WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 1, 298-311. Review Article ISSN 2277– 7105

A REVIEW ON ROLE OF GMP IN PHARMACEUTICAL INDUSTRY AND THEIR BENEFITS

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Article Received on
12 Nov. 2022,

Revised on 02 Dec. 2022,
Accepted on 22 Dec. 2022

DOI: 10.20959/wjpr20231-26645

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ABSTRACT

The term "good manufacturing practise," or simply "GMP," refers to a set of guidelines and industry standards that are intended to assist regulate the quality of pharmaceutical and other consumable items that are introduced to the market. GMP helps producers increase quality and reduce potential liability concerns in addition to safeguarding customers from faulty products. Anyway, that's the gist of it. If we go into more detail, GMP isn't simply a set of laws; it's a whole certification process. Nations all over the world put a lot of effort into setting up regulations and inspecting firms in accordance with those regulations to make sure they are adhering to international standards. If a product hasn't been certified, several nations won't permit its import.

INTRODUCTION

A good manufacturing practice (GMP) is a production and testing practice that helps to ensure a quality product. Many countries have legislated that pharmaceutical and medical device 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 medicine, medical devices or active pharmaceutical products. the world has gathered together to harmonize its practices and guides and the launching of the

FDA current good manufacturing practices – the cGMP; for the 21st century – there has been a growing awareness for the significance of the quality of the pharmaceutical products.

Methods:- A search was made of the following databases: WHO, FDA, ICH, and EU to download their corresponding guidelines. GMPs are 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) to describe these guidelines. Courts may theoretically hold that a drug product is adulterated even if there is no specific regulatory requirement that was violated as long as the process was not performed according to industry standards. 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 named so because of the color of its cover; it is officially known as Rules and Guidance for Pharmaceutical Manufacturers and Distributors.

The most important guidelines that are widely applied in the pharmaceutical industry are:
WHO guidelines.
FDA guidelines.
EU guidelines.
ICH guideline

WHY GMP IS REQUIRED

The Good Manufacturing Practices are prescribed to ensure that Raw materials used in the manufacture of pharmaceuticals are authentic, of prescribed quality and are free from contamination. The manufacture process is as has been prescribed to maintain the standards. Adequate quality control measures are adopted. The manufactured drug which is released for sale has the prescribed quality. To achieve the objectives listed above, each licencee all evolve methodology and Procedures for following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection. However, teaching institutions and registered qualified vaidas, siddhas and Hakeems who prepare medicines on their own to dispense to patients and not selling such drugs in the market are exempted from the purview of G.M.P.

GMP FOR PREMISES AND MATERIALS

General Requirements

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

Building and premises

The building(s) used for the factory shall be Designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948) the premises used for manufacturing, processing, warehousing, packaging labeling and testing purposes shall be Omitted by G.O.I. Notification No.G.S.R.462(E) dt.22106.1982.

Water System

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

Disposal of waste

(i) The disposal of sewage and effluents (solid, liquid and gas) from the manufactory shall be in conformity with their requirements of Environment Pollution Control Board.

(ii) All bio-medical waste shall be destroyed as per the provisions of the Bio Medical Waste (Management and Handling) Rules, 1996.

(iii) Additional precautions shall be taken for the storage and disposal of rejected drugs. Records shall be maintained for all disposal of waste.

(iv) Provisions shall be made for the proper and safe storage of waste materials awaiting disposal. Hazardous, toxic substances and flammable materials shall be stored in suitably designed and segregated, enclosed areas in conformity with Central and State Legislations.

WAREHOSING

Warehousing areas shall be designed and adapted to ensure good storage conditions. Receiving and dispatch bays shall protect materials and products from adverse weather conditions. There shall be a separate sampling area in the warehousing area for active raw materials and exipients. Segregation shall be provided for the storage of rejected, recalled or returned materials or products.

Production area

The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations. Pipe-work, electrical fittings, ventilation open in g sand similar services lines shall be designed, fixed and constructed to avoid creation of recesses.

Ancillary areas

Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas. Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users.

Quality control area

Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physic-chemical, biological, microbiological or radio-isotope analysis. The design of the laboratory shall take in to account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall be provided for a biological, microbiological and radio isotopes testing area.

Personnel

The manufacture shall be conducted under the direct supervision competent technical staff with prescribed qualifications and practical experience in the relevant dosage and / or active pharmaceutical products. The head of the Quality Control Laboratory shall be independent of the manufacturing unit. Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced. Number of personnel employed shall be adequate and in direct proportion to the workload.

Health, clothing and sanitation of workers

Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from tuberculosis, skin and other communicable or contagious diseases. A high level of personal hygiene shall be observed by all those engaged in the manufacturing processes.

Manufacturing operations and controls

All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labeled with the name of the product, batch number, batch size and stage of manufacture. Products not prepared under aseptic conditions are required to be free from pathogens like Salmonella, Escherichia coli, Pyocyanea, etc.

Sanitation in the manufacturing premises

The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material. The manufacturing areas shall not be used for storage of materials, except for the materialϖ being processed.

Raw materials

The licensee shall keep an inventory of all raw materials to be used at any stage ofϖ manufacture of drugs and maintain records as per Schedule U. All incoming materials shall be quarantined immediately after receipt or processing andϖ materials shall be checked to ensure that the consignment corresponds to the order placed. All incoming materials shall be purchased from approved sources under valid purchase vouchers. Raw materials in the storage area shall be appropriately labeled. Labels shall be clearly marked with the following information:

a. Designated name of the product and the internal co dereference, and analytical reference number;
b. Manufacturer’s name, address and batch number;
c. The status of the contents and the manufacturing date, expiry date and re-test date.

