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THE TANZANIA FOOD, DRUGS AND COSMETICS ACT
(CAP 219)

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REGULATIONS

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(Made under section 122(1)(o))

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THE TANZANIA FOOD, DRUGS AND COSMETICS (GOOD MANUFACTURING PRACTICE ENFORCEMENT) REGULATIONS, 2018

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THE TANZANIA FOOD, DRUGS AND COSMETICS ACT

(CAP 219)

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(Made under section 122(1)(o))

THE TANZANIA FOOD, DRUGS AND COSMETICS (GOOD MANUFACTURING PRACTICE ENFORCEMENT) REGULATIONS, 2018

PART I
PRELIMINARY PROVISIONS

Citation

1. These Regulations shall be cited as the Tanzania Food, Drugs and Cosmetics (Good Manufacturing Practice Enforcement) Regulations, 2018

Scope of application

2. These Regulations shall apply in all types of good manufacturing practice inspections for human and veterinary manufacturing facilities of active pharmaceutical ingredients and finished pharmaceutical products to be sold in Mainland Tanzania.

Interpretation

3. In these Regulations, unless the context otherwise requires-

Cap 219

“Act” means the Tanzania Food, Drugs and Cosmetics Act;

“applicant” means any legal or natural person, established within or outside Tanzania, seeking to obtain or having obtained the license to manufacture medicinal products;

“Authority” means the Tanzania Food and Drugs Authority or its acronym ‘TFDA’ established under section 4(1) of the Act;

"conflict of interest" means any interest in any business related to medicines declared by GMP inspector that may affect or reasonably perceived to affect the quality or the result of his work or remediation;

"critical observation" means an observation describing a situation that will most likely result in a non-compliant product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data;

"GMP inspector" means an inspector appointed under the Act who possesses qualification and experience in pharmaceutical manufacturing, quality control and quality assurance;

“inspection” means formal and objective control to identify non-conformances in accordance with standards adopted to assess compliance with these Regulations;

"lead GMP inspector" means a senior GMP inspector who is charged with the responsibility for leading a GMP inspection team to undertake inspection of a specified pharmaceutical manufacturing site;

"major observation"means an observation describing a situation that may have an impact on the product but is not as significant as acritical observation. It may have an indirect impact in the strength, identity, purity or safety of the product. There is reduced usability of the product without a probability of causing harm to the consumer. Observation of a major deficiency puts a question mark on the reliability of the firm’s quality assurance system;

"minor observation" means an observation describing a situation that is a departure from GMP but has no significant impact on the product quality. It has low probability of affecting the quality or usability of the product;

"manufacture" means all operations of purchase of materials and products, production, packaging, quality control, release, storage, shipment of finished products, and the related controls.

"manufacturer" means a company that carries out at least one step of manufacture.

"manufacturing process" means transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

“Minister” means the Minister for the time being responsible for health;

“recall” means an action taken by the manufacturer to remove pharmaceutical product from the market or to retrieve any such product from any person to whom it has been supplied, because the product may-

(a) be hazardous to health;

(b) fail to conform to any claim made by its manufacturer relating to its quality, safety or efficacy; or

(c) not meet the requirements under these Regulations;

"re-qualification" means validation of the GMP inspector after 24 months absence from conducting GMP inspections to ensure the officer possesses the knowledge and skills tocarry out GMP inspections;

"senior GMP inspector " means an officer who by virtue of experience and competence is appointed to conduct GMP inspections and train junior officers in inspections;

"specialized GMP inspector" means a GMP inspector who possesses specialized knowledge and experience in conducting GMP inspections for specialized areas such as microbiology, HVAC, biologicals and APIs;

“validation” means the establishment of documented and objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

“Quality management” means a management function that determines and implements the quality policy that is, the overall intention and direction of an organization as formally expressed and authorized by top management.

“Quality assurance” means a wide- ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.

“Quality control” means the part of GMP concerned with sampling, specifications, testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are neither released for use, nor for sale or supply, until their quality has been judged to be satisfactory.

“Product quality review” means regular, periodic or rolling quality reviews of all medicinal products, including export-only products, conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements.

“Quality risk management” means a systematic process for the assessment, control, communication and review of risks to the quality of a pharmaceutical product.

PART II

TYPES OF GMP INSPECTION AND ADMINISTRATIVE MATTERS

Types of GMP Inspection

4.-(1) There shall be four types of GMP inspection.

(2) The GMP inspections shall be divided into the following categories:

(a) routine inspection;

(b) concise inspection;

(c) follow-up inspection;

(d) special inspection; and

(e) any other types as the Authority may designate.

Routine Inspection

(3) The routine GMP inspection shall be conducted at any time during which the product has been registered but before expiry of validity of registration of such product

Concise Inspection

(4) The Authority shall conduct a GMP Concise inspection where an applicant product complied with the requirements for registration and as such has become eligible for being considered for market authorisation.

Follow up Inspection

(5) The Authority may conduct a follow up inspection with a view to verify the observations of any previous GMP inspection conducted regardless of whether such inspection was done as the first inspection, special or routine inspection

Special Inspection

(6) Unless expressly provided to the contrary, the Authority may conduct GMP inspection to verify compliance with need requirements to any manufacturing

(7) The GMP inspection shall be special if it shall be conducted under the following circumstances:

(a) When there are complaints about a specific product that suggest that there might be defects;

(b) When there is a product recall due to events related to adverse drug reactions;

(c) When there is a need to gather specific information, or to investigate specific operations of the manufacturing processes

Application procedure

5.-(1) Application for GMP inspection shall be made to the Director General by submitting the following:

(a) Dully filled in application form prescribed in the First Schedule of these Regulations;

(b) GMP inspection fee as prescribed in the Fees and Charges Regulations in force;

(c) Latest version of the Site Master File in a format prescribed in the Second Schedule of these Regulations;

(2) Notwithstanding the provision of Regulation 5(1) above, GMP is part of the marketing authorization of the products therefore inspection shall not be conducted to a facility which has not submitted applications for products registration.

GMP desk review

6.-(1) Upon fulfilling requirements of Regulation 5 above, the Authority may conduct GMP assessment of the application by desk documents review.

(2) Criteria to be used for GMP documents desk review shall be as follows;

(a) Facilities must be located in countries with Stringent National Medicines Regulatory Agencies; or

(b) Facilities located in countries which are ICH founding regulatory members; or

(c) Facilities located in countries which are Standing regulatory members; or

(b) Facilities Inspected and approved under the framework of WHO prequalification programme

GMP Certificate and Validity

7.-(1) Upon fulfilling the GMP requirements, the Authority shall issue a Certificate of GMP prescribed in the Fourth Schedule of these Regulations;

(2) The validity of the GMP Certificate shall be three years.

PART III
QUALITY MANAGEMENT

Principle

8.- (1) A manufacturer shall be responsible to ensure:-

(a) The quality of medicinal product manufactured is fit for their intended use

(b) The medicinal product comply with the requirements of market authorization

(c) medicinal product do not place patients at risk due inadequate safety, quality or efficacy

(2). the manufacturer shall implement the quality management with following elements:-

(a) appropriate structure or quality system encompassing the organizational structure

(b) appropriate procedures

(c) appropriate processes and

(d) resource

Quality assurance

9.-(1) A manufacturing facility shall have comprehensively designed and correctly implemented system of quality assurance which incorporates GMP and thus quality control

(2) Quality assurance system appropriate for pharmaceutical product manufacturing shall ensure the following:-

(a) Medicinal products are designed and developed in a way that takes account of the requirements of GMP, GLP and GCP;

(b) Production and control operations are clearly specified in a written form and GMP requirements are adopted;

(c) job description for managerial posts are clearly specified;

(d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

(e) all necessary controls on starting materials, intermediate products, and bulk products and any other in- process controls, calibrations, and validations are carried out;

(f) the finished product is correctly processed and checked as per the defined procedures;

(g)medicinal products are not sold or supplied before the authorized persons have certified;

(h)satisfactory arrangements exist to ensure medicinal products are stored, distributed, and handled to maintain its quality throughout their shelf-life;

(i) there is a procedure for self- inspection and or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;

(j) deviations are reported, investigated and recorded;

(k) there is a system for approving changes that may have an impact on product quality;

(l) regular evaluation of the quality of pharmaceutical products to verify the consistency of the process and ensuring its continuous improvement; and

(m) there is a system for quality risk management;

Good Manufacturing Practice (GMP)

10.-(1) GMP as part of quality assurance shall ensure the products are consistently produced and controlled to the quality standards appropriate to their intended use and requirements of marketing authorization and product specification.

(2) GMP rules shall direct to diminish risks due to cross contamination or mix-ups that cannot be completely prevented through the testing of final products.

(3) GMP shall have the following basic requirements:-

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality that comply with their specifications;

(b) critical steps of manufacturing processes and any significant changes made to the processes are validated;

(c) all necessary facilities are provided, including:

(i) appropriately qualified and trained personnel;

(ii) adequate premises and space;

(iii) suitable equipment and services;

(iv) correct materials, containers and labels;

(v) approved procedures and instructions;

(vi) suitable storage and transport and;

(vii) Adequate personnel, laboratories and equipment for in-process controls under the responsibility of the production management.

(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;

(e) operators are trained to carry out procedures correctly;

(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;

(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(h) the proper storage and distribution of the products minimizes any risk to their quality;

(i) a system is available to recall any batch of product from sale or supply;

(j) Complaints about marketed products are examined; the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent recurrence.

