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A REVIEW ARTICLE ON GOOD MANUFACTURING PRACTICES (ORANGE GUIDE)

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ABSTRACT

The concept of good manufacturing practice (GMP) is well known to every pharmaceutical company in the world. The 'Orange Guide' was first published in 1971 and since then it has become the premier guide for everyone involved in the production of medical products, regularly republished with amendments as regulations and requirements evolve. The 'Orange Guide' is necessary reading for any qualified person who is involved in the manufacture or distribution of medicines, drugs or blood. A set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products. cGMP is just a guideline, system and quality theme for compliance. It is just a way to build quality in a product. Improves productivity and minimizes rejection and mistakes. Designed to ensure that the entire process, from purchase of approved material through detailed, defined production processes, using approved facilities and trained personnel operating in well designed buildings through QC department to final distribution outlets. This results in the achievement of consistent and uniformly good quality products.

Key words: Gmp, Orange guide, Amendments, Well designed, Quality Products, Drugs or blood.

INTRODUCTION

GMP also known as Good Management Practice, Good Manufacturing Practice, Get More Profit, Give more Production, GMP Training without tears.

The 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors', otherwise known as the 'Orange Guide' is published to help companies and individual personnel comply with GMP regulations that govern the international pharmaceutical industry.

The 'Orange Guide' was first published in 1971 and since then it has become the premier guide for everyone involved in the production of medical products, regularly republished with amendments as regulations and requirements evolve. Not only do GMP regulations cover drugs and medicines intended for human use but also blood, which is collected with the purpose of being used in a patient. The 'Orange Guide' is necessary reading for any qualified person who is involved in the manufacture or distribution of medicines, drugs or blood. A set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products. cGMP became official in 1963. Draft was prepared in 1971 and was implemented in June 1988.

Designed to ensure that the entire process, from purchase of approved material through detailed, defined production processes, using approved facilities and trained personnel operating in well designed buildings through QC department to final distribution outlets. This results in the achievement of consistent and uniformly good quality products. cGMP is a set of guidelines that are required by the US FDA for pharmaceutical manufacturers to make use of and develop their own part procedures. To help ensure that quality includes entire manufacturing procedures and are maintained throughout the product life. This starts with raw materials received and through the product creation and testing and does not even end after the product sold and consumed. Follow of cGMP is not compulsory but it is necessary to ensure a greater issue of consumer safety and confidence. Why current – because the requirements are always changing, as they should, to match the current science and change in nature of products and manufacturing.

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cGMP – also defined as "practices which are used to assure that a product or any of its component parts, meets the requirements as to safety, has the identity and strength and meets the quality and purity and characters which it is intended to possess". It is a comprehensive system, designed, documented, implemented and controlled and furnished with personnel equipment and other resources as to provide assurance that products will be consistently of a quality appropriate to their international standards. Thus the attainment of this quality object requires involvement and commitment of a concerned at all stages [1].

OBJECTIVES

To assure quality of a product and finally the safety, well being and protection of patient .To perform every operation with the objectives of maintaining the identity and integrity and products of effective production. To establish systems of control at all levels of manufacturing, right from the receipt of raw materials by continuous working, using correct equipment to dispatch finished goods from factory. cGMP is just a guideline, system and quality theme for compliance. It is just a way to built quality in a product. Improves productivity and minimizes rejection and mistakes.

Ten Principles of GMP

1. Design and construct the facilities and equipments properly
2. Follow written procedures and Instructions
3. Document work
4. Validate work
5. Monitor facilities and equipment
6. Write step by step operating procedures and work on instructions
7. Design ,develop and demonstrate job competence
8. Protect against contamination
9. Control components and product related processes
10. Conduct planned and periodic audits [2]

REQUIREMENTS OF cGMP-

Location and premises
Equipment and machinery
Personnel
General housekeeping and sanitation
Raw materials control
Control of manufacturing operations including labeling and packaging
Quality control
Containers
Distribution and recall
Self inspection
Concept of zero defect

TO SATISFY "FDA"

- SOP's should be written and followed
- Protocols should be prepared
- Validation should be done
- Written procedures should be maintained
- Complete stability programs should be done for products.
- Annual products review
- Calibrations
- Analytical testing and statistical evaluation of raw materials and finished products.
- cGMP training program should be given
- Designated controlled areas and written procedures for storage of received goods, quarantined and finished products should be maintained.
- Plant design
- Paper trail should be in place starting from incoming materials through stability testing
- Thoroughly documented, monitored, tested and evaluated review.
- Complaints or adverse reaction programs in place are written and documented.

FDA Inspector Looks For

- Human behaviour
- Infestation
- Condition of Equipment and Utensils
- Condition of raw materials
- Toilets and Wash room facilities
- Plant construction
- Waste disposal
- Condition of storage and handling of products.

