality (e.g., steam, gas, compressed air, heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available. Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and Cross contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where API s is exposed to the environment. If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination. Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API. Drains should be of adequate size and should be provided with an air brake or a suitable device to prevent back-siphon-age, when appropriate.

C. Water: Water used in the manufacture of API s should be demonstrated to be suitable for its intended use. Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality. If drinking (potable) water is insufficient to ensure API quality and tighter chemical and/or microbiological water quality

specifications are called for, appropriate specifications for Contains Nonbinding Recommendations 11 physical/chemical attributes, total microbial counts, objectionable organisms, and/or endorphins should be established. Where water use in the process is treated by the manufacturer to achieve a defined quality, treatment process should be validated and monitored with appropriate action limits. Where the manufacturer of a non- sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endorphins.

D. Containment: Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillin' s or phallocentrism. The use of dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or toxicity anticancer agents) unless validated inactivation and/or cleaning procedures are established and maintained. Appropriate measures should be established and implemented to prevent cross-contamination from personnel and materials moving from one dedicated area to another. Any production activities (including weighing, milling, or packaging) of highly toxic non pharmaceutical materials, such as herbicides and pesticides, should not be conducted using the buildings and/or equipment being used for the production of API s. Handling and storage of these highly toxic non pharmaceutical materials should be separate from API s.

E. Lighting: Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

F. Sewage and Refuse: Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

G. Sanitation and Maintenance: Contains Nonbinding Recommendations 12 Buildings used in the manufacture of intermediates and API s should be properly maintained and repaired and kept in a clean condition. Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities. When necessary, written procedures should also be established for the use of suitable dentifrices, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and API s.

Process Equipment

A. Design and Construction: Equipment used in the manufacture of intermediates and API s should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitation (where appropriate), and maintenance. Equipment should be constructed so that surfaces that contact raw materials, intermediates, or API s do not alter the quality of the intermediates and API s beyond the official or other established specifications. Production equipment should only be used within its qualified operating range. Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified. A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems). Contains Nonbinding Recommendations 13

B. Equipment maintenance and cleaning; Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment. Written procedures should be established for cleaning equipment and its subsequent release for use in the manufacture of intermediates and API s. cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include the following:

- Assignment of responsibility for cleaning of equipment.
- Cleaning schedules, including, where appropriate, sanitizing schedules.
- A complete description of the methods and materials, including dilution of cleaning agent used to clean equipment.
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning.
- Instructions for the removal or obliteration of previous batch identification.
- Instructions for the protection of clean equipment from contamination prior to use.
- Inspection of equipment for cleanliness immediately before use, if practical.
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

C. Calibration: Control, weighing, measuring, monitoring, and testing equipment critical for ensuring the quality of intermediates or API s should be calibrated according to written procedures and an established schedule. Contains Nonbinding Recommendations 14 Equipment calibrations should be performed using standards traceable to certified standards, if they exist. Records of these calibrations should be maintained. The current calibration status of critical equipment should be known and verifiable. Instruments that do not meet calibration criteria should not be used. Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have influenced the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

D. Computerized Systems: GMP - related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application. Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks. Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available A means of ensuring data protection should be established for all computerized systems. Data can be recorded by a second means in addition to the computer system [2]

[3] Manufacturing Operations And Controls

All manufacturing operations shall be performed by trained personnel under direct supervision of approved technical staff approved by the licensing Authority. All the materials & containers used in mfg. process shall be conspicuously labeled with;

- ♣ Name of product
- ♣ Batch number and batch size
- ♣ Stages of manufacture

Products not prepared under aseptic condition are required to be free from pathogens like, Salmonella, Escherichia coli, PY0 Cyan-ea., etc. The licensee shall prevent mix-up and cross-contaminations of drug materials and drug product by proper air –handling system, pressure different segregation, and status labeling and cleaning. Proper records and Sops thereof shall be maintained.

Sanitation In Manufacturing Premises

Manufacturing premises shall be Cleaned and maintained according to validated cleaning procedure. Manufacturing areas shall not be use as storage or thoroughfare. A Routine sanitation program shall be drawn up and observed. Area shall be Well lightened production area particularly where visual online controls carried out.

