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A Review on Evolution of Good Manufacturing Practices in the Pharmaceutical Industry

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ABSTRACT

Good manufacturing practices (GMP) is a part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP guidelines provide minimum requirements for pharmaceutical or a food product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public**.** Good Manufacturing Practices is part of quality assurance that ensures that products are regularly produced and checked to meet quality standards and marketing authorizations for their intended use. These standards set minimum standards for pharmaceutical or food manufacturers to provide quality, safe products for consumers and society. A component of quality assurance known as "good manufacturing practices" guarantees that goods are continuously produced and controlled to the quality requirements relevant to their intended use and as mandated by the marketing license. GMP rules provide minimum standards that manufacturers of food or pharmaceutical items must fulfill to ensure that their products are safe for consumers and do not pose any risks. The safety and effectiveness of medical products are dependent on the healthcare industry upholding high standards of quality. The manufacture, control and quality assurance of medicines, medical devices and other healthcare items are made easier with the support of a system of rules and regulations known as good manufacturing practices or GMPs. In order to protect patient health and uphold public confidence this research study examines the importance of GMP in the healthcare sector.

KEYWORDS- GMP, Quality, Health

INTRODUCTION

The term GMP was introduced to regulate manufacturing and packaging operations in the pharmaceutical industry. The Medicine Inspector 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, the manufacturing of drug carried out under the Medicines Act. It was a relatively light volume of 20 pages, and was reissue third impression in 1972, with the addition of a 2-page appendix on sterile medicinal products. The color of its cover, it known as the Orange Guide. The second edition (52 pages, including five appendices) was published in 1977. The third edition (110 pages, five appendices) was published in 1983[1]. 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 regulation was similar in concept to the Orange Guide, but enforceable by law whereas the UK guide as an advisory. US congress passed the Federal Ani-tempering Act in 1983, making it a crime to tamper with packaged consumer products [2].

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).[3]

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 been carried out 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)[4]. 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.

Figure.1 Components of GMP

GMP is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designated to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. GMP-is intended to assure that raw materials used in the manufacture of drugs are of i.Known quality ii. Standardized quality iii. Free from contamination.[5] A component of quality assurance known as good manufacturing practice (GMP) makes ensuring that goods are regularly manufactured and controlled to the quality standards necessary for their intended use and as stipulated by the marketing authorization. The primary goal of GMP is to reduce the hazards that are present in the production of pharmaceuticals, which can be broadly divided into two categories incorrect labeling and cross-contamination/mix-ups.[6] Above all, producers must ensure that their products do not put patients at risk by being of insufficient safety, efficacy, or quality. For this reason, risk assessment has become a crucial component of WHO quality assurance recommendations. A component of the entire system for ensuring the quality of drugs is inspections. Pharmaceutical manufacturing facilities are inspected with the intention of either enforcing compliance with Good Manufacturing Practices (GMP) or granting permission to manufacture particular pharmaceutical goods, usually in connection with an application for marketing authorization. In order to remove the risk provided by the infiltration of phony medications, another facet of pharmaceutical inspection involves keeping an eye on the quality of pharmaceutical products along the distribution chain, from the point of manufacture to the point of delivery to the receiver.[7]

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Guide, but enforceable by law whereas the UK guide as an advisory. US congress passed the Federal Ani-tempering Actin 1983, making it a crime to tamper with packaged consumer products **[9]**. In the 1980, US FDA began publishing series of guidance documents that have a major effect on our interpretation of current GMP (cGMP). A "Guide to Inspection of Computerized Systems in Drug Processing" was published in 1983 and "Guideline on General Principles of Process Validation" was published in 1987. March 1997, the US FDA issued 21 CFR Part 11 which dealt with the use of electronic records and signatures. In 2000, US FDA introduced a guidance document on the incorporation of risk management into device development[10]

GOOD MANUFACTURING PRACTICES (GMP) GUIDELINES

Many countries have legislated that pharmaceutical and medical device companies created their own GMP guidelines that correspond with their legislation. Basic concepts of GMP guidelines goal of safeguarding the health of the patient as well as producing good quality medicine, medical devices or active pharmaceutical products**[11]**. The formalization of GMP commenced in the 1960s and their effect in over 100 countries ranging from Afghanistan to Zimbabwe. Examples of these include the following.