Other Manufacturing Aspects

- Building facilities
- Equipments
- Personnel
- Components and other materials used
- Master production and control records for each drug product and each batch should be maintained.
- Reasonable precautions should be taken in production and production control procedures.
- Product containers and operations should be tested.
- Packaging and labeling operations should be controlled.
- Scientifically sound and appropriate standards and specifications and test procedures should be used.
- Distribution records must be maintained
- Stability of finished products must be assured.
- Suitable expiration dates of drug products must be instituted.
- Complaints file should be maintained.
- SOP's should be prepared.

Protocols and validation are important for analytical methods, process controls and air sampling and cleaning procedures. Calibrations should be done for all equipments. Analytical testing and evaluation is important. cGMP training program is important.

cGMP stress on quality control, quality system – quality management, quality assurance and risk assessment tools. Thus the guidance describes "a complete quality system model which if implemented will allow manufacturers to

operate robust, modern quality systems that are fully compliant with cGMP regulations".

This is applicable to manufacturers of finished pharmaceuticals

Seven key concepts are provided by the guidance.

1. Quality – the quality of a pharmaceutical product is defined by its identity, strength, purity and other properties that ensure its safety and effectiveness.
2. Quality by design and product development
3. Risk management and risk assessment
4. Corrective and preventive action
5. Change control
6. Quality unit
7. Six system inspection model

- quality system .
- production system .
- facilities and equipments system .
- lab controls system.
- materials system .
- Packaging and labeling system

Good Manufacturing Practices and Requirements Of Premises, Plant And Equipment For Pharmaceutical Product

Location and surroundings

The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produces disagreeable or obnoxious, odour, fumes, excessive soot, dust, smoke, chemical or biological emissions.

Buildings and premises

The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948).

The premises used for manufacturing, processing, warehousing, packaging, labeling and testing purposes shall be -

(i) compatible with other drug manufacturing operations that may be carried out in the same or adjacent area / section;

(ii) adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to :

(a) avoid the risk of mix-up between different categories of drugs or with raw materials, intermediates and in-process material;

(b) avoid the possibilities of contamination and cross-contamination by providing suitable mechanism;

(iii) Designed / constructed / maintained to prevent entry of insects, pests, birds, vermins, and rodents. Interior surface (walls, floors, and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection;

(v) Air conditioned, where prescribed for the operations and dosage forms under production. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units (wherever applicable) to maintain conditions including temperature and, wherever necessary, humidity as defined for the relevant product. These conditions shall be appropriate to the category of drugs and nature of the operation. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications;

(v) Provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back- flow and/or to prevent insects and rodents entering the premises. Open channels shall be avoided in manufacturing areas and, where provided, these shall be shallow to facilitate cleaning and disinfection;

(vi) The walls and floors of the areas where manufacture of drugs is carried out shall be free from cracks and open joints to avoid accumulation of dust. These shall be smooth, washable, coved and shall permit easy and effective cleaning and disinfection. The interior surfaces shall not shed particles. A periodical record of cleaning and painting of the premises shall be maintained.

Water system

There shall be validated system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce Purified Water conforming to Pharmacopoeial specification. Purified Water so produced shall only be used for all the operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf [3].

Disposal of waste

(vii) The disposal of sewage and effluents (solid, liquid and gas) from the manufactory shall be in conformity with the requirements of Environment Pollution Control Board. (viii) All bio-medical waste shall be destroyed as per the provisions of the Bio- Medical Waste (Management and Handling) Rules, 1996. (ix) Additional precautions shall be taken for the storage and disposal of rejected drugs. Records shall be maintained for all disposal of waste.

Warehousing Area

- Adequate areas shall be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in

quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items.

- Warehousing areas shall be designed and adapted to ensure good storage conditions. They shall be clean, dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature, humidity), these shall be provided, monitored and recorded. Storage areas shall have appropriate house-keeping and rodent, pests and vermin control procedures and records maintained. Proper racks, bins and platforms shall be provided for the storage of materials.
- Receiving and dispatch bays shall protect materials and products from adverse weather conditions.
- Where quarantine status is ensured by warehousing in separate earmarked areas in the same warehouse or store, these areas shall be clearly demarcated. Any system replacing the physical quarantine, shall give equivalent assurance of segregation. Access to these areas shall be restricted to authorized persons.
- There shall be a separate sampling area in the warehousing area for active raw materials and excipients. If sampling is performed in any other area, it shall be conducted in such a way as to prevent contamination, cross- contamination and mix- up.
- Segregation shall be provided for the storage of rejected, recalled or returned materials or products. Such areas, materials or products shall be suitably marked and secured. Access to these areas and materials shall be restricted.
- Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure areas. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authority.
- Printed packaging materials shall be stored in safe, separate and secure areas.
- Separate dispensing areas for β (Beta) lactum, Sex Hormones and Cyto-toxic substances or any such special categories of products shall be provided with proper supply of filtered air and suitable measures for dust control to avoid contamination. Such areas shall be under differential pressure.
- Sampling and dispensing of sterile materials shall be conducted under aseptic conditions conforming to Grade A, which can also be performed in a dedicated area within the manufacturing facility.
- Regular checks shall be made to ensure adequate steps are taken against spillage, breakage and leakage of containers.
- Rodent treatments (pest control) should be done regularly and at least once in a year and record maintained.

