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GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Pooja Darade, Hitesh Hivarkar, Chandrakant Birar, Pratiksha Avhad, Madhavi Darade, Prof. Pravin P. Gadakh
KCT's R. G. Sapkal College of Pharmacy Anjaneri, Nashik

ABSTRACT

A manufacturing authorization holder is responsible for producing pharmaceuticals in a way that is appropriate for the intended purpose, complies with marketing authorization standards, and does not jeopardize patient safety by subpar quality, safety, or efficacy. Senior management bears the responsibility for achieving this quality target, which calls on the involvement and dedication of employees across numerous departments and levels of the organization, as well as suppliers and distributors. To consistently achieve the quality objective, a thorough system of quality assurance that incorporates good manufacturing practices—and, by extension, quality control and quality risk management—must be created and implemented appropriately.

Good Manufacturing Practices (GMP) are a set of guidelines and regulations designed to ensure that products, especially in industries like pharmaceuticals, food, and medical devices, are consistently produced and controlled according to quality standards. These practices cover all aspects of production, from the raw materials to the equipment and staff training. The goal is to minimize risks involved in production that cannot be fully eliminated through testing the final product, such as contamination, mix-ups, and errors. GMP ensures that products are safe for consumption and meet quality specifications.

KEY WORDS : *Good Manufacturing practices , Quality Assurance , Quality Control*

INTRODUCTION

The term GMP was introduced to regulate manufacturing and packaging operations in the pharmaceutical company. Until the mid-1960s, operating procedures for the manufacture of drugs consisted of formulae and the basic methods of making products. Written procedures were often concise and often relied on the individual operator's skill and experience. As batches of medicines increased in number and size, the operating procedures were inadequate to produce consistent and reliable products. Much attention had focused on the purity of medicinal substances. Pharmacopoeias and codices specified formulae for mixtures and other preparation, but gave little detailed information on the methods of preparation. The factors affecting processing and packaging procedures were becoming more apparent and the need for appropriate guidelines was evident (Lund, 1994).

The Medicines Inspectorate of the Department of Health and Social Security of England, in consultation with other interested bodies compiled the guide to GMP also known as the Orange Guide. The first edition of the guide was published in 1971, before any formal inspections of drug manufacturers had beeout under the Medicines Act. It was a relatively light volume of 20 pages, and was reissued as a third impression in 1972, with the addition of a 2-page appendix on sterile medicinal products. Because of the color of its cover, it became known as the Orange Guide. The guide was therefore written at a time when the nature, extent, and special problems of the manufacturer of drugs were not completely known. A second, more substantial edition (52 pages, including five appendices) was published in 1977. A third edition (110 pages, five appendices) was published in 1983 (Lund, 1994). Subsequently, the 2002 edition of Rules and Guidance for Pharmaceutical Manufacturers and Distributors, commonly known as the 'Orange Guide', was published with many changes and additions to the detailed European Community guidelines on GMP. The Medicines and Healthcare products Regulatory Agency (MHRA) has published new edition of the Orange Guide in 2007.

In United States, the first GMP regulations were issued in 1963 and described the GMP to be followed in the manufacture, packaging, and storage of finished pharmaceutical products. GMP regulations were developed by the US FDA and issued the United States CFR Chapter 21 in 1978. The regulations were similar in concept to the Orange Guide, but were enforceable by law whereas the UK guide was advisory. US congress passed the Federal Ani-tempering Act in 1983, making it a crime to tamper with packaged consumer products (Nally, 2007).

IMPORTANCE OF GMP

In the United States the Centre for Drug Evaluation and Research (CDER) promotes and protects public health by assuring that safe and effective drugs are available to Americans. There exits different types of risk with medicines (Figure 1), one of which is a

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preventable adverse event, which can be caused by different reasons. One of the reasons for this event can be a product quality defect. This risk can be avoided by effective implementation of GMP (US FDA CDER, 2001).