a. Pharmaceutical Inspection Convention (PIC):- Guide to GMP for pharmaceutical products-Australia, Austria, Belgium, Canada, Italy, Latvia, Liechtenstein, Denmark, Finland, France, Hungary, Ireland, Malaysia, The Netherlands, Norway, Poland, Portugal, Romania, Singapore, Slovak Republic, Spain, Sweden, Switzerland, and the United Kingdom.

b. Association of South-East Asia Nations (ASEAN): General guidelines Brunei Darussalaam, Indonesia, Lao PDR, Malaysia,Cambodia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

c. European Economic Community (EEC): Guide to GMP for medicinal products Austria, Belgium, Denmark, Ireland, Italy, Luxembourg, the Netherlands, Finland, France, Germany, Greece, Portugal, Spain, Sweden, and the United Kingdom. In general, GMP has been issued guides to the achievement of consistent product quality, with interpretation and individual variations being accepted. GMP enforced in the United States by the US FDA, under Section 501(B) of the 1938 Food, Drug, and Cosmetic Act (21 USCS § 351). The regulations use the phrase "current good manufacturing practices" (cGMP) and it describes the guidelines **[12]**. The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world including country like Nepal. The European Union's GMP (EU-GMP) enforces similar requirements to WHO GMP, as does the Food and Drug Administration's version in the US. Similar GMPs are used in other countries, with Australia, Japan, Canada, Singapore and others having highly developed/sophisticated GMP requirements. In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP commonly referred to as "The Orange Guide", which is officially known as Rules and Guidance for Pharmaceutical Manufacturers and Distributors **[13]**

The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world including country like Nepal. The European Union's GMP (EU-GMP) enforces similar requirements to WHO GMP, as does the Food and Drug Administration's version in the US. Similar GMPs are used in other countries, with Australia, Canada, Japan, Singapore and others having highly developed/sophisticated GMP requirements. In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in what is commonly referred to as "The Orange Guide", which is officially known as Rules and Guidance for Pharmaceutical Manufacturers and Distributors. In general, GMP inspections are performed by national regulatory agencies. GMP inspections are performed in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency (MHRA); in the Republic of Korea (South Korea) by the Korea Food & Drug Administration (KFDA); in Australia by the Therapeutical Goods

Administration (TGA); in South Africa by the Medicines Control Council (MCC); in Brazil by the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil) (ANVISA). In India GMP inspections are carried out by state Food and Drug Administration (FDA) and these FDA report to Central Drugs Standard Control Organization: in Nepal, GMP inspections are carried out by the Department of Drug Administration (DDA), and in Pakistan by the Ministry of Health. Nigeria has National Agency for Food and Drug Administration and Control (NAFDAC). Each of the inspectorates carry out routine GMP inspections to ensure that drug products are produced safely and correctly; additionally, many countries perform pre-approval inspections (PAI) for GMP compliance prior to the approval of a new drug for marketing (Wikipedia, 2012a).

Need of GMP: -

The necessity of Good Manufacturing Practices (GMP) arises from the limitations of final product testing in ensuring quality, efficiency, and safety, as it may not always detect contamination or errors. GMP ensures adherence to predetermined specifications, minimizes contamination risks like microbial contamination, eliminates errors, and facilitates the production of consistent quality products.

Importance of GMP: -

Good Manufacturing Practice (GMP) is crucial in ensuring that pharmaceuticals, food, and other products are consistently produced and controlled to the quality standards appropriate to their intended use.

GMP provide a system of processes, procedures, and documentation to assure a product's identity, strength, quality, and purity. Adhering to GMP standards helps to minimize risks involved in pharmaceutical production, ensuring the safety and efficacy of products for consumers.

Purpose of GMP

The World Health Organization's "good manufacturing guidelines" are interpreted as GMP rules under the National Medicines Regulatory Authority Act No. 5 of 2015. For the purpose of regulating the manufacture of pharmaceuticals, the National Medicines Regulatory Authority (NMRA) thus accepts the WHO GMP principles along with any changes that come forth. It is anticipated that manufacturers will follow Good Manufacturing Practices in all aspects of their business. A GMP inspection or many may be required before pharmaceutical manufacturers are granted site approval in Sri Lanka to seek for marketing authorization. The NMRA is required to periodically conduct normal inspections as well as ad hoc inspections, such as whenproducts are licensed for commercialization in Sri Lanka. Along with all WHO GMP Guidelines, this guideline will be the primary foundation for the GMP inspection of such production facilities.[14,15]

Principles: -

Good Manufacturing Practices (GMP) is a system and process that ensures that products are manufactured and maintained in accordance with quality standards. Key principles include maintaining a clean and hygienic production environment, implementing quality control systems and documenting all processes for traceability and accountability.