Quality control

11.-(1)Quality control as part of GMP shall perform the following activities:-

(a) sampling of raw material, intermediate and finished product

(b) develop specification

(c) carry out testing

(d) documentation

(e) develop release procedure

(f) release of materials, intermediate and finished product

(2) Every pharmaceutical manufacturing facility shall have a quality control department which is independent from production department and any other department

(3) the quality control laboratory shall be under the authority of a person with appropriate qualification and experience

(4) Quality control shall meet the following basic requirement:-

(a) Adequate facilities, trained personnel and approved procedures
(b) Conduct Sampling, inspecting and testing of starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
(c) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.
(d) Test methods must be well documented and validated.
(e) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.
(f) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled.
(g) Records must be made of the results of inspecting and testing starting materials, intermediate, bulk, and finished products against specifications; product assessment shall include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.
(h) No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. Sufficient reference samples of starting materials and products shall be retained to permit future examination of the product if necessary; the retained product shall be kept in its final pack unless the pack is exceptionally large
(i) other duties performed by quality control shall be;
(i) to establish, validate and implement all quality control procedures;
(ii) to evaluate, maintain and store the reference standards for substances;
(iii) to ensure correct labelling of containers of materials and products;
(ii) to ensure that the stability of the active pharmaceutical ingredients and products are monitored;
(iii) to participate in the investigation of complaint related to quality of the product; and

(5) personnel shall have access to production areas for sampling and Investigation where necessary.

Product quality review

12.-(1)Manufacturing facility shall carry regular, periodic or rolling quality review of all medicinal products including export only Products in order to:-

(a) verify consistency of existing process

(b) appropriateness of current specification for starting material and finished Products

(c) establish trends

(d) identify product and process improvements

(2) the review shall be conducted and documented annually, taking into account previous reviews.

(3) the review shall include at least the following information:-

(a) review of starting materials and packaging materials used for the product, especially those from new sources;

(b) a review of critical in-process controls and finished product results;

(c) a review of all batches that failed to meet established specifications and their investigation;

(d) a review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant corrective and preventive actions taken;

(e) a review of all changes made to the processes or analytical methods;

(f) a review of dossier variations submitted, granted or refused;
(g) a review of the results of the stability monitoring programme and any adverse trends
(h) a review of all quality-related returns, complaints and recalls and the investigations performed at that time;
(i) a review of adequacy of any other previous corrective actions on product process or equipment;
(j) for new dossiers and variations to the dossiers, a review of post- marketing commitments;
(k) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water, or compressed gases; and
(l) a review of technical agreements to ensure that they are up to date.

(4) Manufacturer shall carry out evaluation of results of review and assessment whether corrective and preventive action or any revalidation is needed to be done.

(5) Corrective action and preventive action shall be documented
(6) Corrective and preventive action shall be done in a timely and effective manner.

(7)Where market authorization holder is different from manufacturer,

there shall be technical agreement in place between the various parties

with their responsibilities for producing the quality review.

(8) The authorized person responsible for final batch certification, together

with the marketing authorization holder, shall ensure that the quality

review is performed in a timely manner and is accurate.

Quality risk management

13.-(1) A manufacturer shall have a systematic process for assessment, control, communication and review of risk to the quality of pharmaceutical product.

(2) the system shall ensure evaluation of the risk based on scientific knowledge and experience with the process to protect patient.

(3) the formality and documentation of the quality risk management process shall be based on risk level.

Sanitation and hygiene

14.-(1) Every aspect of pharmaceutical products manufacturing shall be carried out in a high level sanitation and hygiene.

(2) Sanitation and hygiene shall cover personnel, premises, equipment and

apparatus, production material and containers, products for cleaning and

disinfection and anything that could be source of contamination of the product.

(3) There are shall be an integrated comprehensive program of sanitation and hygiene

PART IV
PERSONNEL

15.-(1) There are shall be sufficient qualified personnel to carry out all manufacturing activities.

Principle

(2) Responsibilities for every individual shall be clearly understood and recorded.

General

16.-(1) The manufacturer shall have organization chart.

(2) There are shall be adequate number of personnel with necessary qualification and practical experience to carry out manufacturing activities.

(3) All responsible staff shall have their duties recorded in written descriptions and adequate authority to carry out their responsibilities.

(4) Duties for responsible personnel may be delegated to designated deputies of satisfactory qualification level.

(5) There are shall be no gaps or unexplained overlaps in responsibilities of personnel concerned with the application of GMP

(6) All personnel shall be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene.

(7) No unauthorized personnel shall enter production, storage and quality control areas or use them as passage.

Personnel

17.-(1) A manufacturing facility shall have the following key personnel:-

(a) Head of production

(b) Head of quality unit

(c) Head of quality assurance

(d) Head of quality control

(e) Authorized person

(2) The head of production and quality control shall be independent of each other

(3) Key posts shall be occupied by full-time personnel.

(4)The manufacturer shall notify the Authority the name of qualified/ authorized person appointed by manufacturers.

(5) The manufacturer shall notify the Authority of the name of any persons to whom functions have been delegated by the responsible person under sub-regulation (1), and the specific functions which have been delegated to such persons.

(6) Key personnel responsible for supervising the manufacture and quality unit including quality assurance and quality control for manufacture of pharmaceutical products shall possess the qualification with scientific education and practical experience.

(7) The head of production shall have bachelor education in Pharmacy but if not available options shall be for person with at least a bachelor education in the following:
(a) pharmaceutical sciences and technology;
(b) chemistry (analytical or organic) or biochemistry;
(c) chemical engineering;
(d) Veterinary medicine;
(8) The head of quality unit shall have bachelor education in any of the following:
(a) Pharmacy
(b) pharmaceutical sciences and technology,
(c) chemistry (analytical or organic) or biochemistry,
(9) The head of quality control shall have bachelor education in any of the following:
(a) Pharmacy
(b) pharmaceutical sciences and technology,
(c) chemistry (analytical or organic) or biochemistry,
(d) microbiology,
(10) The heads of the production and quality control departments generally shall have some shared, or jointly exercised, responsibilities relating to quality;

(a) the authorization of written procedures and other documents, including amendments;
(b) the monitoring and control of the manufacturing environment;
(c) plant hygiene;
(d) process validation and calibration of analytical apparatus;
(e)training, including the application and principles of quality assurance;
(f) the approval and monitoring of suppliers of materials;
(g) the approval and monitoring of contract manufacturers;
(h) the designation and monitoring of storage conditions for materials and products;
(i) the performance and evaluation of in process controls
(j) the retention of records;
(k) the monitoring of compliance with GMP requirements;
(l) the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

(11) The head of the production department shall have the following responsibilities:

(a) ensure products are produced and stored according to the appropriate documentation in order to obtain the required quality;

(b) to approve the instructions relating to production operations, including the in-process controls and to ensure their strict implementation;

(c) to ensure that the production records are evaluated and signed

(12)The head of the quality unit including quality assurance and quality control department generally shall have the following responsibilities:
(a) to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
(b) to evaluate batch records;
(c) to ensure that all necessary testing is carried out;
(d) to approve sampling instructions, specifications, test methods, and other quality control procedures;
(e) to approve and monitor analyses carried out under contract;
(f) to check the maintenance of the department, premises and equipment;
(g) to ensure that appropriate validations, including those of analytical procedures, and calibrations of control equipment are done;
(h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need;
(i) establishment, implementation and maintenance of the quality system;
(j) supervision of regular internal audits or self-inspections;
(k) participate in external audits (vendor audits);
(l) Participate in validation programmes.

Training

18.-(1) A manufacturer shall provide training as per written programme for all the personnel whose duties take them into production areas or into control laboratories including the technical, maintenance, and cleaning personnel), and any other personnel whose activities could affect the quality of the product.
(2) Recruited personnel shall receive training appropriate to the duties assigned to them in addition to basic training on theory and practice of GMP.
(3) All personnel shall receive continuing training, evaluated and records shall be retrieved as per approved training programme.
(4) Personnel working in areas where contamination is a hazardous such as clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled shall be given specific training.
(5) Visitors or untrained personnel shall not enter production and quality control areas, if necessary they shall be closely supervised and practice personnel hygiene including wearing protective clothing.
(6) Consultants and contract staff shall be qualified for their service and their training records kept.

Personal hygiene

19.-(1) Any person prior or during employment shall undergo health examination.

(2) Notwithstanding the provision of sub-regulation (1), all personnel conducting visual inspection shall undergo periodic eye examination.

(3) Every person engaged with manufacturing process shall be trained in the practise of personal hygiene including washing hands before entering production areas.

(4) Signs and instruction posters for personnel hygiene shall be displayed on respective areas.

(5) Any person with an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.

(6) All employees shall be instructed and encouraged to report to their immediate supervisor any conditions relating to plant, equipment, or personnel) that they consider may adversely affect the products.

(7) Direct contact shall be avoided between the operator's hands and starting materials, primary packaging materials, and intermediate or bulk product.

(8) All personnel shall wear clear body covering appropriate to the duty they perform including hair covering in order to protect product from contamination.

(9) All reusable clothes, shall be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

(10) No person shall be allowed to eat, drink, smoke, chew, store plants, food, drinks, smoking material or personal medicines in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.

(11) Personal hygiene procedures including the use of protective clothing shall apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees such as contractors' employees, visitors, senior managers and inspectors.

PART V
PREMISES

Principle

20.-(1) Premises shall be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design 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 any adverse effect on the quality of products.

General

21.-(1) Premises shall be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

(2) Premises used for the manufacture of drug products shall be suitably designed and constructed to facilitate good sanitation.

(3) Premises shall be maintained and ensured that repair and maintenance operations do not present any hazard to the quality of products.

(4) Premises shall be cleaned and where applicable, disinfected as per written procedures and records maintained.

(5) Electrical supply, lighting, temperature, humidity, and ventilation shall be appropriate and do not adversely affect, directly or indirectly the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

(6) Premises shall be designed and equipped to provide maximum protection against the entry of insects, birds or any other animals. There shall be procedure for rodent and pest control and records shall be maintained.

Production area

22.-(1) In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated, separate and self-contained facilities shall be available for the production of particular pharmaceutical products, such as penicillin, cephalosporin and other highly sensitizing materials and biological preparations like live microorganisms.

(2) The production of certain additional products, such as certain antibiotics, hormones, cytotoxic substances, highly active medicinal products, and non-medicinal products, shall not be conducted in the same facilities.

(3) The manufacture of technical poisons, such as pesticides and herbicides, shall not be allowed in premises used for the manufacture of pharmaceutical products.

(4) Premises shall be laid out to allow production to take place in areas connected in a logical order corresponding to the sequence of the operations, materials flow, personnel movement and to the requisite cleanliness levels.

(5) The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

(6) Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) shall be smooth and free from cracks and open joints, shall not shed particulate matter, and shall permit easy and effective cleaning and, if necessary, disinfection.