Production area

- The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.
- In order to avoid the risk of cross-contamination, separate dedicated and self- contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live micro-organisms. Separate dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as Beta lactum, Sex Hormones and Cyto-toxic substances.
- Working and in-process space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel to avoid cross-contamination and to minimize risk of omission or wrong application of any of manufacturing and control measures.
- Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid accumulation of dust. Service lines shall preferably be identified by colours and the nature of the supply and direction of the flow shall be marked/indicated.

Ancillary areas

- Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.
- Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users. Toilets, separate for males and females, shall not be directly connected with production or storage areas. There shall be written instructions for cleaning and disinfection for such areas.
- Maintenance workshops shall be separate and away from production areas. Whenever spares, changed parts and tools are stored in the production area, these shall be kept in dedicated rooms or lockers. Tools and spare parts for use in sterile areas shall be disinfected before these are carried inside the production areas.
- Areas housing animals shall be isolated from other areas. The other requirements regarding animal houses shall be those as prescribed in rule 150-C(3) of the Drugs and Cosmetics Rules, 1945 which shall be adopted for production purposes.

Quality Control area

- Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio-isotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis.
- Quality Control Laboratories shall be designed appropriately for the operations to be carried out in them. Adequate space shall be provided to avoid mix-ups and cross- contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.
- The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall be provided for biological, microbiological and radioisotopes testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.

- Quality Control Laboratory shall be divided into separate sections i.e. for chemical, microbiological and wherever required, biological Testing. These shall have adequate area for basic installation and for ancillary purposes. The microbiology section shall have arrangements such as airlocks and laminar air flow work station, wherever considered necessary.

Personnel

- The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage form and / or active pharmaceutical products.
- The head of the Quality Control Laboratory shall be independent of the manufacturing unit. The testing shall be conducted under the direct supervision of competent technical staff who shall be whole time employees of the licensee.
- Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced.
- Written duties of technical and Quality Control personnel shall be laid and followed strictly.
- Number of personnel employed shall be adequate and in direct proportion to the workload.
- The licensee shall ensure in accordance with a written instruction that all personnel in production area or into Quality Control Laboratories shall receive training appropriate to the duties and responsibility assigned to them. They shall be provided with regular in-service training.

Health, clothing and sanitation of workers

- The personnel handling Beta-lactum antibiotics shall be tested for Penicillin sensitivity before employment and those handling sex hormones, cytotoxic substances and other potent drugs shall be periodically examined for adverse effects. These personnel should be moved out of these sections (except in dedicated facilities), by rotation, as a health safeguard.
- Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from Tuberculosis, skin and other communicable or contagious diseases. Thereafter, they should be medically examined periodically, at least once a year. Records shall be maintained thereof. The licensee shall provide the services of a qualified physician for assessing the health status of personnel involved in different activities.
- All persons, prior to and during employment, shall be trained in practices which ensure personnel hygiene. A high level of personal hygiene shall be observed by all those engaged in the manufacturing processes. Instructions to this effect shall be displayed in change-rooms and other strategic locations.
- No person showing , at any time , apparent illness or open lesions which may adversely affect the quality of products, shall be allowed to handle starting materials, packaging materials, in-process materials, and drug products until his condition is no longer judged to be a risk.
- All employees shall be instructed to report about their illness or abnormal health condition to their immediate supervisor so that appropriate action can be taken.
- Direct contact shall be avoided between the unprotected hands of personnel and raw materials, intermediate or finished , unpacked products.
- All personnel shall wear clean body coverings appropriate to their duties. Before entry into the manufacturing area, there shall be change rooms separate for each sex with adequate facilities for personal cleanliness such as wash basin with running water, clean towels, or hand dryers, soaps, disinfectants etc. The change rooms shall be provided with cabinets for the storage of personal belongings of the personnel.
- Smoking, eating, drinking, chewing or keeping plants, food, drink and personal medicines shall not be permitted in production, laboratory, storage and other areas where they might adversely influence the product quality [4].