Figure. 2 Different Parts of GMP

Components 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). The manufacturing premises of good design and regularly monitored is the most important component. There should be quality control of finished product, raw materials and packaging materials. The equipment of good design is to be considered and all the equipments are required to be maintained properly. There should be a correct choice of cleaning equipment. The staffs should be trained well and should be wearing protective clothing while on work. There should be written procedures for carrying out the operations.

- Quality Management
- Quality Assurance
- Good Manufacturing Practice (GMP) for Medicinal Products
- Quality Control
- Sanitation and Hygiene
- Qualification and Validation
- Complaints and Product Recall
- Contract Production and Analysis
- Self-Inspection, Quality Audits and Supplier's Audits and Approval
- Personnel, Training and Personal Hygiene
- Premises
- Equipment

- Materials
- Documentation
- Holding and Distribution

QUALITY MANAGEMENT

The holder of a manufacturing authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors **[16]**. In the pharmaceutical industry at large, 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 **[17]**.

QUALITY ASSURANCE (QA)

QA is a wide ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use. QA, therefore, incorporates GMP and other factors such as product design and development **[18]**. The system of QA appropriate for the manufacture of pharmaceutical products should ensure that:

a. Pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP).

b. Production and control operations are clearly specified in a written form and GMP requirements are adopted.

c. Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials.

d. All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.

e. The finished product is correctly processed and checked, according to the defined procedures, pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products.

f. Satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;

g. Deviations are reported, investigated and recorded.

h. Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

Tragic incidents of 20th century vs. birth of GMP

In 1901 children who received antitoxin for diphtheria treatment died of tetanus because the horse serum that had been used to prepare the antitoxin was contaminated with tetanus. Thus, the importance of high-quality raw materials was demonstrated, along with the ability of animal-derived materials to pass diseases both known and unknown. The Biologics Control Act was passed in 1902, to improve the assurance of safety and purity of sera, vaccines, and other biological products. The Food and Drugs Act was first passed and put into law in 1906 and revised as the Food, Drug and Cosmetic Act of 1938 (Shadle 2004). In 1905, a book called The Jungle helped catalyze public opinion for change. "Muckraker" and social reformer Upton Sinclair wrote about the Chicago meat packing industry – the unsanitary conditions in which animals were slaughtered and processed and the practice of selling rotten or diseased meat to the public. He also reported that ground meat sometimes contained remains of poisoned rats and even unfortunate workers who fell into the machinery. Sinclair's main interest was in bringing attention to the miserable working conditions and the plight of the impoverished factory workers, many of whom were immigrants. The Jungle had a major impact on the American public. Congress passed the Pure Food and Drug Act in 1906, and for the first time it became illegal to sell contaminated (adulterated) food or meat (Shadle 2004)[**19**]. In 1937, a public health disaster tragically drove home the need for a stronger federal law. Sulphanilamide, the first "wonder drug" and a popular and effective treatment for diseases like strap throat and gonorrhoea, was formulated into an elixir and marketed for use in children. But the liquid formulation contained a poison, the same chemical used in antifreeze, and it killed 107 people, most of them children. In response, Congress passed the Federal Food, Drugs and Cosmetic (FD & C) Act of 1938. for the first time, companies were required to prove that their products were safe before marketing them (FDA overview). In 1941, nearly 300 people were killed or injured by one company's sulfathiazole tablets, a sulfa drug tainted with the sedative phenobarbital. That incident caused FDA to drastically revise manufacturing and quality control requirements, leading to what would later be called GMPs (Time Line).

Current scenario of international GMP

GMP grew out of the realization that end-point quality testing was insufficient to assure the quality of the individual medication unit (the tablet, the capsule, the vial) dispensed to the patient, but rather quality needed to be assured at each step of the manufacturing process to be as certain as possible that each dosage unit met its quality specifications. Prior to this realization, pharmaceutical product quality was assured by pharmacopoeal "end point" testing (GMP worldwide). Good Manufacturing Practices (GMPs) is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization or product specification. GMP is concerned with both production and quality control. Worldwide, there are different official regulatory statements and guidelines, national and international, on Good Manufacturing Practices for pharmaceutical (or "drug" or "medicinal") products. They may be regulations (as in the US, Japan or Korea), directives (as in the EU), guides (as in the UK), codes (as in Australia), or WHO code (as in many Southeast Asia Countries). Out of them, following stands out as being the most influential and most frequently referenced (Patel and Chotai 2006):

- The US Current Good Manufacturing Practices for Finished Pharmaceuticals regulations (the "US cGMPs")
- The Guide to Good Manufacturing Practice for Medicinal Products of the European Union (the "EC GMP Guide") (Eudralex)
- ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH 2000).
- WHO good manufacturing practices (GMP 2003).