(7) Pipe work, light fittings, ventilation points, and other services shall be designed and sited to avoid the creation of recesses that are difficult to clean. In case of maintenance purposes, they shall be accessible from outside the manufacturing areas.

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

(9) Production areas shall be effectively ventilated, with air-control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled, to the operations undertaken, and to the external environment. These areas shall be regularly monitored during production and non-production periods to ensure compliance with their design specifications.

(10) Where dust is generated during sampling, weighing, mixing, processing operations and packaging of powders measures shall be taken to avoid cross contamination and facilitate cleaning.

(9) Premises for the packaging of medicinal products shall be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

(10) Production areas shall be well lit, particularly where visual on-line controls are carried out.

Storage areas

23.-(1) Storage areas shall be of sufficient capacity to allow orderly storage of various categories of materials and products; starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned, or recalled products.

(2) Storage areas shall be designed or adapted to ensure good storage conditions, clean and dry with sufficient lit and maintained within acceptable temperature limits. If special storage conditions are required of humidity and temperature shall be provided. The conditions shall be controlled, monitored and records maintained.

(3) Receiving and dispatch bays shall be separated and protect materials and products from the weather. Reception areas shall be designed and equipped to allow containers of incoming materials to be cleaned before storage.

(4) Where quarantine status is ensured by storage in separate areas, these areas shall be clearly marked and their access restricted to authorized personnel. If system is used to replace the physical quarantine shall give equivalent security.

(5) Separate sampling area for starting materials shall be provided. In case sampling is performed in the storage area, it shall prevent contamination or cross-contamination.

(6) Storage of rejected, recalled, or returned materials or products shall be segregated.

(7) Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion shall be stored in safe and secure areas.

(8) Printed packaging materials are critical to the conformity of pharmaceutical product to its labelling, and special attention shall be paid to sampling, safe and secure storage of these materials.

Weighing areas

24.-(1) Weighing of starting materials and the estimation of yield by weighing shall be carried out in separate weighing areas designed for that purpose with provisions for control of contamination.

Quality control areas

25.-(1) Quality control laboratories shall be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed shall be separated from each other.

(2) Control laboratories shall be designed to be:-
(a) suitable for the operations to be carried out
(b) with sufficient space to avoid mix-ups and cross-contamination.
(c) with adequate and suitable storage space for samples, reference standards if necessary, with cooling, and records.

(3) The design of the laboratories shall take into account the suitability of construction materials, prevention of fumes, and ventilation.

(4) Shall have a separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

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

Ancillary areas

26.-(1) Rest and refreshment rooms shall be separate from other areas.

(2) Facilities for changing and storing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the number of users. Toilets shall not communicate directly with production or storage areas.

(3) Maintenance workshops shall be separated from production areas and in case, parts and tools are stored in the production area shall be kept in rooms or lockers reserved for that use.

(4) Animal houses shall be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

PART VI
EQUIPMENT

Principle

27.-(1) The layout, design and location of equipment shall 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 any adverse effect on the quality of products.

General

28.-(1) Manufacturing equipment shall be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

(2) Repairs and maintenance operations shall not present any hazard to the quality of the products.

(3) Manufacturing equipment shall be designed so that it can be easily and thoroughly cleaned as per written procedures and stored only in clean and dry condition.

(4) Non-dedicated equipment shall be cleaned according to validated cleaning procedures between productions of different pharmaceutical products to avoid cross contamination.

(5) Cleaning and drying equipment shall be chosen and used so as not to be a source of contamination.

(6) Equipment shall be installed to minimize any risk of error or contamination.

(7) Production equipment shall not present any hazard to the products, all parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

(8)Wherever appropriate, closed equipment shall be used, incase open equipment is used precautions shall be taken to minimize contamination.

(9) Balances and other measuring equipment of an appropriate range and precision shall be available for production and control operations and shall be calibrated and checked at defined intervals using appropriate methods and adequate records maintained.

(10) Measuring, weighing, recording, and control equipment and instruments shall be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments shall be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due shall be clearly indicated on the equipment.

(11) Current drawings of critical equipment and support systems shall be maintained.

(12) Fixed pipe work shall be clearly labeled to indicate the contents and, where applicable, the direction of flow.

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

(14) Water for pharmaceutical use (Purified water, Water for injection) and other water pipes shall be sanitized as per written procedures that detail the action limits for microbial contamination and measures to be taken.

(15) Control-laboratory equipment and instruments shall be suited to the testing procedures undertaken.

(16) Defective equipment shall be removed from production and quality control areas, or at least be clearly labeled as defective.

PART VII

DOCUMENTATION

Principle **29**.-(1) Manufacturers shall have good documentation practice as an essential part of the quality assurance system and as such, shall be related to all aspects of GMP including:

(a) Specifications for all materials and methods of manufacture and control

(b) An audit trail that will permit investigation of the history of any suspected defective batch.

(c) Availability of data needed for validation, review and statistical analysis

(2) Manufacturer shall design and make use of his documents.

(3) Documents shall be free from errors and available in writing.

General 30.-(1) Manufacturer shall design, prepare, review and distribute documents with care. The prepared documents shall comply with the relevant parts of the manufacturing and marketing authorizations.

(2)Manufacturer shall ensure documents:

(a) are approved, signed, and dated by appropriate authorized persons. No document shall be changed without authorization.

(b) have unambiguous contents: the title, nature, and purpose should be clearly stated. Shall be laid out in an orderly fashion and be easy to check.

(c) be regularly reviewed and kept up to date.

(3) Manufacturer shall have a system for revising documents to prevent inadvertent use of the superseded version. Superseded documents shall be retained for a specified period of time.

(4) In case of reproduced documents:

(a) they shall be clear and legible.

(b) working documents from master documents must not allow any error to be introduced through the reproduction process.

(5) Where documents require the entry of data, these entries shall be clear, legible, and indelible. Sufficient space shall be provided for such entries.

(6)In case of any alteration made to a document:

(a) Manufacturer shall sign and date; the alteration shall permit the reading of the original information.

(b) Where appropriate, the reason for the alteration shall be recorded.

(7) Manufacturer shall record and keep complete records when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable.

(8) Manufacturer shall retain records and associated standard operating procedures for at least one year after the expiry date of the finished product.

(9) Manufacturer may keep data and record electronically or may have data-processing systems or by photographic or other reliable means.

(10) Manufacturer shall have Master formulae and detailed standard operating procedures relating to the system in use and the accuracy of the records shall be checked.

(11) If manufacturer is handling documents by electronic data-processing methods,

PART XII
SELF-INSPECTION, QUALITY AUDITS, SUPPLIER AUDITS AND APPROVALS

Principle

78.-(1) Self inspection shall;
(a) evaluate the manufacturer's compliance with GMP in all aspects of production and quality control.
(b) be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.

(c) be performed routinely and on special occasions such as product recalls or repeated rejections, or when an inspection by the health authorities is announced.

(2) The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of GMP objectively.

(3) All recommendations for corrective action should be implemented.

(4) The procedure for self inspection shall be documented.

Items for self-inspection

79. - There shall be established program for self inspection to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements.

Self-inspection team

80.-Management shall appoint a self- inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

81.-The frequency at which self-inspections are conducted may depend on company requirements but shall preferably be at least once a year and described in the procedure.

Self-inspection report

82.-A report shall be made at the completion of a self-inspection with inspection findings, evaluation, conclusion and recommended corrective actions.

Follow-up action

83.-There shall be an effective follow- up program The company management shall evaluate both the self-inspection report and the corrective actions as necessary.

Vendors'/Suppliers' audits and approval

84.-(1) The person responsible for Quality Control shall have responsibility together with other relevant departments for approving vendor/suppliers who can reliably supply starting and packaging materials that meet established specifications.

(2) Before suppliers are approved and included in the approved supplier's list or specifications, shall be evaluated. The evaluation shall take into account a vendor's/supplier's history and the nature of the materials to be supplied. If an audit is required, it shall determine the supplier's ability to conform to GMP standards.

PART XIII

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Principle

85.-(1) The manufacture of sterile products shall be subjected to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination.

(2) Production shall depend on the skill, training and attitudes of the personnel involved and Quality Assurance shall be followed.

(3) Manufacturer shall strictly follow carefully established and validated methods of preparation and procedure.

(4) Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

General

86.-(1) The manufacture of sterile products shall be carried out in clean areas, entry to which shall be through airlocks for personnel and/or for equipment and materials. Clean areas shall be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

(2) The various operations of component preparation, product preparation and filling shall be carried out in separate areas within the clean area.

(3) Manufacturing operations shall be divided into products that are terminally sterilized and those which are conducted aseptically at some or all stages

(4) Clean areas for the manufacture of sterile products shall be classified according to the required characteristics of the environment.

(5) Each manufacturing operation shall require an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

(6) The manufacture of sterile medicinal products shall distinguish four clean grades as follows:

(a) Grade A: The local zone for high risk operations such as filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.

(b) Grade B: Applicable for aseptic preparation and filling, this is the background environment for grade A zone.

(c) Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

(7) The areas shall be monitored during operation in order to control the particulate cleanliness of the various grades.

(8) Where aseptic operations are performed monitoring shall be frequent using methods.

(ii) Sampling methods used in operation shall not interfere with zone protection.

(iii) Results from monitoring shall be considered when reviewing batch documentation for finished product release.

(iv) Surfaces and personnel shall be monitored after critical operations.

(v) Additional microbiological monitoring is also required outside production operations, after validation of systems, cleaning and sanitization.

Isolator technology

87.-(1)Isolators shall be introduced only after appropriate validation and take into account all critical factors of isolator technology.

(2) Monitoring shall be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system

Blow/fill/seal technology

88.-(1) Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used.

(2) The environment should comply with the viable and non- viable limits “at rest” and the viable limit only when in operation.

(3) Blow, fill or seal equipment used for the production of products for terminal sterilization should be installed in at least a grade D environment.

Terminally sterilized products

89.-(1) Preparation of components and most products shall be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilization.

(2) Where there is unusual risk because the product actively supports microbial growth or must be held for a long period before sterilization or is necessarily processed not mainly in closed vessels, preparation shall be done in a grade C environment.