Manufacturing Operations and Controls

- All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. Each critical step in the process relating to the selection, weighing and measuring of raw material addition during various stages shall be performed by trained personnel under the direct personal supervision of approved technical staff.
- The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labeled with the name of the product, batch no., batch size and stage of manufacture. Each label should be initialed and dated by the authorized technical staff.
- Products not prepared under aseptic conditions are required to be free from pathogens like Salmonella, Escherichia coli, Pyocyanea etc.

Precautions against mix–up and cross-contamination

- The licensee shall prevent mix-up and cross-contamination of drug material and drug product (from environmental dust) by proper air-handling system, pressure differential, segregation, status labeling and cleaning. Proper records and Standard Operating Procedures thereof shall be maintained.
- The licensee shall ensure processing of sensitive drugs like Beta-Lactum antibiotics, sex hormones and cytotoxic substances in segregated areas or isolated production areas within the building with independent air-handling unit and proper pressure differentials. The effective segregation of these areas shall be validated with adequate records of maintenance and services.
- To prevent mix-ups during production stages, material under- process shall be conspicuously labeled to demonstrate their status. All equipment used for production shall be labeled with their current status.
- Packaging lines shall be independent and adequately segregated. It shall be ensured that all left-overs of the previous packaging operations, including labels, cartons and caps are cleared before the closing hour.

- Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials and spillages. The line clearance shall be performed according to an appropriate checklist and recorded.
- The correct details of any printing (for example of batch numbers or expiry dates) done separately or in the course of the packaging shall be re-checked at regular intervals. All printing and over-printing shall be authorised in writing.
- The manufacturing environment shall be maintained at the required levels of temperature, humidity and cleanliness.
- Authorised persons shall ensure change-over into specific uniforms before undertaking any manufacturing operations including packaging.
- There shall be segregated secured areas for recalled or rejected material and for such material which are to be re-processed or recovered.

Sanitation in the manufacturing premises

- The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material. A validated cleaning procedure shall be maintained.
- The manufacturing areas shall not be used for storage of materials, except for the material being processed. It shall not be used as a general thoroughfare.
- A routine sanitation program shall be drawn up and observed, which shall be properly recorded and which shall indicate – (a) specific areas to be cleaned and cleaning intervals; (b) cleaning procedure to be followed, including equipment and materials to be used for cleaning; and (c) personnel assigned to and responsible for the cleaning operation.
- The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials so as to minimise the risk of mix-up between different pharmaceutical products or their components to avoid cross- contamination, and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.
- Production areas shall be well lit, particularly where visual on-line controls are carried out.

Raw materials

- The licensee shall keep an inventory of all raw-materials to be used at any stage of manufacture of drugs and maintain records as per Schedule U.
- All incoming materials shall be quarantined immediately after receipt or processing. All materials shall be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation by a 'first in/first expiry' - 'first-out' principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed.
- All incoming materials shall be purchased from approved sources under valid purchase vouchers. Wherever possible, raw materials should be purchased directly from the producers.
- Authorised staff appointed by the licensee in this behalf, which may include personnel from the quality control department, shall examine each consignment on receipt and shall check each container for integrity of package and seal. Damaged containers shall be identified, recorded and segregated.
- If a single delivery of material is made up of different batches, each batch shall be considered as a separate batch for sampling, testing and release.
- Raw materials in the storage area shall be appropriately labeled. Labels shall be clearly marked with the following information : (a) designated name of the product and the internal code reference, where applicable, and analytical reference number; (b) manufacturer's name, address and batch number; (c) the status of the contents (e.g. quarantine, under test, released, approved, rejected); (d) the manufacturing date, expiry date and re-test date.
- There shall be adequate separate areas for materials "under test", "approved ", and "rejected" with arrangements and equipment to allow dry, clean and orderly placement of stored materials and products, wherever necessary, under controlled temperature and humidity.
- Containers from which samples have been drawn shall be identified.
- Only raw materials which have been released by the Quality Control Department and which are within their shelf-life shall be used. It shall be ensured that shelf- life of formulation product shall not exceed with that of active raw materials used.
- It shall be ensured that all the containers of raw materials are placed on the raised platforms/racks and not placed directly on the floor..

Equipment

- Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products. Each equipment shall be provided with a log book , wherever necessary.
- Balances and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw-material stores, production and in-process control operations and these shall be calibrated and checked on a scheduled basis in accordance with Standard Operating Procedures and records maintained.
- The parts of the production equipment that come into contact with the product shall not be reactive, additive or adsorptive to an extent that would affect the quality of the product.
- To avoid accidental contamination, wherever possible, non-toxic/edible grade lubricants shall be used and the equipment shall be maintained in a way that lubricants do not contaminate the products being produced.