Raw Materials

The licensee Keep an inventory of all raw materials to be used at any stage of production of drugs and maintain records as per Schedule U. All materials shall store under appropriate storage condition & follow 'first in/first expire'– 'first out' rule. Raw material from each batch checked for quality & appropriately labels the storage area. There shall be adequate separate area for materials "under test", "approved ", and "rejected" with arrangement and equipment. It allows dry, clean and orderly placement of stored materials and products, wherever necessary, under controlled temperature. And humidity. Only raw materials which have been released by the quality control department and which are within their shelf- life shall be used. It shall be ensured that shelf life of formulation product shall not exceed with that of active raw material used. It shall be ensured that all the containers of raw materials are placed on the raised platforms/racks and not placed directly on the floor.

Equipments

Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimize the risk of errors and permit effective cleaning and maintenance to avoid cross- contamination, build –up of dust or dirt and in general any adverse effect on the quality of product. Balance and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in process control operation and these shall be calibrated and checked on a scheduled basis in accordance with SOP and record maintained. To avoid accidental contamination, wherever possible, nontoxic / edible grade lubricant shall be used and the equipment shall be maintained in a way that lubricants don't Contaminate the products being produced. Defective equipment shall be removed from production and quality control areas or appropriately labeled.

Documentation And Records

- It is the essential part of the Quality assurance system. as such, shall be Related to all aspect of GMP.
- Its aim is to define the specification for all materials, method of mfg. and control, to
- ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a batch of a drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch.,
- Documents shall be approved, signed and dated by appropriate and authorized persons.
- Document designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.
- The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the mfg. Of pharmaceutical product are traceable. Records and associate d SOP shall be retained for at least one year after the expiry date of the finished product.

Labels And Other Printed Materials

1. Necessary for identification of the drugs and their use.
2. Printed in bright colour and legible manner.
3. All containers and equipment shall bear appropriate labels.
4. Different colour coded labels can be used.

5. Printed packaging materials & leaflets shall be stored separately to avoid mix-up.
6. Packaging, labeling and release shall be done after approval of QC department. Records of receipt and use of all material shall be maintained.

Quality Assurance

- To understand key issues in quality assurance/quality control.
- To understand specific requirements on organization, procedures, processes and resources.
- To develop actions to resolve current problems.

Quality Control System

☐ E quality control laboratory may be divided into chemical, instrumentation, micro control shall be concerned with sampling, specification, testing, documentation, a release procedure.

☐ It is not confined to laboratory operations but shall be involved in all decisions concerning the quality of the product.

¨ The department shall have other duties such as to establish, evaluate, validate and implement all Quality control procedure and methods.

☐ All the batches released after certification of QC department.

¨ Maintain reference/retained sample from each batch.

☐ The area of the biological and biological testing.

☐ Adequate area having the required storage conditions shall be provided Keeping references samples. The quality control department shall evaluate maintain and storage reference samples.

☐ There shall be authorized and dated specifications for all materials, products, reagents.

☐ The quality control department shall conduct stability studies of the products to ensure and assign their shelf life at the prescribed conditions of storage. All records of such studies shall be maintained.

☐ in charge of quality Assurance shall investigate all product complaints thereof shall be maintained

¨ All instruments shall be calibrated, and testing procedures validated before these are adopted for routine testing. Periodical calibration of instrument and validation of procedures shall be carried out.

☐ Pharmacopoeias, reference standard, reference spectra, other references materials and technical books, as required, shall be available in the quality control laboratory of the licensee.

Specifications

♦ For raw material & packaging material.
♦ For product containers & closures.
♦ For in-process & bulk products.
♦ or finished product.
♦ For preparation of containers & closures.

Master Formula Records: -

Related to –

- ✓ All mfg. procedures for each product.
- ✓ Batch size to be manufactured.