(3) Filling of products for terminal sterilization shall be done in at least a grade C environment.

(4) Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background.

(5) Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

Aseptic preparation

90.-(1) Components after washing shall be handled in at least a grade D environment.

(2) Handling of sterile starting materials and components, unless subjected to sterilization or filtration through a micro- organism-retaining filter later in the process, should be done in a grade A environment with grade B background.

(3) Preparation of solutions which are to be sterile filtered during the process shall be done in a grade C environment; if not filtered, the preparation of materials and products shall be done in a grade A environment with a grade B background.

(4) Handling and filling of aseptically prepared products shall be done in a grade A environment with a grade B background.

(5) Transfer of partially closed containers, as used in freeze drying, shall, prior to the completion of stoppering, be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.

(6) Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

Personnel

91.-(1) Only the minimum number of personnel required shall be present in clean areas; this is particularly important during aseptic processing

(2) Inspections and controls shall be conducted outside the clean areas as far as possible.

(3) All personnel (including those concerned with cleaning and maintenance) employed in such areas shall receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology.

(5) Staff who have been engaged in the processing of animal tissue materials or of cultures of micro- organisms other than those used in the current manufacturing process shall not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.

(6) High standards of personnel hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations shall be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard shall be decided by a designated competent person

(7) Changing and washing shall follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.

(9) The clothing and its quality shall be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

(10) Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves shall be regularly disinfected during operations. Masks and gloves shall be changed at least at every working session.

(11) Clean area clothing shall be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

Premises

92.-(1) In clean areas, all exposed surfaces shall be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

(2) To reduce accumulation of dust and to facilitate cleaning there shall be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors shall be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.

(3) False ceilings shall be sealed to prevent contamination from the space above them.

(4) Pipes and ducts and other utilities shall be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

(5) Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.

(6) Changing rooms shall be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room shall, in the “at rest” state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. Hand washing facilities should be provided only in the first stage of the changing rooms.

(7) Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/ or audible warning system should be operated to prevent the opening of more than one door at a time.

(8) A filtered air supply shall maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and shall flush the area effectively. Adjacent rooms of different grades shall have a pressure differential of 10-15pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk., that is, the immediate environment to which a product and cleaned components which contact the product are exposed.

(9) It shall be demonstrated that air-flow patterns do not present a contamination risk., e.g. care shall be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.

(10) Indicators of pressure differences shall be fitted between areas where these differences are important. These pressure differences shall be recorded regularly or otherwise documented.

Equipment

93.-(1) A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (e.g. in a sterilizing tunnel).

(2)Equipment, fittings and services shall be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilization is required, it shall be carried out after complete reassembly wherever possible.

(3) When equipment maintenance has been carried out within the clean area, the area shall be cleaned, disinfected and/or sterilized where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.

(4) Water treatment plants and distribution systems shall be designed, constructed and maintained so as to ensure areliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections shall be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.

(5) All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems shall be subject to validation and planned maintenance; their return to use should be approved.

Sanitation

94.-(1) The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

(2) Disinfectants and detergents shall be monitored for microbial contamination. dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

(3) Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

Processing

95.-(1) Precautions to minimize contamination shall be taken during all processing stages including the stages before sterilization.

(2) Preparations of microbiological origin shall not be made or filled in areas used for the processing of other medicinal product. Vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

(3) Selection of the nutrient medium for validation of aseptic processing should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

(4) The process simulation test (media fill) shall imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps.

(5) Process simulation tests shall be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification the HVAC system, equipment, process and number of shifts.

(6) Process simulation tests shall be repeated at least twice a year per shift and process.

(7) The number of containers used for media fills shall be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth but a contamination rate of less than 0.1% with 95% confidence limit is acceptable. The manufacturer should establish alert and action limits. Any contamination should be investigated.

(8) Water sources, water treatment equipment and treated water shall be monitored regularly for chemical and biological contamination. and, as appropriate, for endotoxins. Records shall be maintained of the results of the monitoring and of any action taken.

(9) Activities in clean areas and especially when aseptic operations are in progress shall be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity.

(10) Containers and materials liable to generate fibers shall be minimized in clean areas.

(11) The interval between the washing and drying and the sterilization of components, containers and equipment as well as between their sterilization and use shall be minimized and subject to a time-limit appropriate to the storage conditions.

(12) The time between the start of the preparation of a solution and its sterilization or filtration through a micro-organism-retaining filter shall be minimized. There shall be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

(13) The bioburden shall be monitored before sterilization. There shall be working limits on contamination immediately before sterilization which are related to the efficiency of the method to be used. Where appropriate the absence of pyrogens shall be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

(14) Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilized. and passed into the area through double-ended sterilizers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Noncombustible gases shall be passed through micro-organism retentive filters

(15) The efficacy of any new procedure shall be validated. and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

Sterilization

96.-(1) All sterilization processes shall be validated.

(2) Before any sterilization process is adopted its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed shall be demonstrated by physical measurements and by biological indicators where appropriate.

(3) The validity of the process shall be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

(4) Validated loading patterns should be established for all sterilization processes.

(5) Biological indicators shall be considered as an additional method for monitoring the sterilization. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls.

(6)There shall be a clear means of differentiating products which have not been sterilized from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilized.

(7) Sterilization records shall be available for each sterilization run. They should be approved as part of the batch release procedure.

Sterilization by heat

97.-(1) Each heat sterilization cycle shall be recorded on a time temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision.

(2) The position of the temperature probes used for controlling andor recording should have been determined during the validation and, where applicable, also checked against a second independent temperature probe located at the same position.

(3) Chemical or biological indicators may also be used, but shall not take the place of physical measurements.

(4) Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced. This time must be determined for each type of load to be processed.

(5) After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized, unless it can be shown that any leaking container would not be approved for use.

Moist heat

98.-(1) Both temperature and pressure shall be used to monitor the process. Control instrumentation shall normally be independent of monitoring instrumentation and recording charts.

(2) Where automated control and monitoring systems are used for these applications they shall be validated to ensure that critical process requirements are met.

(3) The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilization period.

(4)For Sterilizers fitted with adrain at the bottom of the chamber, it may be necessary to record the temperature at this position, throughout the sterilization period.

(5) There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

Dry heat

99.-The process used shall include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins shall be used as part of the validation.

Filtration of medicinal products which cannot be sterilized in their final container

100.-(1) If the product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container.

(2) Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized microorganism retaining filter, immediately prior to filling, may be done.

(3) The integrity of the sterilized filter shall be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test.

(4) The same filter shall not be used for more than one working day unless such use has been validated.

Finishing of sterile products

101.-(1) Container shall be closed by appropriately validated methods. Containers closed by fusion such as glass or plastic ampoules shall be subject to 100% integrity testing.

(2) Containers sealed under vacuum shall be tested for maintenance of that vacuum after an appropriate, pre-determined period.

(3) Filled containers of parenteral products shall be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background.

(4) Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection.

Quality Control

102.-(1) Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination,

(2) Products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;

(3) Products which have been heat sterilized in their final containers, consideration shall be given to taking samples from the potentially coolest part of the load.

PART XIV
MANUFACTURE OF BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE

Principle

103.-(1) The manufacture of biological medicinal products shall involve certain specific considerations arising from the nature of the products and the processes.

(2) The ways in which biological medicinal products are produced, controlled and administered shall make some particular precautions necessary.

(3) Control of biological medicinal products shall involve biological analytical techniques which have a greater variability than physico-chemical determinations.

(4) In process controls shall take a great importance in the manufacture of biological Medicinal products.

Personnel

104.-(1) The manufacturing establishment and its personnel shall be under the authority of a person who has been trained in the techniques used in manufacturing biological substances and who possesses the scientific knowledge upon which the manufacture of these products is based. The personnel shall include specialists with training appropriate to the products made in the establishment.

Premises and Equipment

105.-(1) Building shall be located, designed constructed, adapted and maintained to suit the operations to be carried out within them.
(2) Laboratories, operating rooms and all other rooms and buildings used for the manufacture of biological products shall be designed and constructed of
materials of the highest standard so that cleanliness, especially freedom form dust, insects and vermin, can be maintained.

Animal Quarters and Care

106.-(1) Animals shall be accommodated in separate buildings with self contained ventilation systems.
(2) The buildings' design and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin.
(3) Facilities for animal care shall include isolation units for quarantine of incoming animals and provision for vermin-free food storage.

Production

107.-(1) Standard operating procedures shall be available and maintained up to date for all manufacturing operations.
(2) The source, origin and suitability of starting materials shall be clearly defined.
(3) Where necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available.
(4) In such cases, release of a finished product is conditional on satisfactory results of these tests.
(5) Where sterilisation of starting materials is required, it shall be carried out where possible by heat.
(6) Where necessary, other appropriate methods may also be used for inactivation of biological materials such as irradiation.

Labeling

108.-(1) All products shall be clearly identified by labels. The labels used shall remain permanently attached to the containers under all storage conditions and an area of the container shall be left uncovered to allow inspection of the contents.
(2) If the final container is not suitable for labeling such as a capillary tube it shall be in a labeled package.
(3) The information given on the label on the container and the label on the package shall be approved by the Authority.

Quality Control

109.-(1) The quality-assurance and/or quality-control department shall have the following principal duties:
(a) to prepare detailed instructions for each test and analysis;
(b) to ensure adequate identification and segregation of test samples to avoid mix-up and cross contamination
(c) to ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
(d) to release or reject raw materials and intermediate products, if necessary;
(e) to release or reject packaging and labeling materials and the final containers in which drugs are to be placed;
(f) to release or reject each lot of finished preparation;
(g) to evaluate the adequacy of the conditions under which raw materials, intermediate products and finished biological preparations are stored;
(h) to evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;
(i) to establish expiry dates on the basis of the validity period related to specified storage conditions;

PART XV
QUALIFICATION AND VALIDATION

Principle

110.- (1) Manufacturers shall identify validation work needed to prove control of the critical aspects of their operations.
(2) Manufacturers shall ensure that significant changes to the facilities, equipment and processes, which may affect the quality of the product, are validated.
(3) Manufacturers shall use a risk assessment approach to determine the scope and extent of validation.