The other regulation referred by the Indian pharmaceutical manufacturers is Schedule M "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products" The Drugs And Cosmetics Act And Rules, India (Schedule 2005). The glance of major GMP regulatory agencies or guidelines is highlighted in Tables 2 and 3 respectively. The related site contains detailed information pertaining to GMP.

Good manufacturing practice for herbal medicines

The general principles of GMP are set out in the parent guidelines (see section II). Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, are covered by other guidelines [20] The first critical step of their production where the application of GMP starts should be clearly designated (see subsection 16.1). This is of particular importance for those products which consist solely of comminuted or powdered herbal materials.

Sanitation and hygiene

Because of their origin, herbal materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, herbal products that may be especially prone to microbiological contamination are produced. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene during manufacture is necessary.

Water supply to the manufacturing unit should be monitored, and, if necessary treated appropriately to ensure consistency of quality.

Waste from the manufacturing unit should be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste-bins should be available, emptied and cleaned as needed, but at least daily.

Qualification and validation

Qualification of critical equipment, process validation and change control are particularly important in the production of herbal medicines with unknown therapeutically active constituents. In this case, the reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches.

The written procedure should specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.

A formal change control system should be established to evaluate the potential effects of any changes on the quality of the herbal medicines, particularly content of the active ingredients. Scientific judgement should be used to determine which additional testing and validation studies are appropriate to justify a change in a validated process

Complaints

The person responsible for handling complaints and deciding on the measures to be taken to deal with them should have appropriate training and/or experience in the specific features of the quality control of herbal medicines. There are basically two types of complaint, product quality complaints and adverse reactions/events.

The first type of complaint may be caused by problems such as faulty manufacture, product defects or deterioration as well as, particular to herbal medicines, adulteration of the herbal material. These complaints should be recorded

in detail and the causes thoroughly investigated (e.g. by comparison with the reference samples kept from the same batch). There should also be written procedures to describe the action to be taken.

Product recalls

The product recall procedure depends very much on the national regulations. There should be a standard operating procedure (SOP) for storage of recalled herbal medicines in a secure segregated area, complying with the requirements specified under subsection 12.1 (Storage areas), while their fate is decided.

Contract production and analysis

The contract partner should have adequate premises and equipment for the production of herbal medicines according to GMP. Validated methods should be applied for cleaning the equipment and premises carefully before using them to produce different herbal medicinal, food or cosmetic products. In the case of raw materials used for producing food, it is realistic to require manufacturing departments to be separated from those where the plant raw material will be cut or powdered for use in the preparation of medicines.

Self-inspection

At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines.

Personnel

General guidance in relation to personnel involved in the manufacture of medicinal products is given in the parent guide (see section II). The release of herbal medicines should be authorized by a person who has been trained in the specific features of the processing and quality control of herbal materials, herbal preparations and finished herbal products.Personnel dealing with the production and quality control of herbal medicines should have adequate training in the specific issues relevant to herbal medicines.

Training

The personnel should have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, photochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of herbal medicines).Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

Personal hygiene

Personnel entrusted with the handling of herbal materials, herbal preparations and finished herbal products should be required to have a high degree of personal hygiene and to have received adequate training in maintaining appropriate standards of hygiene. The personnel should not work if they have infectious diseases or skin diseases. Written procedures listing the basic hygiene requirements should be made available.

Premises

As a general principle, premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to WHO good manufacturing practices for pharmaceutical products: main principles (see section II).Because of their potential for degradation and infestation with certain pests as well as their sensitivity to microbiological contamination, production, and particularly storage, of herbal materials and herbal preparations assume special importance.

Storage areas

Storage areas should be well organized and tidy. Special attention should be paid to cleanliness and good maintenance. Any accidental spillage should be cleaned up immediately using methods that minimize the risk of cross contamination of other materials, and should be reported.The set-up of storage areas depends on the type of materials stored. The areas should be well labelled and materials stored in a such a way as to avoid any risk of cross-contamination. An area should be identified for the quarantine of all incoming herbal materials.