- Defective equipment shall be removed from production and Quality Control areas or appropriately labeled.

Documentation and records

Documentation is an essential part of the Quality assurance system and, as such, shall be related to all aspects of Good Manufacturing Practices (GMP). Its aim is to define the specifications for all materials, method of manufacture and control, to ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a batch of a drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch.

- Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.
- Documents shall be approved, signed and dated by appropriate and authorized persons.
- Documents shall specify the title, nature and purpose. They shall be laid out in an orderly fashion and be easy to check. Reproduced documents shall be clear and legible. Documents shall be regularly reviewed and kept up to date. Any alteration made in the entry of a document shall be signed and dated.
- The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated Standard Operating Procedures (SOP) shall be retained for at least one year after the expiry date of the finished product.
- Data may be recorded by electronic data processing systems or other reliable means, but Master Formulae and detailed operating procedures relating to the system in use shall also be available in a hard copy to facilitate checking of the accuracy of the records.

Wherever documentation is handled by electronic data processing methods, authorized persons shall enter or modify data in the computer. There shall be record of changes and deletions. Access shall be restricted by 'passwords' or other means and the result of entry of critical data shall be independently checked. Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available.

Labels and other Printed Materials

- Labels are absolutely necessary for identification of the drugs and their use. The printing shall be done in bright colours and in a legible manner. The label shall carry all the prescribed details about the product.
- All containers and equipment shall bear appropriate labels. Different colour coded labels shall be used to indicate the status of a product (for example: under test, approved, passed, rejected).
- To avoid chance mix-up of printed packaging materials, product leaflets, relating to different products, shall be stored separately.
- Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the Quality Control Department of the licensee.
- Prior to packaging and labeling of a given batch of a drug, it shall be ensured by the licensee that samples are drawn from the bulk and duly tested, approved and released by the quality control personnel.
- Records of receipt of all labelling and packaging materials shall be maintained for each shipment received indicating receipt, control reference numbers and whether accepted or rejected. Unused coded and damaged labels and packaging materials shall be destroyed and recorded.
- The label or accompanying document of reference standards and reference culture shall indicate concentration, lot number, potency, date on which container was first opened and storage conditions, where appropriate.

Quality Assurance

This is a wide ranging concept concerning all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that products are of the quality required for their intended use.

- The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that:
  - The pharmaceutical products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practices (hereinafter referred as GMP) and other associated codes such as those of Good Laboratory Practices (hereinafter referred as GLP) and Good Clinical Practices (herein after referred as GCP);
  - Adequate arrangements are made for manufacture, supply, and use of the correct starting and packaging materials;
  - Adequate controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
  - The finished product is correctly processed and checked in accordance with established procedures.
  - The pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of pharmaceutical products;

Self inspection and Quality audit

It may be useful to constitute a self inspection team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it. 15. 1. To evaluate the manufacturer's compliance with GMP in all aspects of production and quality control, concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results, evaluation, conclusions and recommended corrective actions with effective follow

up program. The recommendations for corrective action shall be adopted.

- The program shall be designed to detect shortcomings in the implementation of Good Manufacturing Practice and to recommend the necessary corrective actions. Self-inspections shall be performed routinely and on specific occasions, like when product recalls or repeated rejections occur or when an inspection by the licensing authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of Good Manufacturing Practice objectively; all recommendations for corrective action shall be implemented.
- Written instructions for self-inspection shall be drawn up which shall include the following : (a) Personnel. (b) Premises including personnel facilities. (c) Maintenance of buildings and equipment. (d) Storage of starting materials and finished products. (e) Equipment. (f) Production and in-process controls. (g) Quality control. (h) Documentation. (i) Sanitation and hygiene. (j) Validation and revalidation programmes. (k) Calibration of instruments or measurement systems. (l) Recall procedures. (m) Complaints management. (n) Labels control. (o) Results of previous self-inspections and any corrective steps taken [5].

Quality Control System

Quality control shall be concerned with sampling, specifications, testing, documentation, release procedures which ensure that the necessary and relevant tests are actually carried and that the materials are not released for use, nor products released for sale or supply until their quality has been judged to be satisfactory. It is not confined to laboratory operations but shall be involved in all decisions concerning the quality of the product. It shall be ensured that all quality control arrangements are effectively and reliably carried out. The department as a whole shall have other duties such as to establish, evaluate, validate and implement all Quality Control Procedures and methods.