Planning for validation

111- (1) Manufacturers shall plan all validation activities.

(2) Manufacturers shall clearly define and document key elements of a validation programme in a validation master plan or equivalent document.

(3) The validation master plan shall be a summary document which is brief, concise and clear

(4) The validation master plan shall contain data on at least the following-

~~(a) validation policy;~~

(b) organizational structure of validation activities;

(c) summary of facilities, systems, equipment and processes to be validated;

(d) documentation format; the format to be used for protocols and reports;

(e) planning and scheduling;

(f) change control;

(g) reference to existing documents; and

(i) in case of large scale manufacturing, it may be necessary to ~~create separate validation master plans~~

Documentation

112.-(1) A written protocol shall be established to specify how qualification and validation will be conducted.

(2) The protocol shall be reviewed and approved and specify critical steps and acceptance criteria.

(3) A report that cross-references the qualification and/or validation protocol shall be prepared, summarizing the results obtained, commenting on any deviations observed and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies.

(4) Any changes to the plan as defined in the protocol shall be documented with appropriate justification.

(5) After completion of a satisfactory qualification, a formal release for the next step in qualification and validation shall be made as a written authorization.

Design qualification

113.-(1) The first element of the validation of new facilities, systems or equipment shall be design qualification.

(2) The compliance of the DQ with GMP shall be demonstrated and documented by the manufacturer.

Installation qualification

114.-(1) Installation qualification shall be performed on new or modified facilities, systems and equipment.

(2) IQ shall include, but not be limited to the following:-

a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;

b) collection and collation of supplier operating and working instructions and maintenance requirements;

c) calibration requirements; and

d) verification of materials of construction.

Operational qualification

115.-(1) Operational qualification shall follow IQ.

(2) OQ shall include, but not be limited to the following:-

(a) tests that have been developed from knowledge of processes, systems and equipment;

(b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as "worst case" conditions.

(3) The completion of a successful operational qualification shall allow for the finalization of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements.

(4) OQ shall permit for a formal "release" of the systems and equipment.

Performance qualification

116.-(1) Performance qualification shall follow successful completion of IQ and OQ.

(2) PQ shall include, but not be limited to the following:-

a) tests, using production materials, qualified substitutes or simulated

products, that have been developed from knowledge of the process and the facilities, systems or equipment; and

b) tests to include a condition or set of conditions encompassing upper and lower operating limits.

(3) Albeit PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

Qualification of established (in-use) facilities, systems and equipment

117.-(1) Evidence shall be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. (2) Calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records shall be documented.

Process validation

118.-(1) Process validation shall be categorized as follows:-

(a) Prospective validation;

(b) Concurrent validation; and

(c) Retrospective validation.

(2) Subject to sub-regulation (1) (a), prospective validation shall normally be completed prior to the distribution and sale of the medicinal product.

(3) Prospective validation shall include, but not be limited to the following:-

(a) short description of the process;

(b) summary of the critical processing steps to be investigated;

(c) list of the equipment or facilities to be used including measuring, monitoring and recording equipment together with its calibration status;

(d) finished product specifications for release;

(e) list of analytical methods, as appropriate;

(f) proposed in-process controls with acceptance criteria;

(g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;

(h) sampling plan;

(i) methods for recording and evaluating results;

(j) functions and responsibilities; and

(k) proposed timetable.

(4) Using prospective validation process including specified components, a series of batches of the final product may be produced under routine conditions.

(5) In theory the number of process runs carried out and observations made shall be sufficient to allow for the normal extent of variation and trends to be established and to provide sufficient data for evaluation.

(6) It is generally considered acceptable that three consecutive batches or runs within the finally agreed parameters would constitute a validation of the process.

(7) Batches made for process validation shall be the same size as the intended industrial scale batches.

(8) If it is intended that validation batches be sold or supplied, the conditions under which they are produced shall comply fully with the requirements of GMP, including the satisfactory outcome of the validation exercise, and where applicable, the marketing authorization.

(9) Subject to sub-regulation (1) (b), in exceptional circumstances, where prospective validation is not possible, it may be necessary to validate processes during routine production, to be referred as concurrent validation.

(10) The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.

(11) Documentation requirements for concurrent validation are the same

Cleaning validation

119.-(1) Cleaning validation shall be performed in order to confirm the effectiveness of a cleaning procedure.

(2) The rationale for selecting limits of carry-over of product residues, cleaning agents and microbial contamination shall be logically based on the materials involved.

(3) The limits shall be achievable and verifiable.

(4) Validated analytical methods having sensitivity to detect residues or contaminants shall be used.

(5) The detection limit for each analytical method shall be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

(6) Cleaning procedures for product contact surfaces of the equipment shall be validated.

(7) Consideration may be given to non-contact parts and the intervals between use and cleaning as well as cleaning and reuse shall be validated.

(8) Cleaning intervals and methods shall be determined.

(9) For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes.

(10) A single validation study utilizing a “worst case” approach may be carried out which takes account of the critical issues.

(11) Three consecutive applications of the cleaning procedure shall be performed and shown to be successful in order to prove that the method is validated.

(12) “Test until clean” shall not be considered as an appropriate alternative to cleaning validation.

(13) Products which simulate the physico-chemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

Change control

120**.-** (1) Written procedures shall be in place to describe the actions to be
taken if a change is proposed to a starting material, product component, process equipment, process environment or site, method of production or testing or any other change that may affect product quality or reproducibility of the process.
(2) Change control procedures shall ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of desired quality and consistent with the approved specifications.
(3) All changes that may affect product quality or reproducibility of the process shall be formally requested, documented and accepted.
(4) The likely impact of the change of facilities, systems and equipment on the product shall be evaluated, including risk analysis.
(5) The need for, and the extent of, requalification and revalidation shall be determined.

~~Revalidation~~

121.-(1) Facilities, systems, equipment and processes, including cleaning, shall be periodically evaluated to confirm that they remain valid.
(2) Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation under these Regulations.

PART XVI
COMPUTERIZED SYSTEM

~~Principle~~

122.-(1) Manufacturers may use computerized systems to replace manual operations.
(2) In case computerized systems are used, there shall be no resultant decrease in product quality or quality assurance.
(3) Subject to sub-regulation (1), consideration shall be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

Personnel

123.-(1) When computerized systems are used, there shall be closest co-operation between key personnel and those involved with computer systems.

(2) Persons in responsible positions shall have the appropriate training for the management and use of systems within their field of responsibility which utilizes computers.

(3) Appropriate expertise shall be available and used to provide advice on aspects of design, validation, installation and operation of computerized systems.

Validation

124.-(1) The extent of validation necessary for computerized systems, shall depend on a number of factors including the use to which the system is to be put, whether it is prospective or retrospective and whether or not novel elements are incorporated.

(2) Validation shall be considered as part of the complete life cycle of a computer system.

(3) Subject to sub-regualtion (2), this cycle shall include stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and changing.

System

125.-(1) Attention shall be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.

(2) A written detailed description of the system shall be produced including diagrams as appropriate, and kept up to date.

(3) The system shall describe the principles, objectives, security measures and scope and the main features of the way in which the computer is used and how it interacts with other systems and procedures.

(4) The user of a computerized software shall take all reasonable steps to ensure that it has been produced in accordance with a system of quality assurance.

(5) The system shall include, where appropriate, built-in checks of the correct entry and processing of data.

(6) Before a system using a computer is brought into use, it shall be thoroughly tested and confirmed as being capable of achieving the desired results.

(7) If a manual system is being replaced, the two shall be run in parallel for a time, as part of the testing and validation.

(8) Data shall only be entered or amended by persons authorized to do so. (9) (9) Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals.

(10) There shall be a defined procedure for the issue, cancellation, and alteration of authorization to enter and amend data, including the changing of personal passwords.

(11) Consideration shall be given to systems allowing for recording of attempts to access by unauthorized persons.

(12) When critical data are being entered manually there shall be an additional check on the accuracy of the record which is made.

(13) subject to sub-regualtion (12), the check may be done by a second operator or by validated electronic means.

(14) The system shall record the identity of operators entering or confirming critical data.

(15) Authority to amend entered data shall be restricted to nominated persons.

(16) Any alteration to an entry of critical data shall be authorized and recorded with the reason for the change.

(17) Consideration shall be given to the system creating a complete record of all entries and amendments to be reffered as an “audit trail”.

(18) Alterations to a system or to a computer programme shall only be made in accordance with a defined procedure which shall include provision for validating, checking, approving and implementing the change.

(19) Subject to sub-regulation (18), an alteration shall only be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration shall be recorded.

(20) Every significant modification shall be validated.

PART XVII
WATER FOR PHARMACEUTICAL USE

Water requirements and uses

126.-(1) Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds.

General requirements for pharmaceutical water systems

127.-(1) Pharmaceutical water production, storage and distribution systems shall be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality.

(2) They shall not be operated beyond their designed capacity.

(3) Water shall be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination such as with dust and dirt.

Water quality specifications

128.-(1) Companies wishing to supply multiple markets shall set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

Drinking water

129.-(1) Drinking-water shall be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.

Purified water

130.-(1) Purified water (PW) shall be prepared from a potable water source as a minimum-quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation.

Highly purified water

131.-(1) Highly purified water (HPW) shall be prepared from potable water as minimum quality feed-water. HPW is a unique specification for water found only in the European Pharmacopoeia.
(2) This grade of water shall meet the same quality standard as water for injections (WFI) including the limit for endotoxins, but the water-treatment methods are not considered to be as reliable as distillation.
(3) Highly purified water may be prepared by combinations of methods such as reverse osmosis, ultra filtration and deionization.

Water for injections

132.-(1) Water for injections (WFI) shall be prepared from potable water as a minimum-quality feed-water. WFI is not sterile water and is not a final dosage form. It is an intermediate bulk product. WFI is the highest quality of pharmacopoeial WPU.

Other grades of water

133.-(1) When a specific process requires a special non-pharmacopoeial grade of water, this shall be specified and shall at least satisfy the pharmacopoeial requirements of the grade of WPU required for the type of dosage form or process step.