Production areas

Production areas should comply with the general requirements of WHO good manufacturing practices for pharmaceutical products: main principles (see Section II). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. Moreover, the special nature of the production of herbal medicines requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism should be employed to prevent accumulation of fumes and vapours. To facilitate cleaning and to avoid cross-contamination, adequate precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g. by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

Equipment

Processing of herbal materials may generate dust or material which is susceptible to pest-infestation or microbiological contamination and cross contamination. Effective cleaning of the equipment is therefore particularly important. Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment should be dried immediately after cleaning to prevent the growth of microorganisms. Cleaning with compressed air and brushes should be done with care and avoided if possible, as these methods increase the risk of product contamination.

Non-wooden equipment should be used unless tradition demands wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets, hoppers, etc.), this should be dedicated, unless otherwise justified. When such equipment is used, it is advisable that it does not come into direct contact with chemicals or contaminated material. If the use of wooden equipment is unavoidable, special consideration must be given to its cleaning as wooden materials may retain odours, be easily discoloured and are easily contaminated.

Materials

All incoming herbal materials should be quarantined and stored under appropriate conditions that take into account the degradability of herbal materials and herbal preparations Only permitted substances should be used for fumigation, and allowable limits for their residues together with specifications for the apparatus used should be set according to the national regulations.

Reference samples and standards

The reference standard for a herbal medicine may be a botanical sample of the herbal material; a sample of the herbal preparation, e.g. extract; or a chemically defined substance, e.g. a known active constituent, a marker substance or a known impurity. The reference standard should be of a quality appropriate to its purpose. If the herbal medicine is not described in a recognized pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the medicinal plant (e.g. if the whole medicinal plant is a tree) should be

available. All reference standards should be stored under appropriate conditions to prevent degradation. Their expiry and/or revalidation date should be determined and indicated.

Documentation

The general principles for documentation are set out in the WHO good manufacturing practices for pharmaceutical products: main principles (see section II).

Specifications

The specifications for herbal starting materials, for herbal preparations and finished herbal products are primarily intended to define the quality rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring safety and efficacy. Consistent quality for herbal medicines (finished herbal products) can only be assured if the starting herbal materials are defined in a rigorous and detailed manner. In some cases more detailed information may be needed on aspects of collection or agricultural
production. For instance, the selection of seeds, conditions of cultivation and harvesting are important aspects in producing a reproducible quality of herbal medicines [*7*]. Their characterization (which also includes a detailed evaluation of the botanical and phytochemical aspects of the medicinal plant, manufacture of the herbal preparation and the finished herbal product) is therefore essential to allow the establishment of specifications which are both comprehensive and relevant.

Good documentation is an essential part of the QA system and GMP. The various types of documents used should be fully defined in the manufacturer's quality management system (QMS). The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products **[21]**. Given below is a list of the most common types of documents along with a brief description of each.

Site Master File: A document describing the GMP related activities of the manufacturer.

Quality Manual: A global company document that describes, in paragraph form, the regulations and/or parts of the regulations that the company is required to follow.

Policies: Documents that describe in general terms, and not with step-by-step instructions, how specific GMP aspects (such as security, documentation, health, and responsibilities) will be implemented.

Standard Operating Procedures (SOPs): Step-by-step instructions for performing operational tasks or activities.
Batch Records: These documents are typically used and completed by the manufacturing department. Batch records provide step-by-step instructions for production-related tasks and activities, besides including areas on the batch record itself for documenting such tasks.

Test Methods: These documents are typically used and completed by the quality control (QC) department. Test methods provide step-by-step instructions for testing supplies, materials, products, and other production-related tasks and activities, e.g., environmental monitoring of the GMP facility.

Logbooks: Logbooks are used for documenting the operation, maintenance, and calibration of a piece of equipment. Logbooks are also used to record critical activities, e.g., monitoring of clean rooms, solution preparation, recording of deviation, change controls and its corrective action assignment.

Batch processing record- A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved manufacturing formula and processing instructions, and should contain the following information: a. The name and batch number of the product. b. Dates and times of commencement, of significant intermediate stages and of completion of production. c. Identification of the operator who performed each significant step of the process and, where appropriate, the name of any person who checked these operations. d. The batch number and analytical control number as well as the quantities of each starting material actually weighed. e. A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained. f. The product yield obtained at different and pertinent stages of manufacture. g. Notes on special problems including details, with signed authorization for any deviation from the manufacturing formula and processing instructions. h. Approval by the person responsible for the processing operations.