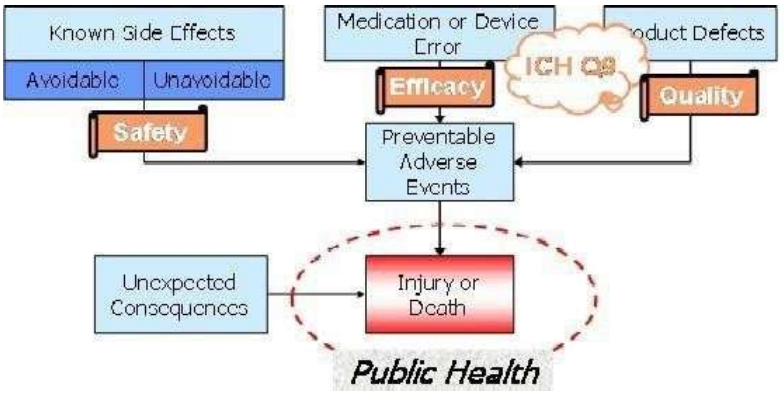


Fig. 1. Sources of Risk from Drug Products (Source: USFDACDER 2001)

Sulfanilamide a drug used to treat Streptococcal infections, had been shown to have dramatic curative effects and had been used safely for some time in tablet and powder form The company's chief chemist and pharmacist, Harold Cole Watkins, experimented and found that Sulfanilamide would dissolve in diethylene glycol. The company control laboratory tested the mixture for flavor, appearance, and fragrance and found it satisfactory. Immediately, the company compounded a quantity of Sulfanilamide elixir and sent shipments-all over the country (USA). The new formulation had not been tested for toxicity. At the time the food and drugs law did not require that safety studies be done on new drug.

Because no pharmacological studies had been done on the new Sulfanilamide preparation, Watkins failed to note one characteristic of the solution. Diethylene glycol, a chemical normally used as antifreeze, is a deadly poison. The useof an oral Sulfanilamide elixir has caused the death of 107 people, many of them children before the problem was discovered.

During 1960's Thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. When regulatory agencies gave permission to sell the drug for those indications, they knew nothing of its serious side effects .It turned out to be teratogenic: It caused serious deformities in developing fetues Children whose mothers took Thalidomide in the first trimester were born with severely deformed arms and legs (Immel 2005). Sharp, (1991) reported that at least 109 infants in Nigeria have died due to failure to follow GMP. This was caused due to the supply of mislabeled ethylene glycol as propylene glycol.

Effective implementation of GMP would also provide the cost benefit to the manufacturers, by avoiding the cost of failures such as cost of waste, of rework, of recall, of consumer compensation, of company reputation, and of regulatory action suspending operations.

Good manufacturing practices for pharmaceutical product

The component of quality management known as "good manufacturing practices" makes sure that goods are regularly produced and controlled in accordance with the quality standards relevant to their intended use, as mandated by licensing agreements, approvals for clinical trials, or product specifications. Good manufacturing methods address both quality assurance and productivity.

1) All manufacturing processes are precisely defined, methodically examined for related risks in the context of scientific knowledge and experience, and demonstrated to be capable of reliably producing pharmaceutical products that meet their specifications and are of the necessary quality.
2) Qualification and validation are performed.
3) All necessary resources are provided, including the following, namely- (a) sufficient and appropriately qualified and trained personnel.
   (b) Adequate premises and space.
   (c) Suitable equipment and services.
   (d) Appropriate materials, containers and labels.
   (e) Approved procedures and instructions.
   (f) Suitable storage and transport.
   (g) Adequate personnel, laboratories and equipment are in process controls.
   (h) Books necessary for ensuring compliance with the requirements relating to product development, manufacturing

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and quality control testing such as the Drugs and Cosmetics Act, 1940, the Drugs Rules,1945, the Indian Pharmacopoeia (Current Edition) and other relevant books and guidance documents officially issued by the Ministry of Health and Family Welfare, Government of India.

4) Instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided.
5) Procedures are carried out correctly and personnel are trained to do so.
   Records are made (manually or by recording instruments or by both) during manufacture to show
6) That all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive action is implemented.
7) records covering manufacture and distribution, which enable the complete history of a batch to be traced ,are retained in a comprehensible and accessible form.
8) the proper storage and distribution of the products which minimizes any risk to their quality.
   a system is available to recall any batch of product from sale or supply; and (10) complaints about marketed products are examined, the causes of quality defects investigated and appropriate aretaken in respect of the defective products to prevent recurrence (WHOTRS 961).

COMPONANTS OF GMP

GMP requires that the manufacturing process is fully defined before being initiated and all the necessary facilities are provided. In practice, personnel must be adequately trained, suitable premises and equipment used, correct materials used, approved procedures adopted, suitable storage and transport facilities available, and appropriate records made. The essential components of GMP are summarized in Figure 2 (Lund, 1994).



Fig 2: Five p's for GMP

consolidated components of GMP will cover all the requirements made by different authorities and also satisfy he WHO GMP guidelines for manufacturing of drugs.

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Fig 3: Consolidated Components Of GMP

❖ **Quality management**

Quality management is usually defined as the aspect of management function that determines and implements the "quality policy", i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management (WHOTRS 961, 2011). The basic elements of quality management are: an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources; and systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality.

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❖ **Quality Assurance (QA)**

Quality assurance is a set of activities for ensuring quality in the processes by which product are developed . Quality assurance aims to prevent defects with a focus on the process use to make the product. It is a proactive quality process. The goal of quality assurance is to improve development and taste processes so that defects do not arise when the product is being developed
Prevention of quality problems through planned and systematic activities including documentation . establish a good quality management system and assessment of its adequacy periodic conformance audits of the operations of the system.

The QA department is responsible for ensuring that the quality policies adopted by a company are followed . it helps to identify and prepare the necessary SOPs relative to the control of quality . it must determine that the product meets all the applicable specifications and that it was manufactured according to the internal standards of GMP . quality assurance also holds responsible for quality monitoring or audit functions .

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Quality assurance functions to asses operations continually and to advise and guide them towards full compliance with all applicable internal and external regulations (Patel KT, & Chotai NP. 2011).



Fig 4: Quality Assurance

❖ **Product Quality Review**

Regular periodic or rolling quality reviews of all licensed medicinal products, including export-only products, should be 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. Such reviews should should include at least:

(i) a review of starting materials including packaging materials used for the product, especially those from new sources;
(ii) a review of critical in-process controls and finished product results;
(iii) a review of all batches that failed to meet established specification(s) and their investigation;
(iv) a review of all significant deviations or non-conformances, the related investigations, and the effectiveness of resultant corrective and preventative actions taken;
(v) a review of all changes made to the processes or analytical methods;
(vi) a review of dossier variations submitted, granted or refused;
(vii) a review of the results of the stability monitoring programme and any adverse trends
(viii) review of all quality-related returns, complaints and recalls and the investigations performed at the time
(ix) a review of adequacy of any other previous corrective actions on product process or equipment;
(viii) for new dossiers and variations to the dossiers, a review of post-marketing commitments
(ix) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water, or compressed gases; and
(x) a review of technical agreements to ensure that they are up to date (WHOTRS 961 ,2011)