Application of specific waters to processes and dosage forms	134.-(1) Product licensing authorities define the requirement to use the specific grades of WPU for different dosage forms or for different stages in washing, preparation, synthesis, manufacturing or formulation. The grade of water used should take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used. HPW can be used in the preparation of products when water of high quality(i.e. very low in microorganisms and endotoxins) is needed, but the process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeial monographs for WFI. WFI should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections. WFI should also be used for the final rinse after cleaning of equipment and components that come into contact with injectable products as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied. When steam comes into contact with an injectable product in its final container, or equipment for preparing injectable products, it should conform to the specification for WFI when condensed.

Water purification methods: General considerations	135.-(1) The specifications for WPU found in compendia (e.g. pharmacopoeias) are generally not prescriptive as to permissible water purification methods other than those for WFI. The chosen water purification method, or sequence of purification steps, must be appropriate to the application in question. The following should be considered when selecting the water treatment method: the water quality specification; • the yield or efficiency of the purification system; • feed-water quality and the variation over time (seasonal changes); • the reliability and robustness of the water-treatment equipment in operation; • the availability of water-treatment equipment on the market; • the ability to adequately support and maintain the water purification equipment; and • the operation costs.
Production of drinking-water	136.-(1) Drinking-water is derived from a raw water source such as a well, river or reservoir. There are no prescribed methods for the treatment of raw water to produce potable drinking-water from a specific raw water source. Typical processes employed at a user plant or by a water supply authority include: • filtration; • softening; • disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection); • iron (ferrous) removal; • precipitation; and • reduction of specific inorganic/ organic materials.
Production of purified water	137.-(1) There are no prescribed methods for the production of PW in the pharmacopoeias. Any appropriate qualified purification technique or sequence of techniques may be used to prepare PW. Typically ion exchange, ultra filtration and/or reverse osmosis processes are used. Distillation can also be used.

Production of highly purified water	138.-(1) There are no prescribed methods for the production of HPW in any major pharmacopoeia, including the European Pharmacopoeia. Any appropriate qualified purification technique or sequence of techniques may be used to prepare HPW. Typically ion exchange, ultrafiltration and/ or reverse osmosis processes are used. The guidance provided in section 5.3 for PW is equally applicable to HPW.
Production of water for injections	139.-(1) The pharmacopoeias prescribe or limit the permitted final water purification stage in the production of WFI. Distillation is the preferred technique; it is considered a more robust technique based on phase change, and in some cases, high temperature operation of the process equipment. The following should be considered when designing a water purification system: • the feed-water quality; • the required water quality specification; • the optimum generator size to avoid over-frequent start/stop cycling; • blow-down and dump functions; and • cool-down venting to avoid contamination ingress.
Water purification, storage and distribution systems: General considerations	140.-(1) This section applies to WPU systems for PW, HPW and WFI. The water storage and distribution should work in conjunction with the purification plant to ensure consistent delivery of water to the user points, and to ensure optimum operation of the water purification equipment. The storage and distribution system should be considered as a key part of the whole system, and should be designed to be fully integrated with the water purification components of the system.

Materials that come into contact with systems for water for pharmaceutical use	141.-(1) This section applies to generation equipment for PW, HPW and WFI, and the associated storage and distribution systems. The materials that come into contact with WPU, including pipe work, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives. • Compatibility. All materials used should be compatible with the temperature and chemicals used by or in the system. • Prevention of leaching. All materials that come into contact with WPU should be non-leaching at the range of working temperatures. • Corrosion resistance. PW, HPW and WFI are highly corrosive. To prevent failure of the system and contamination of the water, the materials selected must be appropriate, the method of jointing must be carefully controlled, and all fittings and components must be compatible with the pipe work used.
System sanitization and bioburden control	142.-(1) Water treatment equipment, storage and distribution systems used for PW, HPW and WFI should be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for san- itizing or sterilizing the system after intervention for maintenance
Storage vessel requirements	143.-(1) The water storage vessel used in a system serves a number of important purposes. The design and size of the vessel should take into consideration the following elements; Capacity Contamination control considerations

Requirements for water distribution pipework	144.-(1) The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled. Filtration should not usually be used in distribution loops or at takeoff user points to control biocontamination. Such filters are likely to conceal system contamination. • Temperature control and heat Exchangers Circulation pumps • Biocontamination control techniques
Start-up and commissioning of water systems	145.-(1) Planned, well-defined, successful and well documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system setup, and controls loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.
Qualification of water system	146.-(1) WPU, PW, HPW and WFI systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). A three phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.
Performance Qualification (PQ): Phase 1	147.-(1) A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation.
Performance Qualification (PQ): Phase 2	148.-(1) A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purposes during this phase.

Performance Qualification (PQ): Phase 3	149.-(1) Phase 3 typically runs for 1 year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features. • Demonstrate extended reliable performance. • Ensure that seasonal variations are evaluated. • The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.
Continuous system monitoring	150.-(1) After completion of phase 3 of the qualification program for the WPU system, a system review should be undertaken. Following this review, a routine monitoring plan should be established based on the results of phase 3. Monitoring should include a combination of online instrument monitoring of parameters such as flow, pressure, temperature, conductivity and total organic carbon, and offline sample testing for physical, chemical and microbiological attributes. Offline samples should be taken from points of use and specific sample points. Samples from points of use should be taken in a similar way to that adopted when the water is being used in service.
Maintenance of water systems	151.-(1) WPU systems should be maintained in accordance with a controlled, documented maintenance program that takes into account the following: • defined frequency for system elements; • the calibration program • SOPs for specific tasks; • control of approved spares; • issue of clear maintenance plan and instructions; • review and approval of systems for use upon completion of work; and • record and review of problems and faults during maintenance.
System reviews	152.-(1) WPU (PW, HPW and WFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, operations and maintenance.

PART XVIII
HEATING, VENTILATION AND AIR-CONDITIONING SYSTEMS FOR NON-STERILE PHARMACEUTICAL DOSAGE FORMS

Heating, ventilation and air-conditioning system

153.-(1) Every pharmaceutical dosage forms shall be manufactured under installed and retained heating, ventilation and air-conditioning system to ensure that the quality of pharmaceutical products are not compromise.

(2) The system shall be well-designed to provide comfortable conditions for operators of the manufacturing including architectural layouts with regard to the airlock positions, doorways and lobbies.

Prevention of contamination and cross-contamination

154.-(1)There shall be prevention of contamination and cross-contamination as an essential design to be inspected by the Authority within the system of heating, ventilation and air-conditioning of the Manufacturing site.

(2) The design of the heating, ventilation and air-conditioning system shall be shown in the drawings of pharmaceutical manufacturing plant.

Temperature, relative humidity and ventilation

155.- (1)The system temperature, relative humidity and ventilation shall not adversely made to affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment;

production of sterile pharmaceutical products as part of GMP

156.-The GM inspectors shall use the production of sterile pharmaceutical products as the basic part of GMP manufacturing of pharmaceutical dosage forms.

PART XIX
QUALITY RISK MANAGEMENT

Quality Risk Management

157.-(1) All manufacturers shall maintain two primary principles of Quality Risk Management to be considered by the Authority for quality assurance of pharmaceutical products as provided hereunder:
(a) evaluation of the risk to quality which shall be based on scientific knowledge and linked to the protection of the patient; and
(b) the level of effort, formality and documentation of the Quality Risk Management process which shall be commensurate with the level of risk.
(2) Beside the principles provided under sub regulation (1) the Quality Risk Management methodology shall :
(a) when applied, processes using Quality Risk Management methodologies be dynamic, iterative and responsive to change; and
(b) systematically analyse products and processes to ensure the best scientific rationale is in place to improve the probability of success;
(c) identify important knowledge gaps associated with processes that need to be understood to properly identify risks provide a communication process that will best interface with all relevant parties involved;
(d) Facilitate the transfer of process knowledge and product development history to ease product progression along the life-cycle and to supplement already available knowledge about the product; and
(e) Enable the pharmaceutical industry to adopt a risk-based approach to development as circumstances of applicable guidelines by the Authority may allow.

Duties and ability of the personnel

158.- The Manufacturers shall keep personnel with specific knowledge and expertise available at the manufacturing site to ensure effective planning and completion of Quality Risk Management activities;

(a) conduct a risk analysis;

(b) identify and analyse potential risks;

(c) identify, evaluate risks and determine which risks should be controlled and which ones can be accepted;

(d) recommend and implement adequate risk control measures; and

(e) devise procedures for risk review, monitoring and verification.

Risk assessment of the product

159.-(1) At any time when the risk assessment to the product is conducted, the manufacturer shall need to determine the safety and efficacy of product in addition to the its quality concerns and where applicable; all the risks that may be reasonably expected to occur in the activity under evaluation shall be listed for verification by inspectors.
Subject to the provision of sub regulation (1) potential risks to be considered shall include:

(a) materials and ingredients;

(b) physical characteristics and composition of the product;

(c) processing procedures;

(d) microbial limits, where applicable;

(e) premises;

(f) equipment;

(g) packaging;

(h) sanitation and hygiene;

(i) personnel - human error;

(j) utilities; and

(k) supply chain.

Assessment of products

160.-(1) Where a risk assessments and controls are made to the product for an ongoing activity, it shall:-

(a) be subject to periodic and the frequency of review; and

(b) be appropriate for the nature of the activity;

(2) Specific corrective actions shall be developed to prevent recurrence of instances where there have been deviations from established risk control measures, especially for high risks;

(3) The actions shall ensure that the risk is brought under control as soon as possible in compliance with the established deviation handling procedures; and

(4) Specific corrective actions shall be developed in advance for each identified risk including what is to be done when a deviation occurs, who is responsible for implementing the corrective actions, and that a record will be kept and maintained of the actions taken.

Manufacturer to conduct Risk review and keep records

161.-(1) Every manufacturer shall have appropriate systems in place to ensure that the output of the Quality Risk Management process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original Decision; and
(2) Records and documents associated with risk review shall be signed and dated by the person carrying out the review and by a responsible official of the quality unit of the company.