- Every manufacturing establishment shall establish its own quality control laboratory manned by qualified and experienced staff.
- The area of the quality control laboratory may be divided into Chemical, Instrumentation, Microbiological and Biological testing.
- Adequate area having the required storage conditions shall be provided for keeping reference samples. The quality control department shall evaluate, maintain and store reference samples.
- Standard operating procedures shall be available for sampling, inspecting, and testing of raw materials, intermediate, bulk finished products and packing materials and, wherever necessary, for monitoring environmental conditions.
- There shall be authorized and dated specifications for all materials, products, reagents and solvents including test of identity, content, purity and quality. These shall include specifications for water, solvents and reagents used in analysis.
- No batch of the product shall be released for sale or supply until it has been certified by the authorised person(s) that it is in accordance with the requirements of the standards laid down.
- Reference/retained samples from each batch of the products manufactured shall be maintained in a quantity which is at least twice the quantity of the drug required to conduct all the tests, except sterility and pyrogen/Bacterial Endotoxin Test performed on the active material and the product manufactured. The retained product shall be kept in its final pack or a simulated pack for a period of three months after the date of expiry.
- Assessment of records pertaining to finished products shall include all relevant factors, including the production conditions, the results of in- process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack. Assessment records should be signed by the in-charge of production and countersigned by the authorised quality control personnel before a product is released for sale or distribution.
- Quality control personnel shall have access to production areas for sampling and investigation , as appropriate.
- The quality control department shall conduct stability studies of the products to ensure and assign their shelf life at the prescribed conditions of storage. All records of such studies shall be maintained.
- The in-charge of Quality Assurance shall investigate all product complaints and records thereof shall be maintained.
- All instruments shall be calibrated and testing procedures validated before these are adopted for routine testing. Periodical calibration of instrument and validation of procedures shall be carried out.
- Each specifications for raw materials, intermediates, final products, and packing materials shall be approved and maintained by the Quality Control Department. Periodic revisions of the specifications shall be carried out whenever changes are necessary.
- Pharmacopoeiae, reference standards, working standards, reference spectra, other reference materials and technical books, as required, shall be available in the Quality Control Laboratory of the licensee.

Specification

- For Raw materials and Packaging materials :- They shall include,- (a) the designated name and internal code reference; (b) reference, if any , to a pharmacopoeial monograph; (c) qualitative and quantitative requirements with acceptance limits; (d) name and address of manufacturer or supplier and original manufacturer of the material; (e) specimen of printed material; (f) directions for sampling and testing or reference to procedures; (g) storage conditions; and (h) maximum period of storage before re-testing.
- For Product Containers and Closures
  - All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable

validated test methods, sample sizes, specifications, cleaning procedure and sterilization procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, adsorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used.

- Whenever bottles are being used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, they should be rinsed with de-ionised water or distilled water, as the case may be.
- For in-process and bulk products.— Specifications for in-process material, intermediate and bulk products shall be available. The specifications should be authenticated.
- For Finished Products. – Appropriate specifications for finished products shall include :- (a) the designated name of the product and the code reference; (b) the formula or a reference to the formula and the pharmacopoeial reference; (c) directions for sampling and testing or a reference to procedures; (d) a description of the dosage form and package details; (e) the qualitative and quantitative requirements, with the acceptance limits for release; (f) the storage conditions and precautions, where applicable , and (g) the shelf-life.
- For preparation of containers and closures. – The requirements mentioned in the Schedule do not include requirements of machinery, equipments and premises required for preparation of containers and closures for different dosage forms and categories of drugs. The suitability and adequacy of the machinery, equipment and premises shall be examined taking into consideration the requirements of each licensee in this respect.

Master Formula Records

There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by the competent technical staff i.e. head of production and quality control. The Master Formula shall include :-

- The name of the product together with product reference code relating to its specifications;
- The patent or proprietary name of the product along with the generic name, a description of the dosage form, strength, composition of the product and batch size;
- Name, quantity, and reference number of all the starting materials to be used. Mention shall be made of any substance that may ‘disappear‘ in the course of processing;
- A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- A statement of the processing location and the principal equipment to be used;
- The methods, or reference to the methods, to be used for preparing the critical equipment including cleaning, assembling, calibrating, sterilizing;
- Detailed stepwise processing instructions and the time taken for each step;
- The instructions for in-process controls with their limits;

The requirements for storage conditions of the products, including the container, labelling and special storage conditions where applicable;

- Any special precautions to be observed;
- Packing details and specimen labels.

19. Packaging Records

There shall be authorised packaging instructions for each product, pack size and type. These shall include or have a reference to the following

(a) name of the product; (b) description of the dosage form, strength and composition; (c) the pack size expressed in terms of the number or doses, weight or volume of the product in the final container; (d) complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material; (e) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied; (f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin; (g) description of the packaging operation, including any significant subsidiary operations and equipment to be used; (h) details of in-process controls with instructions for sampling and acceptance; (i) upon completion of the packing and labeling operation, a reconciliation shall be made between number of labeling and packaging units issued, number of units labeled, packed and excess returned or destroyed. Any significant or unusual discrepancy in the numbers shall be carefully investigated before releasing the final batch.