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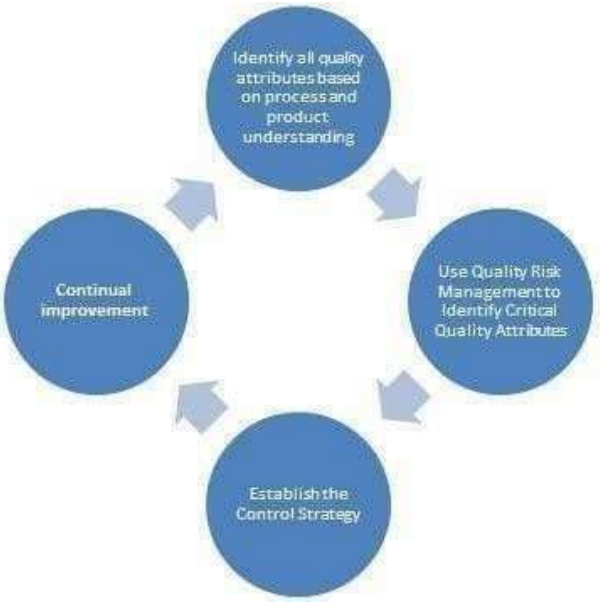


Fig 6 : Product Quality Review

❖ **Quality Risk Management (QRM)**

Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

Quality Risk Management shall ensure that the -

(a) evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;

(b) risk. level of effort, formality and documentation of the QRM process is commensurate with the level of risk (Nally, 1998).



Fig 7: Risk Management Process

❖ **Quality Control (QC)**

QC is that part of GMP which is concerned with sampling, specifications and testing, and with the

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organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product. QC as a whole will also have other duties, such as to establish, validate and implement all QC procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labeling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients(APIs) and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring (WHOTRS 961 2011).

❖ **Sanitation and Hygiene**

A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of medicine products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. Premises used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed. Records should be maintained. (Sharp, 2005).

Substance	Suitable conc.	Effects on bacteria	Effects on spores	Effects on vegetative fungi	advantages	disadvantages
ethanol	70%	Good	fair	Fair	Quick acting, evaporate rapidly	Limited range of effects , flammable
phenols	0.5-3%	excellent	good	excellent	Broad range of effects	Corrosive on some surfaces
Formaldehyde	-	excellent	good	Good	Broad range of effect	Premises not accessible during treatment
Isopropanol	70-90%	good	good	Good	Quick acting, Leaving no residue	Not the most effective
Iodine and iodophors	75-150 ppm	excellent	good	excellent	Effective in low conc.	Can be corrosive , stain some surfaces
Chlorine compounds	1-4%	excellent	good	excellent	Brode range of effect	corrosive
Quaternary ammonium compounds	1-5%	good	fair	Fair	Some cleaning effects , odourless	Inactivated by soap detergents

Tabel1: Disinfectants for premises (Sharp 2005)

❖ **Personal hygiene**

- All personnel shall be trained in the practices of personal hygiene. A high level of personal hygiene shall be observed by all those concerned with manufacturing processes. In particular, personnel shall be instructed to wash and sanitize their hands before entering production areas. Signs to this effect shall be posted and instructions are complied with.
- Any person shown at any time to have 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 drugs until his or her health condition is no longer judged to be a risk.
- 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.
- Direct contact shall be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk products

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Fig 8: Personal Hygiene

- To ensure protection of the product from contamination, personnel shall wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, shall be stored in a separate closed containers until properly laundered and, if necessary, disinfected or sterilized.
- Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines shall not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.
- Personal hygiene procedures, including the wearing of protective clothing, shall apply to all persons entering production areas, whether they are temporary or full-time employees or non employees, e.g., contractors' employees, visitors, senior managers and inspectors (ASEAN, 2000).

❖ **Qualification and Validation**

In accordance with GMP, each pharmaceutical company shall identify what qualification and validation work is required to prove that the critical aspects of their particular operation is controlled. The key elements of a qualification and validation programme of a company shall be clearly defined and documented in a validation master plan.