Verification of Quality Risk Management process and methodologies

162.-(1) The manufacturer shall carry on frequency verification to be used to confirm the proper functioning of the Quality Risk Management process including:
(a) review of the Quality Risk Management process and its records;
(b) Confirmation that identified risks is kept under control.
(2) Initial verification of the planned Quality Risk Management activities shall be considered necessary to determine whether the system is scientifically and technically sound to effectively control identified risks.

Risk communication and documentation

163.(1) Communication of the Quality Risk Management process shall be made to stakeholders engaged in both the data collection process for the risk assessment and the decision-making for risk control to ensure commitment and support for the Quality Risk Management;
(2) The output of the Quality Risk Management process and associated risk analysis justifying the approach shall be documented and endorsed by the industry's quality unit and management; and
(3) The information shall be communicated to stakeholders for their support.

Mitigation Plans

164.-(1) Manufacturers shall have a risk mitigation plans in place to apply where any risk to patient safety is posed or where multiple failures in systems occur, the mitigation plans shall be sufficiently robust to cover posed risk.

Training and education of relevant personnel in industry

165.-(1) Every Industry shall:-
(a) train employees to understand what Quality Risk Management is,
(b) possess the skills necessary to apply it properly, and be appropriately resourced to enable the effective practice of the Quality Risk Management principles;
(c) develop training programme to support Quality Risk Management activities, working instructions and procedures drawn up to clarify the strategy and define the tasks of all involved in these activities; and
(d) Provide specific training as required to enhance awareness to staff responsible for managing and reviewing risks who shall also receive formal training in the relevant procedures.

Responsibilities

166.-(1) The pharmaceutical manufacturers shall form teams for conducting Quality Risk Management process which shall involve experts in the appropriate areas in addition to individuals who are knowledgeable on the subject.
(2) In case of external experts, a technical agreement or other equivalent document with the experts may be made where a GMP responsibility is assumed or in the alternative a contract staff may be involved to lead or participate in risk assessments;
(3) The extent of involvement and responsibility accountability shall be documented in a technical agreement or other equivalent document between the individual and the pharmaceutical Industry;
(4) In case of authorized person, it shall be important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents;
5) All effective matrix team leadership shall be required to take responsibility for coordinating Quality Risk Management across various functions and departmentsof their organization and ensuring that the respective activities are adequately defined, planned, resourced, deployed and reviewed;
(6) The leader and team shall need to identify critical resources to progress the Quality Risk Management activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the Quality Risk Management process.

Complaint handling and investigation

167.-(1) Handling and investigation of quality complaints shall be done in accordance with written Standard Operating Procedures available at the site.

(2) The scope and depth of the investigation including whether a desk review or on-site inspection will be done shall be based on risk assessment made.

Duty of GMP Inspectors for Quality Risk Management

168.-(1) Inspectors shall assess whether a manufacturer has appropriate skills, scientific knowledge as well as product and process knowledge for the Quality Risk Management procedure being inspected to include, but not limited to:-

general approach to both planned and unplanned risk assessment and include scope, responsibilities, controls, approvals, management systems, applicability and exclusions;

(b) personnel with appropriate qualifications, experience and training including their responsibilities with regard to Quality Risk Management being clearly defined;

(c) senior management should be involved in the identification and implementation of Quality Risk Management principles within the company;

(d) the risk management procedures for each area of application should be clearly defined;

(e) Quality assurance principles shall be applied to Quality Risk Management-related documentation such as review, approval, implementation and archiving.

PART XX
ACTIVE PHARMACEUTICAL INGREDIENTS

Principle

169.-(1) Every manufacturer shall design an Active Pharmaceutical Ingredients referred to as an " API Starting Material" as a raw material, intermediate, or that can be used in the production of an API and be incorporated as a significant structural fragment into the structure of the API;

(2) An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house; and

(3) The manufacturer shall designate and document the rationale for the point at which production of the API begins.

PART XXI
WASTE MANAGEMENT FOR MEDICINAL PRODUCT MANUFACTURERS

Hazardous Waste

170.-(1) Manufacturers shall ensure that Hazardous waste pharmaceuticals involving antineoplastic agents, radioactive agents, hormonal products, penicillins and solvents from laboratory shall be segregated and managed;

Non-Hazardous Pharmaceutical Waste

171.-(1) Without prejudice to regulations 19 of these regulations, Non-Hazardous Pharmaceutical Waste comprised of all other pharmaceutical waste not included in sub regulation (1) above shall be controlled.

(2) Subject to any environmental regulation on force, waste disposal can be done primarily by land filling or closure of existing dump sites; or

(3) Modern sanitary landfills that are not dumps engineered facilities used for disposing of solid wastes on land without creating hazards to public health or safety.

(4) In case of liquid effluent which poses a safety or contamination risk, the effluent shall be treated in Effluent Treatment Plant before being discharged to any municipal drain.

PART XXII
CONDUCTING OF GMP INSPECTION

Inspections

172.-(1) The Authority shall conduct GMP inspection for the purpose of ensuring that-
(a) Manufacturers comply with the requirements of these Regulations; and
(b) Non-conformances against these Regulations are identified.
(2) The Authority may serve a notice to manufacturers requiring them to furnish with such information concerning their compliance with these Regulations as shall be specified in the notice
(3) Any manufacturer that receives an order or information in accordance with sub-regulation (2) shall provide the information requested within the period specified in the notice.
(4) In the event of any serious adverse event or any serious adverse reaction or suspicion thereof, of the product manufactured by the manufacturer, the Authority shall request such information or conduct such inspections in accordance with this regulation as he shall consider appropriate.

Appointment of GMP inspectors

173.-(1) The Authority shall appoint GMP inspectors to inspect domestic and overseas manufacturing facilities where medicines used in Tanzania are manufactured.
(2) GMP inspectors shall have the relevant qualification in terms of academic education, training and experience in order to effectively take part in inspection of pharmaceutical manufacturing facilities.

Powers of GMP Inspectors

174.-(1) For the purposes of enforcing compliance or conducting inspections, a GMP inspector appointed in accordance with these Regulations shall, upon production of evidence that he is so authorized, have the right-

(a) at any reasonable time to enter any premises, other than premises used only as a private dwelling house, which he has reason to believe it is necessary for him to visit, including any premises of any person who carries out any of the activities referred to in these Regulations

(b) to carry out at those premises during that visit inspections, examinations, tests and analyses as he considers necessary;

(c) to require the production of, and inspect any article or substance at, the premises;

(d) to require the production of, inspect and take copies of, or extracts from, any book, document, data or record (in whatever form it is held) at, or (in the case of computer data or records) accessible at the premises;

(e) to take possession of any samples for examination and analysis and any other article, substance, book, document, data, record (in whatever form they are held) at, or (in the case of computer data or records) accessible at, the premises;

(f) to question any person whom he finds at the premises and whom he has reasonable cause to believe is able to give him relevant information;

(g) to require any person to afford him such assistance as he considers necessary with respect to any matter within that person's control, or in relation to which that person has responsibilities; and

(h) to require, as he considers necessary, any person to afford him such facilities as he may reasonably require that person to afford him; but nothing in this sub - regulation shall be taken to compel the production by any person of a document of which he would on grounds of legal professional privilege be entitled to withhold production on an order for disclosure in an action in the court or, as the case may be, on an order for production of documents in an action in the court.

(2) If a justice of peace is satisfied by any written information on oath that there are reasonable grounds for entry into any premises, other than premises used only as a private dwelling house, for any purpose mentioned in sub - regulation (1), and admission to the premises has been refused or is likely to be refused and notice of intention to apply for a warrant under this sub - regulation has been given to the occupier; an application for admission, or the giving of such notice, would defeat the object of the entry; or the premises are unoccupied or the occupier is temporarily absent and it might defeat the object of the entry to await his return, the justice may, by warrant signed by him, which shall continue in force for any reasonable time, authorize an inspector to enter the premises, if need be by force.

(3) An inspector entering premises by virtue of sub-regulation (1) or of a

Conducting of GMP inspection

175.-(1) Upon arrival to the inspection site, GMP inspectors shall convene a pre-inspection meeting with the inspectee; the leading inspector shall preside the meeting.
(2) GMP Inspectors shall walk through every section of the plant, ask questions and carefully review records and areas of the manufacturing sites. Inspectors may take photographs to support their observations.
(3) The inspectors shall list down all non-compliance findings in the memorandum form as prescribed in the Third Schedule of these Regulations;
(4) After inspection the GMP inspectors shall convene a closing meeting highlighting issues observed during inspection and sign a memorandum form with the inspectee.

Joint GMP inspection

176.-(1) The Authority may participate in the joint GMP inspection with regulatory Authorities from other countries such as East African Partner States and unless notified, these Regulations shall apply.

PART XXIII
GENERAL PROVISIONS

Objections to suspensions and revocations

177.-(1) Any GMP authorization holder or applicant who-

(a) objects to any suspension or revocation of authorisation, or to any notice served;

(b) objects to the refusal of authorisation or the imposition of any condition, may notify the Director General of its desire to make written representations to, or be or appear before and be heard by, a person appointed by the Director General for that purpose.

(2) Any notification of an objection pursuant to sub-regulation (1) shall be made within fourteen days of service on the notice to which the notification pursuant to sub-regulation (1) relates.

(3) Where the Authority receives a notification pursuant to sub-regulation (1), he shall appoint a person to consider the matter.

(4) The person appointed pursuant to sub - regulation (3) shall determine the procedure to be followed with respect to the consideration of any objection.

(5) The person appointed pursuant to sub-regulation (3) shall consider any written or oral objections made by the objector or complainant in support of its objection, and shall make a recommendation to the Authority.

(6) A recommendation made pursuant to sub - regulation (5) shall be made in writing to the Authority, and a copy of it shall be sent to the complainant concerned, or to its nominated representative.

(7) The Authority shall take into account any recommendation made pursuant to sub - regulation (5).

(8) Within fourteen days of receipt of any recommendation made pursuant to sub-regulation (5), the Director General shall inform the complainant whether he accepts the recommendation and, if he does not accept it, of the reasons for his decision.