Batch Packaging Records.-

- A batch packaging record shall be kept for each batch or part batch processed. It shall be based on the relevant parts of the packaging instructions, and the method of preparation of such records shall be designed to avoid transcription errors.
- Before any packaging operations begins, checks shall be made and recorded that the equipment and the work stations are clear of the previous products, documents or materials not required for the planned packaging operations, and that the equipment is clean and suitable for use [6].

Batch Processing Records.

- There shall be Batch Processing Record for each product. It shall be based on the relevant parts of the currently approved Master Formula. The method of preparation of such records included in the Master Formula shall be designed to avoid transcription errors;
- Before any processing begins, check shall be performed and recorded to ensure that the equipment and work station are clear of previous products, documents or materials not required for the planned process are removed and that equipment is clean and suitable for use.
- During processing, the following information shall be recorded at the time each action is taken and the record shall be dated and signed by the person responsible for the processing operations:

(a) the name of the product, (b) the number of the batch being manufactured, (c) dates and time of commencement, of significant intermediate stages and of completion of production, (d) initials of the operator of different significant steps of production and where appropriate, of the person who checked each of these operations, (e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed, (f) any relevant processing operation or event and major equipment used, (g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained, (h) the amount of product obtained after different and critical stages of manufacture (yield), (i) comments or explanations for significant deviations from the expected yield limits shall be given, (j) notes on special problems including details, with signed authorization, for any deviation from the master formula, (k) addition of any recovered or reprocessed material with reference to recovery or reprocessing stages.

Standard Operating Procedures (SOPs) and Records, regarding.-

Receipt of Materials

- There shall be written Standard Operating Procedures and records for the receipt of each delivery of raw, primary and printed packaging material.
- The records of the receipts shall include;

(a) the name of the material on the delivery note and the number of the containers; (b) the date of receipt; (c) the manufacturer's and / or supplier's name; (d) the manufacturer's batch or reference number; (e) the total quantity, and number of containers, quantity in each container received; (f) the control reference number assigned after receipt; (g) any other relevant comment or information.

- There shall be written standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.
- There shall be Standard Operating Procedures available for each instrument and equipment and these shall be placed in close proximity to the related instrument and equipment.

Sampling

- There shall be written Standard Operating Procedures for sampling, which include the person(s) authorized to take the samples.
- The sampling instructions shall include: (a) the method of sampling and the sampling plan, (b) the equipment to be used, (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality, (d) the quantity of samples to be taken, (e) instructions for any required sub-division or pooling of the samples, (f) the type of sample container to be used, (g) any specific precautions to be observed, especially in regard to sampling of sterile or hazardous material.

Batch Numbering

- There shall be Standard Operating Procedures describing the details of the batch (lot) numbering set up with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.
- Batch numbering standard operating procedures applied to a processing stage and to the respective packaging stage shall be same or traceable to demonstrate that they belong to one homogenous mix.
- Batch number allocation shall be immediately recorded in a logbook or by electronic data processing system. The record shall include date of allocation, product identity and size of batch.

Testing

There shall be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed shall be recorded.

Records of analysis

- The records shall include the following data. (a) name of the material or product and the dosage form, (b) batch number and, where appropriate the manufacturer and / or supplier; (c) references to the relevant specifications and testing procedures, (d) test results, including observations and calculations, and reference to any specifications (limits), (e) dates of testing; (f) initials of the persons who performed the testing; (g) initials of the persons who verified the testing and the detailed calculations, (h) a statement of release or rejection, and (i) signature and date of the designated responsible person.
- There shall be written standard operating procedures and the associated records of actions taken for: (a) equipment assembly and validation; (b) analytical apparatus and calibration; (c) maintenance, cleaning and sanitation; (d) personnel matters including qualification, training, clothing, hygiene; (e) environmental monitoring; (f) pest control; (g) complaints; (h) recalls made; (i) returns received.

Reference samples

- Each lot of every active ingredient, in a quantity sufficient to carry out all the tests , except sterility and pyrogens/Bacterial Endotoxin Test, shall be retained for a period of 3 months after the date of expiry of the last batch produced from that active ingredient.
- Samples of finished formulations shall be stored in the same or simulated containers in which the drug has been actually marketed. 24. Reprocessing And Recoveries .–
- Where reprocessing is necessary, written procedures shall be established and approved by the Quality Assurance Department that shall specify the conditions and limitations of repeating chemical reactions. Such re-processing shall be validated.
- If the product batch has to be reprocessed, the procedure shall be authorized and recorded. An investigation shall be carried out into the causes necessitating re -processing and appropriate corrective measures shall be taken for prevention of recurrence. Re-processed batch shall be subjected to stability evaluation.