Includes: -

- → Name of product with reference code.
- → Patent & proprietary name with generic name.
- → Description of dosage form.
- → Name, quantity & reference no. Of all starting material.
- → A statement of expected final yield & the principal equipment to be used. Detailed SOP with the time taken for each step.
- → Requirements for storage conditions of the products, containers, labeling
- → Packaging detail and specimen labels.

Packaging Records: -

There shall be Authorized packaging instructions for each product, pack size & type that include;

★ Name of product with other description.

★ Volume of product in final container.
★ Complete list of all the packaging materials with.
★ Quantities size & type.
★ Description of packaging operations.
★ Detail of in process control

- **Batch Processing Records**: -

There shall be Batch processing Record for each product. It shall be based on the parts of the currently approved master formula. Before any processing begins, check shall be performed and recorded to ensure that the equipment and workstation are clear of previous products, documents or materials not required for the planned process are removed and that equip0ment is clean a suitable for use. During processing, the following information shall be recorded at time each action is taken and the record shall be dated and signed by the person responsible for the processing operations:

- Name po0f the product
- No. of the batch being manufactured
- Date and time of commencement
- Initials of the operator of the different significant steps of production and were
- Appropriate, of the person who checked each of these operations.
- Batch no.
- Equipment's used.
- Records of the IPQC. Amount of then product obtained at different and critical stages of manufacture. [3]

[4] Materials Management:

A. General controls: There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials. Manufacturers of intermediates and/or API s should have a system for evaluating the suppliers of critical materials. Materials should be purchased against an agreed specification, from a supplier, or suppliers, approved by the quality unit(s). If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer. Contains Nonbinding Recommendations 20 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

B. Receipt and Quarantine: Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling [including] correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested, as appropriate, and released for use. Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), Means of providing this assurance could include one or more 0f the following

• certificate of cleaning
• testing for trace impurities
• audit of the supplier large storage

containers and their attendant manifolds, filling, and discharge lines should be appropriately identified. Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

C. Sampling and Testing of Incoming Production Materials: At least one test to verify the

identity of each batch of material should be conducted, except for the materials described below. A supplier's certificate of analysis can be used in place of performing other tests, provided

that the manufacturer has a system in place to evaluate suppliers. Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Complete analyses should be conducted on at least three batches before reducing inhouse testing. Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

D. Storage: Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination. Materials stored in fibre drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection. Materials should be stored under conditions and for a period that have no adverse effect on their quality and should normally be controlled so that the oldest stock is used first. Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use. Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

E. Re-evaluation: Materials should be re-evaluated, as appropriate, to determine them suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

Production And In-Process Controls

A. Production Operations: Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use Weighing and measuring devices should be of suitable accuracy for the intended use

If the material is subdivided for later use in production operations.

The contain receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code
- Receiving or control number
- Weight or measure of material in the new container
- Re-evaluation or retest date if appropriate

Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

B. Time Limits: If time limits are specified in the master production instruction these time limits should be met to ensure the quality of intermediates and API s. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing. Contains Nonbinding Recommendations 23 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

C. In-process Sampling and Controls: Written procedures should be established to monitor

the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and API s. In-process controls and their acceptance criteria should be defined based on the information gained during the developmental stage or from historical data. The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in process

controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps). Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

D. Blending Batches of Intermediates or API s: For this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuges loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending. Out-of-specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an Contains Nonbinding Recommendations 24 established process and should have been individually tested and found to meet appropriate specifications prior to blending. Acceptable blending operations include, but are not limited to:

• Blending of small batches to increase batch size

• Blending of railings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch Blending processes should be adequately controlled and documented, and the blended batch should be tested for conformance to established specifications, where appropriate.

E. Contamination Control: Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue to the wall of a microphone, residual layer of damp crystals remaining in centrifuge bowl after dis charge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of grandaunts or microbial contamination that may adversely alter the established API impurity profile. Production operations should be conducted in a manner that prevents contamination of intermediates or API s by other materials. Precautions to avoid contain to avoid contamination should be taken when API s are handled after purification.

Packaging And Identification Labeling Of Api S And Intermediates

A. General: There should be written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing, release, and handling of packaging and labeling materials. Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable. Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether and r accepted or rejected.