(9) Where the Director General is notified of an objection pursuant to sub-regulation (1)(a) before the date upon which the suspension or revocation or the notice is due to take effect, the suspension or revocation of a notice in respect of which the objection is made shall not take effect until-

(a) the person appointed pursuant to sub - regulation (3) has considered the matter in accordance with the provisions of this regulation and made a recommendation; and

(b) the Director General has informed the complainant concerned of his decision with regard to the recommendation pursuant to sub - regulation (8).

(10) Subject to sub-regulation (9), where the Director General is notified of an objection pursuant to sub-regulation (1)(a), within the period specified in sub-regulation (2), to a suspension, revocation or other notice which has already taken effect on the date the notification was made, the suspension, revocation or notice in respect of which the objection is made shall cease to have effect until-

(a) the person appointed pursuant to sub - regulation (3) has considered the matter in accordance with the provisions of this regulation and made a recommendation; and

(b) the Director General has informed the complainant concerned of his decision with regard to the recommendation pursuant to sub - regulation (8).

(11) The provisions of sub-regulation (10) shall not apply-

(a) in relation to a suspension or revocation, or a notice served, which takes immediate effect in accordance with these Regulations; or

(b) in any other case, where the Director General determines that it is necessary in the interests of public safety for the suspension, revocation or notice to take effect on the date originally specified, and serves a notice in writing to that effect on the establishment concerned.

Appeals

178.-(1) Notwithstanding the provisions of regulation 38, any person aggrieved by a decision of the Authority may, within sixty days appeal in writing to the Minister.

(2) The appellant shall copy a notice of the appeal to the Authority who shall within fourteen days submit a written response to the Minister and copy the appellant.

(3) Where the Minister is of the opinion that a case has been made, he may summon parties for additional information or make a decision to allow or dismiss the appeal.

Offences and penalties

179. Any person who contravenes or fails to comply with these Regulations or directly or indirectly aids any other person to do what is prohibited under these Regulations shall be guilty of an offence and on conviction, shall be liable to the penalty prescribed by the Act.

Compounding of offences

180.-(1) The Director General, Inspector or any other authorized person may, subject to and in accordance with the provisions of these Regulations, if he is satisfied that a person has committed an offence against these Regulations, compound such offence by accepting from such person a sum of money in respect of which the offence has been committed.

(2) The sum of money payable under sub-regulation (1) shall not exceed five times the maximum amount of the fine prescribed as being payable in respect of such offence.

(3) The Power conferred by this section shall be exercised where a person admits that he has committed an offence and agrees in writing in the prescribed form to the offence being dealt with under this regulation.

(4) The Director General or officer exercising powers under this regulation shall give to the person from whom he receives any sum of money under subsection (2) a receipt which shall be in a prescribed form.

(5) Any sum of money received under this regulation shall be paid into the Authority.

(6) If any proceedings are brought against any person for an offence against these Regulations, it shall be a good defence if such person proves that the offence with which he is charged has been compounded under this regulation.

DODOMA ***UMMY M.MWALIMU***
(MP)

.....January, 2018 *Minister for Health, Community Development, Gender, Elderly and Children*

SCHEDULES

FIRST SCHEDULE
(Made under regulation 5(1)(a)

TFDA	APPLICATION FOR GOOD MANUFACTURING PRACTICE INSPECTION FOR PHARMACEUTICAL MANUFACTURING FACILITIES	F01/DMC/MCIE/SOP/013 Rev #: 0

1. PARTICULARS OF THE APPLICANT/LICENSE HOLDER

Name_____

Physical
Address_____

Country_____Telephone_____

Fax_____mail_____

2. PARTICULARS OF SITE TO BE INSPECTED

Name of
site_____

Physical Address (if different from 1. above)

_____

_____

Country_____Tel_____

Fax_____Email:_____

Note: *Separate application to be filled in for each individual site*

3. CONTACT PERSON ON SITE

Name of contact person_____

Tel: _____Fax:_____

Email: _____

4. AUTHORISED REPRESENTATIVE/AGENT IN THE COUNTRY

Name of Local Technical Representative_____

Tel:_____

5. TYPE OF MEDICINES

Type of medicines manufactured (*Tick where applicable*)

(a) Human ☐ (b) Veterinary ☐ (c) Both (a) and (b) ☐

6. REGISTRATION OF PRODUCTS

Have you registered any product in the country YES ☐ NO ☐

Have you submitted application dossiers for registration? YES ☐ NO ☐

If YES, list the products applicable. (*Attach a separate sheet if needed*)

_____

_____

_____

_____

7. LINES TO BE INSPECTED

DOSAGE FORM	Tick where applicable	*CATEGORY	**ACTIVITIES
Tablets			
Capsules			
Injections (SVP)			
Injections (LVP)			
Oral liquids			
Creams/Ointments/lotions			
Others (specify)			

*Category means any of the following:

Beta lactam, Non-beta lactam, Biologicals,Vaccines, Hormones, Cytotoxic products.

**Activity means any of the following:

- Formulation (dispensing, mixing, blending)
- Processing (compression, emulsification etc)
- Packing
- Quality Control
- Warehousing (raw material, finished products)

8. APPLICANT DECLARATIONS

I hereby certify that the above information is correct and apply for Good Manufacturing Practice inspection of the above-named site.

Signature of Applicant and stamp ……. Date……

Print Name……..

NOTES:

1. *Please submit a hard and soft copy of the Site Master File together with this application.*
2. *This application must be submitted together with the appropriate GMP inspection fee as prescribed in TFDA Fees and Charges Regulations in force.*
3. *As part of product registration process, only applicant who submitted dossiers for registration will apply for GMP inspection. GMP inspection will not be conducted for facilities which have not submitted product registration dossiers*

9. FOR OFFICIAL USE ONLY

9.1 INSPECTION TYPE (*Please tick where applicable*)

☐ First Inspection

☐ Re – inspection after failure

☐ Renewal inspection (Previous inspection date…….)

☐ Other (please specify)……

9.2 OFFICERS ASSIGNED FOR INSPECTION

NO.	NAME OF INSPECTOR	DEPARTMENT	CONTACT (e-mail & telephone)
1.			
2.			
3.			
4.			

SECOND SCHEDULE

(Made under regulation 5(1)(c)

FORMAT FOR PREPARATION OF SITE MASTER FILE FOR PHARMACEUTICAL MANUFACTURING FACILITIES

1. GLOSSARY
2. SCOPE
3. LAY OUT OF THE SITE MASTER FILE
4. CONTENT OF SITE MASTER FILE
5. GENERAL INFORMATION

a. Contact information on the manufacturer

b. Authorized pharmaceutical manufacturing activities of the site

c. Any other manufacturing activities carried out on the site.

6. QUALITY MANAGEMENT

a. The quality management system of the manufacturer

b. Brief description of the quality management systems run by the company and reference to the

Standards used.

c. Responsibilities related to the maintaining of the quality system including senior management
d. Information on activities for which the site is accredited and certified, including dates and contents of accreditations, and names of accrediting bodies.
e. Release procedure of finished products

7. MANAGEMENT OF SUPPLIERS AND CONTRACTORS

8. PRODUCT QUALITY REVIEWS

a. Brief description of methodologies used.

9. PERSONNEL

a. Qualifications, experience, and responsibilities of technical personnel should be included as Annex 5.

b. Outline of arrangements for basic and in-service training and how records are maintained.

c. Personnel hygiene requirements, including clothing.

10. PREMISES AND EQUIPMENT

a. Premises

b. Nature of construction and finishes

c. Brief description of planned preventive maintenance programmes for premises and of the recording system.

d. Brief description of other relevant utilities, such as steam, compressed air, nitrogen.

e. Availability of written specifications and procedures for cleaning manufacturing areas

f. Equipment

g. Brief description of the procedures used for cleaning major equipment.

h. Brief description of planned preventive maintenance programmes for equipment and of the recording system.

i. Brief description of the company's Qualification and calibration policy, including the recording system. Reference should be made to the Validation master plan.

11. DOCUMENTATION

a. Arrangements for the preparation, revision, distribution and archiving of necessary documentation for manufacture should be stated.

b. Brief description of the validation master plan

c. Brief description of the change control procedure

d. Any other documentation related to product quality that is not mentioned such as microbiological controls on air and water).

12. PRODUCTION

a. Type of products

b. Process validation

c. Material management and warehousing

d. Arrangements for the handling of rejected materials and products.

13. QUALITY CONTROL

14. DISTRIBUTION, COMPLAINTS, PRODUCTS DEFECT AND RECALL

15. SELF-INSPECTION

16. SHELF LIFE / STABILITY DETERMINATION PROGRAM

a. General policy for the determination of the shelf-life and stability of products manufactured at the site.

17. REFERENCES

18. REVISION HISTORY

THIRD SCHEDULE

(Made under regulation 175(3)

TFDA

F01/DMC/MCIE/SOP/008
Rev #: 0

INSPECTION MEMORANDUM FORM

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F01/DMC/MCIE/SOP/008

Rev #: 0

INSPECTION MEMORANDUM FORM

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Name of inspector: Signature: 1………………………. ……………. 2………………………. ……………. 3………………………. …………….	Name of inspectee: Signature: 1……………………. ………………… 2……………………. ………………… 3……………………. …………………

FOURTH SCHEDULE

(Made under regulation 7(1)

TANZANIA FOOD AND DRUGS AUTHORITY

CERTIFICATE OF GOOD MANUFACTURING PRACTICES (GMP)

Made under Section 20 (2a) of Tanzania Food, Drugs and Cosmetics Act, Cap 219

GMP Certificate No.....

On the basis of the Inspection carried out on ..... We certify that .....located at ..... has been found to comply with Good Manufacturing Practice requirements for dosage forms and categories of medicines listed below:

S/N	**Dosage Forms**	**Categories of Medicines**	**Manufacturing Operations**

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured lies with the manufacturer and /or marketing authorization holder.

This certificate shall remain valid until ..... It becomes invalid if the dosage forms, operations and /or categories certified herewith are changed or if the site is no longer considered to be in compliance with current GMP.

_____ _____

Date **DIRECTOR GENERAL**

Note:

1. This Certificate certifies the status of the site described above
2. This Certificate shall remain valid for a period of 3 years from the date of issue.