Qualification and validation shall establish and provide documentary evidence that—

(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for good manufacturing practices [design qualification (DQ)];

(b) The premises, supporting utilities and equipment have been built and installed in compliance with their design specifications [installation qualification (IQ)];

(c) The premises, supporting utilities and equipment operate in accordance with their design specifications [operational qualification (OQ)];

(d) a specific process shall consistently produce a product meeting its predetermined specifications and quality attributes [process validation (PV), also called performance qualification (PQ)](PIC/S, 2004

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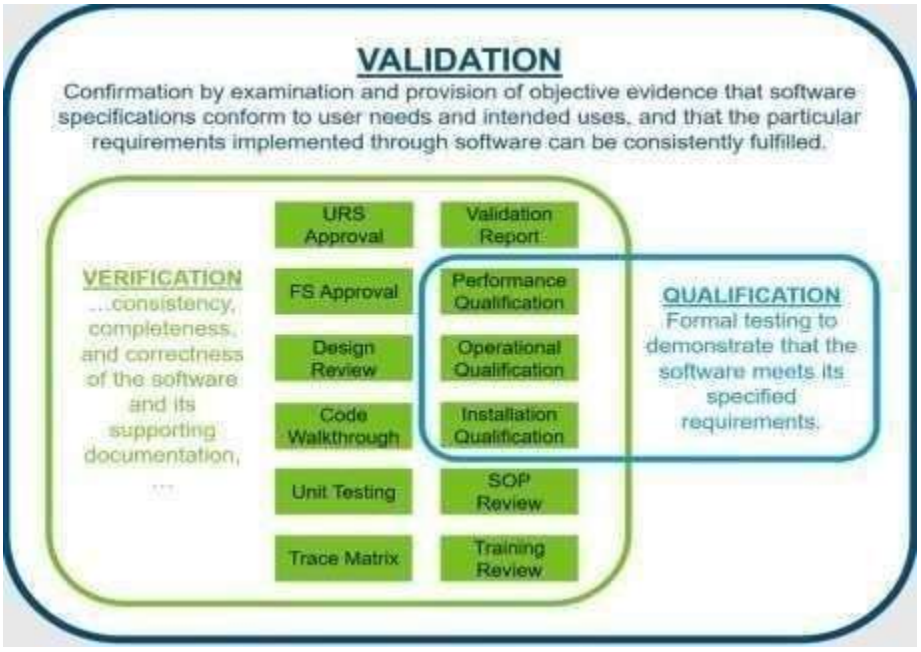


Fig 9 : Qualification and Validation

❖ **Complaints and Product Recalls**

The records of production, packaging, and distribution of drug and the retained samples provide the basis for assessing the validity and seriousness of the alleged deviations that precipitated the complaint. The complaint file itself also plays an important role in determining whether any other similar complaints have been received on the lot in question, or on any other lots of the same product. The evaluation of complaints serves several valuable purposes. First, there is the urgent need to confirm whether consumers are potentially at risk and to initiate any appropriate action. A second value is the review of the product and its production process to establish whether any modifications are required. Third is the need to rapidly respond to the customer, thereby attempting to maintain confidence in the product and company.



Fig 10: Effective Complaint Management Strategy

Manufacturers should have a written recall procedure, with nominated persons responsible for implementing it as necessary, within, or outside of, normal working hours. Distribution records should be maintained, which will facilitate effective recall, and the written procedure should include emergency and off-hours contacts and telephone numbers (Sharp, 2005).

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The complaints and defect report procedure is intended to be operated in conjunction with a "COMPLAINT/DEFECT REPORT" record (Figure 5), a copy of which, as is indicated, should form part of the SOP. Copies of this report form should be provided to all persons in the organization who may possibly be the first recipients of a complaint. They should be trained in its use and in the crucial importance of taking all such reports very seriously. As the complaints and defect report SOP indicates, if the complaints (etc.) procedure leads to a conclusion to recall (or freeze), then the recall (or freeze) procedure must be implemented. It is vital that this SOP is kept up to date, particularly in regard to internal and external names, addresses, and phone numbers, and that it is regularly shown (by "dummy runs") to be operable at any time (Huber, L. 2012).