Batch packaging record-A batch packaging record should be kept for each batch or part batch processed. The batch packaging record should contain the following information: a. The name and batch number of the product. b. The date and times of the packaging operations. c. Identification of the operator who performed each significant step of the process and, where appropriate, the name of any person who checked these operations. d. Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls. e. Details of the packaging operations carried out, including references to equipment and the packaging lines used. f. Whenever possible, samples of printed packaging materials used, including specimensof the batch coding, expiry dating and any additional overprinting. g. The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. h. Approval by the person responsible for the packaging operations.

Quality Control System (QCS): -

- Quality control will include testing, documentation and release procedures.
- By sampling. Standards that are not limited to laboratory studies should be considered in all options.
- About good things. Other responsibilities of this department include the development, measurement, evaluation and implementation of all quality control systems and procedures.
- All products are shipped after approval by QC department. "All equipment and testing procedures must be calibrated and verified before use in routine testing. Equipment calibration and verification procedures should be performed regularly.
- Pharmacopoeias, reference standards, reference spectra, other reference materials and technical information (if required) must be available at the licensee's quality control facility.[22]

Common problems in GMP Execution: -

1. Organization:

- Lack of Commitment.
- Lack of Execution Resources.

2. Equipment: -

- Not calibrated.
- No balance test before use.
- Rust Incorrect storage location.

3. Layout and Construction: -

- Protecting the environment is not enough.

- There is no quarantine.

4. Documentation and recording: -

- No signature, no counter check.
- Made Improper correction.
- No written procedure.
- Incomplete complaint record.

5. Labelling: -

- Status not defined clearly.
- Poor labelling control.
- Release label not kept securely.

IMPORTANCE OF GMP

Good Manufacturing Practices are a critical system that all manufacturing facilities should implement. They help ensure the proper design, monitoring, and control of the manufacturing processes and facilities. Companies that adhere to these standards help to assure the identity, strength, and quality of their products. When implemented, GMP can help to cut down on facility losses and waste and also help to protect the company, consumer, and the environment from harm.

The Current Good Manufacturing Practices are set by the FDA and give manufacturers across all industries a set of standards to strive for. They help facilities earn and maintain the trust of consumers who want to know the products they buy are manufactured in safe, well-regulated environments, and to government standards.

Good Manufacturing Practices in food industry manufacturers are especially vital these days, due to the increasing number of food recalls occurring.

CONCLUSION

Good Manufacturing Practices (GMP) are important guidelines for the quality, safety and effectiveness of pharmaceuticals, foods and other products. By following GMP standards, companies can maintain consistency in their production processes, reduce the risk of contamination or errors, and ultimately produce quality products that comply with legal requirements. In general, GMP plays an important role in protecting public health and ensuring consumers have confidence in the products they use. 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. GMP is a testing and production procedure that aids in guaranteeing a well-built product. Pharmaceutical businesses are required by law in many nations to adhere to GMP protocols, and these countries have also established their own GMP rules that are in keeping with their legal frameworks. The fundamental principles behind each of these standards are essentially consistent with the end objectives of protecting patient health and manufacturing high-quality medications. Only with meticulous planning, QA system development and GMP application in practice can the quality objective be met. Extensive attention to detail and a thorough understanding of the many GMP components which should be integrated from the beginning of product development and manufacturing facilities to production are necessary for the effective implementation of GMP.

The last few years has seen the FDA steer industry further in the direction of a quality-by-design (QbD) approach, and away from the quality-by-testing (QbT) approach traditionally taken by the pharmaceuticals sector. This move has largely been lauded by business as a sensible move likely to ensure consistent quality of the end product. The shift in focus is expected to bring about a well-needed modernization to the sector and allow new ideas the breeding ground needed to flourish. As pharmaceutical manufacturing evolves from an art to a science and engineering based activity, application of this enhanced science and engineering knowledge in regulatory decision–making, establishment of specifications, and evaluation of manufacturing processes should improve the efficiency and effectiveness of both manufacturing and regulatory decision–making, A Process and Analytical Technology (PAT) initiative has been initiated by the FDA and designed to revolutionize and improve many pharmaceutical processes. A regulatory framework, PAT discusses possible routes and opportunities to promote and encourage opportunities for innovation. Thus, it is necessary to continue with the efforts already made, which provided the current state of GMP, overcoming barriers and reaching new goals, promoting public and individual health, leading to a better quality of life for society in general.

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