- Recovery of product residue may be carried out, if permitted, in the master production and control records by incorporating it in subsequent batches of the product.

Distribution records

- Prior to distribution or dispatch of given batch of a drug, it shall be ensured that the batch has been duly tested, approved and released by the quality control personnel. Pre-dispatch inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched. Detailed instructions for warehousing and stocking of Large Volume Parenterals, if stocked, shall be in existence and shall be complied with after the batch is released for distribution. Periodic audits of warehousing practices followed at distribution centers shall be carried out and records thereof shall be maintained. Standard Operating Procedures shall be developed for warehousing of products.
- Records for distribution shall be maintained in a manner so as to facilitate prompt and complete recall of the batch, if and when necessary.

Validation And Process Validation

- Validation studies shall be an essential part of Good Manufacturing Practices and shall be conducted as per the pre-defined protocols. These shall include validation of processing, testing and cleaning procedures.
- A written report summarizing recorded results and conclusions shall be prepared, documented and maintained.
- Processes and procedures shall be established on the basis of validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Critical processes shall be validated, prospectively or retrospectively.
- When any new master formula or method of preparation is adopted, steps shall be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified shall be demonstrated to yield a product consistently of the required quality.
- Significant changes to the manufacturing process, including any change in equipment or materials that may affect product quality and / or the reproducibility of the process, shall be validated.

Product recalls

- A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard.
- There shall be an established written procedure in the form of Standard Operating Procedure for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated promptly so as to effectively reach at the level of each distribution channel.
- The distribution records shall be readily made available to the persons designated for recalls.
- The designated person shall record a final report issued , including a reconciliation between the delivered and the recovered quantities of the products.
- The effectiveness of the arrangements for recalls shall be evaluated from time to time.
- The recalled products shall be stored separately in a secured segregated area pending final decision on them.

Complaints and Adverse Reactions

- All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated/evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.
- Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned Licensing Authority.
- There shall be written procedures describing the action to be taken, recall to be made of the defective product. 29. Site Master File .– The licensee shall prepare a succinct document in the form of 'Site Master File' containing specific and factual Good Manufacturing Practices about the production and/or control of pharmaceutical manufacturing preparations carried out at the licensed premises. It shall contain the following

General information

(a) brief information of the firm; (b) pharmaceutical manufacturing activities as permitted by the licensing authority; (c) other manufacturing activities, if any, carried out on the premises; (d) type of products licensed for manufacture with flowcharts mentioning procedures and process flow; (e) number of employees engaged in the production, quality control, storage and distribution; (f) Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis; (g) short description of the Quality Management system of the firm; (h) products details registered with foreign countries.

Personnel

(a) organisational chart showing the arrangement for quality assurance including production and quality control; (b) qualification, experience and responsibilities of key personnel; (c) outline for arrangements for basic and in-service training and how the records are maintained; (d) health requirements for personal engaged in production; (e) personnel hygiene requirements, including clothing.

Premises

(a) simple plan or description of manufacturing areas drawn to scale; (b) nature of construction and fixtures / fittings; (c) brief description of ventilation systems. More details should be given for critical areas with potential risk of airborne contamination (schematic drawing of systems). Classification of the rooms used for the manufacture of

sterile products should be mentioned; (d) special areas for the handling of the highly toxic, hazardous and sensitizing materials; (e) brief description of water systems (schematic drawings of systems), including sanitation; (f) description of planned preventive maintenance programs for premises and of the recording system.

Equipment
(a)brief description of major equipment used in production and quality control laboratories (a list of equipment required); (b) description of planned preventive maintenance programs for equipment and of the recording system; (c) qualification and calibration, including the recording systems and arrangements for computerised systems validation.

Sanitation
(a) availability of written specifications and procedures for cleaning manufacturing areas and equipment.

Documentation
(a) arrangements for the preparation, revision and distribution of (b) necessary documentation for the manufacture; (b) any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls about air and water)

Production
(a) brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters; (b) arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage; (c) arrangements for the handling of rejected materials and products; (d) brief description of general policy for process validation.

Quality control
(a) description of the quality control system and of the activities of the quality control department. Procedures for the release of the finished products.

Loan licence manufacture and licensee
(a) description of the way in which compliance of Good Manufacturing Practices by the loan licensee shall be assessed.

Distribution, complaints and product recall
(a) arrangements and recording system for distribution; (b) arrangements for the handling of complaints and product recalls.

Self-Inspection
(a)short description of the self-inspection system indicating whether an outside, independent and experienced external expert was involved in evaluating the manufacturer's compliance with Good Manufacturing Practices in all aspects of production [8].

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