COMPLAINT/DEFECT REPORT Page 1 of 1

1. Date Complaint/Report received ..... Time ……..
2. Received by …….
3. Received from:
   Name.....Address:
   Telephone number ..... Fax number.....e-mail
   ……
4. Name/address/phone numbers, etc. of other contacts/persons/organizations:

5. Product(s) involved:
6. Batch/lot numbers:
7. Name of complaint/report (attach any written correspondence)

8. Have samples been returned for examination? (Give details)

9. Are samples available for collection/examination? (Give details)

10. Results of investigations/Tests (attach other sheets as necessary)

11. Conclusions, and decision on action to be taken

Signed …… Date……

12. Letter(s) sent to ……Date …….
13. Also considered necessary to inform: Done/Date:

Fig. 11. Complaint/Defect Report Record (Source: Sharp, 2005)

❖ **Self-inspection, quality audits and supplier's audits/approval**

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. Management appoints a self-inspection team consisting of experts in their respective fields and familiar with GMP.

The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. A report should be made at the completion of a self-inspection. The report should include: (a) self-inspection results; (b) evaluation and conclusions; and (c) recommended corrective actions. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up

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programme. It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (WHOTRS 961 2011).

❖ **Personnel, training and personal hygiene**

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written job descriptions (WHOTRS 961, 2011). Personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their need (Sharp 2005).. In order to effectively monitor and control virtually all GMP documents/activities in a facility, the quality professional should have a very high level of knowledge ,skills, and experience (Nally, 2007).

❖ **Premises**

Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products (Sharps , 2005)

The choices of materials of construction for manufacturing facilities are numerous. Some examples are presented here

A) Walls

Walls in manufacturing areas, corridors, and packaging areas should be of plaster finish on high- quality concrete blocks or gypsum board. The finish should be smooth, usually with enamel or epoxy paint. They should be washable and able to resist repeated applications of cleaning and disinfecting agents. Internally, there should be no recesses that cannot be cleaned, and a minimum

of projecting ledges, shelves, fixtures and fittings (US FDA. 2004).

B) Floors.

Floor covering should be selected for durability as well as for cleanability and resistance to the chemicals with which it is likely to come into contact. Terrazzo provides a hard-wearing finish; both tiles and poured-in-place finishes are available. The latter is preferable for manufacturing areas; if tiles are used, care must be taken to ensure effective sealing between the tiles, which, otherwise, could become a harboring area of dirt and microorganisms (US FDA. 2004).

A) Ceilings.

Suspended ceilings may be provided in office areas, laboratories, toilets, and cafeterias. They usually consist of lay-in acoustical panels of non brittle, non friable, non asbestos and non combustible material. Manufacturing areas require a smooth finish, often of seamless plaster or gypsum board. All ceiling fixtures such as light fittings, air outlets and returns should be designed to assure ease of cleaning and to minimize the potential for accumulation of dust (US FDA. 2004).

B) Services.

In the building design, provisions must be made for drains, water, steam, electricity, and other services to allow for ease of maintenance. Access should, ideally, be possible without disruption of activity within the actual rooms provided with the services. Doors and window-frames should all have a smooth, hard, impervious finish, and should close tightly. Window and door frames should be fitted flush, at least on sides facing inward to processing areas. Doors, except emergency exits, should not open directly from production areas to the outside world. Any emergency exit doors should be kept shut and sealed, and designed so as to be openable only when emergency demands. Despite the space-saving advantages, sliding doors should be avoided because of the difficulty of maintaining the sliding gear in a clean condition (Signore & Jacobs,2005).

C) Layout concept

The layout design of the facility must minimize the possibility of mix-ups or contamination.

