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REVIEW ARTICLE

CURRENT GOOD MANUFACTURING GUIDELINES FOR MEDICINAL PRODUCT

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ABSTRACT

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. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance Incorporating Good Manufacturing Practice, and thus Quality Control and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance systems should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the manufacturing authorization and for the authorized person

Keywords: Good Manufacturing Practice, Quality control, Quality assurance, authorized

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 reissued 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 1983¹.

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 Anti-tampering

Act in 1983, making it a crime to tamper with packaged consumer products².

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 development³.

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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 products⁴. 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.

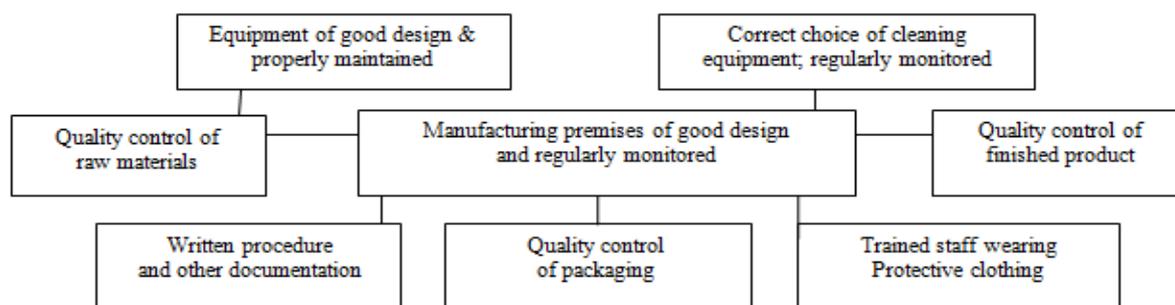
b. Association of South-East Asia Nations (ASEAN):-

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. The regulations use the phrase "current good manufacturing practices" (c GMP) and it describes the guidelines.⁵

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 made⁶. The essential components of GMP.



Components of Good Manufacturing Practice

Indian schedule M for GMP and requirements of premises, plant and equipment for pharmaceutical products. Part I includes general requirements, Warehousing area, Production area, Quality control area, Personnel, Ancillary area, Health, clothing and sanitation of workers, Manufacturing operations and controls, Sanitation in the manufacturing premises, Raw materials, Equipment, Documentation and Records, Labels and other printed materials, Quality assurance, Self inspection and quality audit, Quality control system, Specification, Master formula records, Packing records, Batch packaging records, Batch processing records, Standard operating procedures (SOPs) and records, Reference samples, Reprocessing and recoveries, Distribution records, Validation and process validation, Product recalls, Complaints and adverse reactions and Site-master file. Part I-A to part I-E mentions about the specific requirements for manufacture of different products and Part I-F mentions about the specific requirements of premises, plant and materials for manufacture of active pharmaceutical ingredients (bulk drugs). Part II describes the

Requirement of plant and equipments for various dosage forms⁴.

GOOD MANUFACTURING SERVICES –THE GENERAL/CURRENT STATE-

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 suppliers and by the distributors⁷. 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 management⁸.

QUALITY ASSURANCE

Quality Assurance 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 medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide. 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 within the company, by the company's suppliers and by the distributors. 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 development⁹.

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.

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS (GMP)

Good Manufacturing Practice is that part of Quality Assurance which ensures that Medicinal 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. Good Manufacturing Practice is concerned with both production and quality control. GMP is aimed primarily at diminishing the risks inherent in any pharmaceutical production¹⁰ The basic requirements of GMP are that:

- all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
- critical steps of manufacturing processes and significant changes to the process are validated;
- all necessary facilities for GMP are provided including:
 - a. appropriately qualified and trained personnel;
 - b. adequate premises and space;
 - c. suitable equipment and services;
 - d. correct materials, containers and labels;
 - e. approved procedures and instructions;
 - f. suitable storage and transport;
- iv. Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- v- Operators are trained to carry out procedures correctly;
- vi. Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected⁹. Any significant deviations are fully recorded and investigated;
- vii. Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- viii. The distribution (wholesaling) of the products minimizes any risk to their quality;
- ix. A system is available to recall any batch of product, from sale or supply;
- x. complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent re-occurrence¹¹

Sanitation and Hygiene

High level of sanitation and hygiene should be practiced in every aspect of manufacturing pharmaceutical products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive program of sanitation and hygiene¹²

Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

Personal hygiene procedures including requirement of using protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees on company property, e.g. contractor's employees, visitors, senior management and inspectors.