B. Packaging Materials: Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation recommended storage. Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits. If containers are reused, they should be cleaned in accordance with documented procedures, and all previous labels should be removed or defaced.

C. Label Issuance and Control: Access to the label storage areas should be limited to authorized personnel. Procedures should be established to reconcile the quantities of labels issued, used, and

returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

D. Packaging and Labeling Operations: There should be documented procedures designed to ensure that correct packaging materials and labels are used. Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

Storage And Distribution

A. Warehousing Procedures: Contains Nonbinding Recommendations 27 Facilities should be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics. Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been made.

B. Distribution Procedures: API s and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). API s and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation is in place. API s and intermediates should be transported in a manner that does not adversely affect their quality. Special transport or storage conditions for an API or intermediate should be stated on the label. The manufacturer should ensure that the contract accepts or (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions. A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall. [4]

[5] Contract Manufacturers (Including Laboratories) Contract

All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance. Special consideration should be given to the prevention of cross contamination and to maintaining traceability. Companies should evaluate any contractors (including laboratories) to ensure GMP compliance of the specific operations occurring at the contractor sites. There should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including the quality measures, of each party. A contract should permit a company to audit its contractor's facilities for compliance with GMP. Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it

under the contract without the company's prior evaluation and approval of the arrangements. Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available. Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

Agents, Brokers, Traders, Distributors, Repackers, And Relabellers

A. Applicability: This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate. All agents, brokers, traders, distributors, re pockets, and relabels should comply with GMP as defined in this guidance.

B. Traceability of Distributed API s and Intermediates: Agents, brokers, traders, distributors, re pockets, or relabels should maintain complete traceability of API s and intermediates that they distribute. Documents that should be retained and available include the following: Contains Nonbinding Recommendations 40

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

C. Quality Management: Agents, brokers, traders, distributors, re pockets, or relabels should establish, document and implement an effective system of managing quality, as specified in Section 2.

D. Repackaging, Relabeling, and Holding of API s and Intermediates: Repackaging, Relabeling, and holding API s and intermediates should be performed under appropriate GMP controls, as stipulated in this guidance, to avoid mix-ups and loss of API or intermediate identity or purity. Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

E. Stability: Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

F. Transfer of Information: Agents, brokers, distributors, replaces relabel should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer. The agent, broker, trader, distributor, repacked, or relabeled who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied. The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between Contains Nonbinding Recommendations 41 the authorized agents and the original API or intermediate manufacturer. (In this context authorized refers to authorized by the manufacturer.) The specific guidance for certificate of analysis included in Section 11.4 should be met.

G. Handling of Complaints and Recalls: Agents, brokers, traders, distributors, replaces, or relabels should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention. If the situation warrants, the agents, brokers, traders, distributors, replaces, or relabels should review the complaint with the original API or intermediate manufacturer to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party. Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, replaces, or relabels should include any response received from the original API or intermediate manufacturer (including date and information provided).

H. Handling of Returns: Returns should be handled as specified in Section 14.5. The agents,

brokers, traders, distributors, replaces, or relabels should maintain documentation of returned API s and intermediate [5]

[6] Components Of Gmp

GMP requires that the manufacturing process is fully defined before being initiated and all the necessary facilities are provided. In practice,

Figure:2 Components of GMP

used, approved procedures adopted, suitable storage and transport facilities available, and appropriate records made. The essential components of GMP are summarized Components of Good Manufacturing Practice Indian Schedule M for GMP and requirements of premises, plant and equipment for pharmaceutical products. Part I includes general requirements, Warehousing. Part I includes general requirements, Warehousing area, Production area, Quality control area, Personnel, Ancillary area, Health, clothing and sanitation of workers, Manufacturing operations and controls, Sanitation in the manufacturing premises, Raw materials, Equipment, Documentation and Records, Labels and other printed materials, Quality assurance, Self-inspection and quality audit, Quality control system, Specification, Master formula records, Packing records, Batch packaging records, Batch processing records, Standard operating procedures (SOP's) and records, Reference samples, Reprocessing and recoveries, Distribution records, Validation and process validation, Product recalls, Complaints and adverse reactions and Site-master file. Part I-A to part I-E mentions about the specific requirements for manufacture of different products and Part I-F mentions about the specific requirements of premises, plant and materials for manufacture of active pharmaceutical ingredients (bulk drugs). Part II describes the Requirement of plant and equipment's for various dosage forms. Consolidated Components of Good Manufacturing Practices. [6]

[7] Quality Management

Quality management is a core principle of GMP as it is essential that all veterinary products are fit for their intended use and do not place target species at risk due to inadequate safety, quality, efficacy, purity or identify.