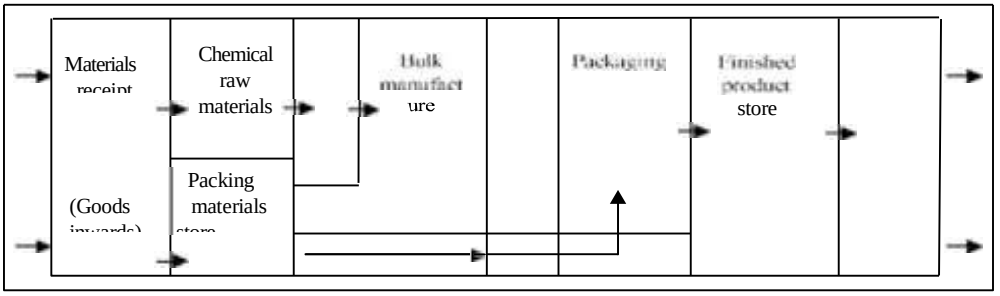


Fig. **12. Simple Single-Story Linear Flow Pattern for Pharmaceutical Manufacturing. Sampling Quarantine and** Release Stages not shown. Not a scale (Source: Sharp, 2000)

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F) Heating, Ventilation and Air-Conditioning (HVAC)

HVAC play an important role in ensuring the manufacture of quality medicinal products. A well designed HVAC system will also provide comfortable conditions for operators. HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross-contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system (WHOTRS, 937 2006).

F) Lighting

Lighting levels should be adequate to permit operators to do their work properly, accurately, and attentively. Lighting of production and packaging areas should be sufficiently bright to enable good vision (Table 4). Although daylight is preferable from a number of aspects, it needs to be noted that a number of pharmaceutical products and materials are affected by UV light

G) Water for Pharmaceutical Use (WPU)

Water is the most widely used substance in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds

a. Drinking Water is unmodified except for limited treatment of the water derived from a natural or stored source.

b. Purified Water (PW) should 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 (WHOTRS, 929 2005).

H) Electricity

In general the electricity supply is made through concealed wiring with five wires (three phase wires, one neutral wire and one ground wire) for three-phase connections and three wires (one phase wire, one neutral wire and one ground wire) for single-phase connections using suitable size wires. Conductors of a three- phase system are usually identified by a colour code, to allow for balanced loading and to assure the correct phase rotation for induction motors (Wikipedia. (2012b).

❖ **Equipment**

Manufacturing equipment should be capable of producing products, materials, and intermediates that are intended and that conform to the required or specified quality characteristics. Furthermore, the equipment must be designed and built so that it is possible (and relatively easily possible) to clean it thoroughly. Surfaces that come into contact with products should have smooth, polished finishes, with no recesses, crevices, difficult corners, uneven joints, dead-legs, projections, or rough welds to harbor contamination or make cleaning difficult. Equipment must also be capable of withstanding repeated, thorough cleaning. Traces of previous product, at levels that might be acceptable in other industries, are totally unacceptable in the manufacture of medicines. there are two major concerns:

1. The possibility of contamination, or degradation, of the product by the material from which the equipment is constructed
2. The action of the product, or material in-process, on the material from which the equipment is constructed (Chaloner-Larsson, 1997) .



Fig 14 : Granulation Line

❖ **Materials**

Material can be active drug or inactive substances

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- **Maintenance and Storage of Material :**

Materials must be procured only from approved suppliers how have consented to provide materials in keeping with quality specifications of the drug product manufacturer
It is advisable for pharmaceuticals manufacturers to enter into contracts with specific vendors after performing a vendor audit that provides an assurance of row materials

- **Receiving Handling and Storage of Material :**

Specific written procedures must be prepared to describe how materials will be received

, identified, stored , handled , sampled , tasted accordingly approved or rejected and these procedures must be followed by written when receiving materials , the consignments must be visually examined and the labels checked to confirm the content, quantity integrity of seals and to verify that there is no damage or contamination
Any damaged containers found must be separated , details recorded and inform to the suppliers .
The materials must be stored under quarantine until samples have been drawn and tasted have performed .