To assure protection of the product from contaminations as well as the safety of the personnel, they should wear clean body-coverings appropriate to the duties they perform, including appropriate hair covering. Soiled uniforms and soiled cleaning cloths (if reusable) should be stored in separate closed containers until properly laundered.

Detailed hygiene programmes should be established and adapted to the different needs within the manufacturing area. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out periodically for the work and personal health. Visual inspectors should also undergo periodic eye examination.

The areas, surfaces, and equipment in and on which products are made must be kept clean. Dirt, and the microbes that it can harbor, must not get into or on products. Disinfectants can be inactivated by dirt. Dirt (particularly oily or greasy films and protein like matter) can also protect microorganisms against the action of disinfectants. So, before disinfection, it is important to first clean surfaces. Where gross amounts of dirt are present, it may be necessary to first remove most of it by scrubbing. Then surfaces may be cleaned by the application of a cleaning agent, followed by rinsing¹³.

Validation

Validation is defined as the establishing of documented evidence which provides a high degree of assurance that

a planned process will consistently perform according to the intended specified outcomes. Validation studies should reinforce GMP and be conducted in accordance with defined procedures. Results and conclusions should be recorded. When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing¹⁴.

Qualification of systems and equipment is therefore a part of process of validation. It is a requirement of food and drug, pharmaceutical regulating agencies like FDA's guidelines. Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

- Equipment validation
- Facilities validation
- HVAC system validation
- Cleaning validation
- Process Validation
- Analytical method validation
- Computer system validation
- Packaging validation

Premises

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination.

Premises must be located, constructed, adapted, designed, and maintained to suit the operations to be carried out. The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products¹⁵. The choices of materials of construction for manufacturing facilities are numerous. Some examples are presented subsequently¹⁶.

- **a. Walls:** Walls in manufacturing areas, packaging areas and corridors should be of plaster finish on high-quality concrete blocks or gypsum board. The finish should be smooth, usually with enamel or epoxy paint. They should be washable and able to resist repeated applications of cleaning and disinfecting agents.
- **b. Floors:** Floor covering should be selected for durability as well as for clean ability and resistance to the chemicals with which it is likely to come into contact. Epoxy flooring provides a durable and readily cleanable surface.
- **c. Ceilings:** Suspended ceilings may be provided in office areas, toilets, laboratories and cafeterias. They usually consist of lay-in acoustical panels of non brittle, non friable, non asbestos and non

combustible material. Manufacturing areas require a smooth finish, often of seamless plaster or gypsum board. All ceiling fixtures such as light fittings, air outlets and returns should be designed to assure ease of cleaning and to minimize the potential for accumulation of dust.

- **d. Services:** In the building design, provisions must be made for drains, steam, electricity, water and other services to allow for ease of maintenance. Access should, ideally, be possible without disruption of activity within the actual rooms provided with the services. Doors and window-frames should all have a hard, smooth, impervious finish, and should close tightly. Window and door frames should be fitted flush, at least on sides facing inward to processing areas. Doors, except emergency exits, should not open directly from production areas to the outside world. Any emergency exit doors should be kept shut and sealed, and designed so as to be open able only when emergency demands¹⁷

Equipment

Manufacturing equipment should be capable of producing materials, products and intermediates that are intended and that conform to the required or specified quality characteristics. The equipment must be designed and built so that it is possible to clean it thoroughly. Surfaces that come into contact with products should

have polished finishes, smooth 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. Between batches all manufacturing equipment must be thoroughly cleaned and disinfected or sterilized¹⁸.

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.

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 from the inception of the manufacturing building and product development till the production.

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