Quality management within GMP covers:

- Quality Assurance
- Quality Control
- Product Quality Reviews
- Quality Risk Management

Figure:3 difference of quality assurance and quality control

[8] **Quality risk management**

About guidance on Quality Risk Management, ICH Q9 document containing guidelines on GMP to be followed in this context was elaborated. This guideline specifically provides principles and examples of tools of Risk Quality that can be applied to all aspects of pharmaceutical quality including the development, manufacture, distribution and inspection processes and submission/review of the entire life cycle of substances, medicinal products, biologic and biotechnology products including the development, manufacture, distribution and inspection and submission/review of the entire life cycle of substances, medicinal products, biologic and biotechnology products, including the use of starting materials, solvents, recipients, packaging and labelling materials, that allow for more effective and consistent risk-based decisions, either by regulators or the Industry. It is not intended to create new expectations beyond current requirements. The purpose of this guideline is to provide a systematic approach of quality risk management and serves as a base or resource, independent, supporting other documents relating to the quality of ICH and complements existing quality practices, requirements, standards and guidelines in the scope of Pharmaceutical Industry and regulatory environment, thus remaining optional character. Quality risk management can be applied not only in the manufacturing environment, but also in connection with the pharmaceutical development and preparation of quality part of the dossier for MA. The guidelines also apply to regulatory authorities in the field of pharmaceutical evaluation of the quality of the dossier for MA, GMP inspections and treatment of suspicions of quality defects.

Premises;

premises must be located, constructed, adapted, designed, and maintained to suit the operations to be carried out. The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products [20]. The choices of materials of construction for manufacturing facilities are numerous. Some examples are presented subsequently.

a. Walls: Walls in manufacturing areas, packaging areas and corridors should be of plaster finish on high-quality concrete blocks or gypsum board. The finish should be smooth, usually with enamel or epoxy paint. They should be washable and able to resist repeated applications of cleaning and disinfecting agents.

b. Floors: Floor covering should be selected for durability as well as for clean ability and resistance to the chemicals with which it is likely to come into contact. Epoxy flooring provides a durable and readily cleanable surface.

c. Ceilings: Suspended ceilings may be provided in office areas, toilets, laboratories and cafeterias. They usually consist of lay-in acoustical panels of non-brittle, non-friable, non-asbestos and non-combustible material. Manufacturing areas require a smooth finish, often of seamless plaster or gypsum board. All ceiling fixtures such as light fittings, air outlets and returns should be designed to assure ease of cleaning and to minimize the potential for accumulation of dust.

d. Services: In the building design, provisions must be made for drains, steam, electricity, water and other services to allow for ease of maintenance. Access should, ideally, be possible without disruption of activity within the actual rooms provided with the services. Doors and window-frames should all have a hard, smooth, impervious finish, and should close tightly. Window and door frames should be fitted flush, at least on sides facing inward to processing areas. Doors, except emergency exits, should not open directly from production areas to the outside world. Any emergency exit doors should be kept shut and sealed, and designed so as to be open able only when emergency demand. [8]

CONCLUSION: emphasizes its vital role in ensuring that products, particularly in the pharmaceutical, food, and cosmetic industries, are produced consistently to the highest quality standards. GMP ensures safety, quality, and efficacy by maintaining strict guidelines and processes throughout the production cycle. It helps minimize risks such as contamination, errors, and defects, and ensures that products are safe for consumer use. Compliance with GMP is essential for protecting public health, ensuring regulatory approval, and maintaining consumer trust.

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