- **Sampling :**

Representative samples must be drawn from each shipment of each lot. If different batches are present in a single shipment ,samples must be drawn from each of those. The quantity must be sufficient to perform all required tests and reserve when specified Statistical criteria must also be used to determine quantity og samples drawn.
Samples must be drawn from the bottom ,middle and top of the containers and marked Samples-holding containers shall be labelled with details of name of material, lot numbers, container numbers, date of sampling, name of person collecting the samples.

- **Testing of samples :**

At least one specific test must be performed to verify the materials identity .
Tests must be carried out to determine conformity with predetermined Specifications for quality, strengths and purity.
Materials that are liable to contamination with adulterants, or insect infestations or filth must be examined for such contaminants.
If materials are prone to microbial contamination, microbiological testes must be performed to test for it.

- **Approval/Rejection of Materials**

All materials that meet the manufacturers quality requirements of identity, quality, purity and strength and other tests are to be approved for use. Materials not meeting these requirements must be rejected.

- **Labeling**

Labels must carry the name of the product the company's unique reference code , manufacturers name and address, there assigned batch number. labels are given as : QUARANTINE, black print on a yellow background, for RELEASED green print on a white background, and for REJECTED red print on a white background.

- **Handling Rejected Materials :**

Rejected materials must be identified with appropriate labels and kept in a quarantine until it safely get disposed . there use in manufacturing operations must be avoided

- **Containers and closers**

It must not be additive , reactive or absorptive.
They should not cause a change in the identity , safety , quality , strength or purity of drug They must protect the formulations from contamination and deterioration They must be clean and if required sterilize to remove contamination

❖ **Documentation**

Good documentation is an essential part of the QA system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a medicine for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer
(WHO TRS, 961 2011).

The objectives are, in short :

1. To state clearly, in advance and in writing, what is to be done.
2. To do it — in accordance with those instructions .
3. To record what was done and the results of doing it.

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❖ **Holding and distribution**

It cannot, indeed must not, be considered that concern for the quality of the products of the pharmaceutical industry may cease at the point where the product is filled, sealed, labeled, and approved or released by QC. True QA should extend right up to the point where the product is delivered to the ultimate consumer — the patient. Certainly, there will come a point where the influence that the manufacturer is able to exert will significantly decline. For example, the manufacturer can do little more than advise the dispensing pharmacist on the correct handling and storage of his drug products. Thereafter, the influence of the manufacturer becomes distinctly tenuous. Despite warnings and advice to patients given in enclosure leaflets, it does seem that many patients neither handle nor take their medicines properly. That said, it is incumbent upon pharmaceutical manufacturers to ensure that having manufactured, packaged and labeled their products, the quality (i.e., "fitness") of these product remains unimpaired for as far along the supply chain as they are able to exert influence. Manufacturers who distribute via external wholesale dealers should thus ensure that any such wholesale dealer is, indeed, in possession of an authorized consolidated components of GMP will cover all the requirements made by different authorities and also satisfy the WHO GMP guidelines for manufacturing of drugs.

CONCLUSION

GMP is a production and testing practice that helps to ensure in built quality product. Many countries have legislated that pharmaceutical companies must follow GMP procedures , and have created their own GMP guidelines that correspond with their legislation. Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicines

The holder of a manufacturing authorization must manufacture quality medicines so as to ensure the products fit for the intended use, comply with the requirement of marketing authorization and place patients in safe with adequacy, quality and efficacy of the product. Quality objective can be achieved only through careful planning and implementation of QA system and practical implementation of GMP. The effective implementation of GMP requires extensive care and knowledge about the different components of GMP that should be incorporated form the inception of the manufacturing building and product development till the production.

The compliance to QA/GMP does not happen by accident. The GMP compliance can be achieved as the result of careful planning and installation of quality system. The manufacturers remain responsible for product quality till the shelf life of the product. The effective implementation of GMP requires top level commitment and support from all level of employees of the organization and different external bodies such as government regulatory agencies, material suppliers, distributor, wholesalers, retailers, medical practitioners and the end users of the medicines.

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