Equipment

For effective operations, the tablet production department shall be divided into four distinct and separate sections as follows:-

a. Mixing, Granulation and drying section.
b. Tablet compression section.
c. Packaging section (strip/blister machine wherever required).
d. Coating section (wherever required)

The Coating section shall be made dust free with suitable exhaust system to remove excess powder and fumes resulting from solvent evaporation. Area minimum additional area of thirty square meters for coating section for basic installation and ten square meters for ancillary area is recommended. The manufacture of hypodermic tablets shall be conducted under aseptic conditions in a separate air-conditioned room, the walls of which shall by smooth and washable. The manufacture of effervescent and soluble/dispersible tablets shall be carried out in air conditioned and dehumidified areas.

Quality assurance

The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that pharmaceutical products are designed and developed in a way that takes account of the requirement of Good Manufacturing Practices and other associated codes such as those of Good Laboratory Practices and Good Clinical Practices. Adequate arrangements are made for manufacture, supply and use of the correct starting and packaging materials. The finished product is correctly processed and checked in accordance with established procedures; THE pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of pharmaceutical products.

Self inspection and quality audit

To evaluate the manufacturer's compliance with GMP in all aspects of production and supplemented with a quality audit procedure for assessment of all or part of system with the specific purpose of improving it. Written instructions for self-inspection shall be up which shall include the following:

1. Premises including personnel facilities.
2. Maintenance of buildings and equipment.
3. Storage of starting materials and finished products, Equipment.
4. Production and in-process controls.
5. Quality control.

6. Sanitation and hygiene.
7. Documentation.
8. Validation and revalidation programmers.
9. Calibration of instruments or measurement system.
10. Recall procedures.
11. Complaints management.
12. Labels control.
13. Result of previous self-inspections and any corrective steps taken.

Validation and process validation

Validation studies shall be an essential part of Good Manufacturing Practices and shall beϖ conducted as per the pre-defined protocols. A written report summarizing recorded results and conclusions shall be prepared, documented and maintained. When any new master formula or method of preparation is adopted, steps shall be taken to demonstrate its suitability for routine processing. Significant changes to the manufacturing process, including any changes in equipment or materials that may affect product quality and/or the reproducibility of the process, shall be validated.

Requirements for manufacture of Oral solid dosage forms (tablets) General

The processing of dry materials and products creates problems of dust control and cross-contamination. Special attention is therefore, needed in the design, maintenance and use of premises and equipment in order to overcome these problems. Wherever required, enclosed dust control manufacturing system shall be employed.

Sifting, Mixing and Granulation

Unless operated as a closed system, mixing, siftingϖ and blending equipments shall be fitted with dust extractors. Residues from sieving operations shall be examined periodically for evidence of the presence of unwanted materials.

Compressions (Tablets)

Each tablets compressing machine shall be provided with effective dust control facilities to avoid cross contamination. Unless the same product is being made on each machine, or unless the compression machine itself provides its own enclosed air controlled environment, the machine shall be installed in separate cubic.

Coating (Tablets)

Air supplied to coating pans for drying purposes shall be filtered air and of suitable quality. The area shall be provided with suitable exhaust system and environmental control (temperature, humidity) measures.

Printing (Tablets)

Special care shall be taken to avoid product mix-up during any printing of tablets and capsules. Where different products, or different batches of the same product, are printed. Simultaneously, the operations shall adequately be segregated.

Packaging (Strip and Blister)

Care shall be taken when using automatic tablet and capsule counting strip and blister packaging equipment to ensure that all rogue tablets, capsules or foils from packaging operation are removed after\before a new packaging operation is commenced. Integrity of individual packaging strips and blisters shall be subjected to vacuum test periodically to ensure leak profess of each pocket strip and blister and records maintained.

Compilation of Key Gmp Requirements In Tablet Manufacturing

Quality management

The holder of a manufacturing authorize on 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.

Quality assurance

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that: Production and control operations are clearly specified and Good Manufacturing Practice.ϖ Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials. All necessary controls on intermediate products, and any other in-process controls and validations are carried out; The finished product is correctly processed and checked, according to the defined procedures.

Quality control

The basic requirements of Quality Control are that: Adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate.

For monitoring environmental conditions for GMP purposes;

The finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorization, are of the purity required, and are enclosed within their proper containers and correctly labeled. Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation relevant production documentation and an assessment of deviation from specified procedures.

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 normally be conducted and documented annually. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified. Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review.

Personnel

The heads of Production and Quality Control must be independent from each other. For medicinal products manufactured within the European Community, a qualified person must ensure that each batch has been produced and tested/checked in accordance with the directives and the marketing authorization.

Key Personnel include the head of Production, the head of quality control, and if at least one of these persons is not responsible for the duties described in article 51 of Directive 2001/83/EC1, the qualified person(s) designated for the purpose.

Training

The manufacturer should provide training for all the personnel whose duties take them in to production areas or into control laboratories and for other personnel whose activities could affect the quality of the product. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas.

Personnel hygiene

Detailed hygiene programmers should be Established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. All personnel should receive medical examination upon recruitment. Every person entering the manufacturing are as should wear protective garments appropriate to the operations to be carried out. Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes in to contact with the products.

Premises and equipment

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

Production area

Premises should preferably be laid out in such away as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to their qui site cleanliness level Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection. Drains should be of adequate size, and have trapped gullies.

Storage areas

Storage areas should be of sufficient capacity to allow orderly storage categories of materials and products. Storage areas should be designed or adapted to ensure good storage conditions. Receiving and dispatch bays should protect materials and products from the weather. There should normally be a separate sampling area for starting materials. Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

Quality control areas

Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biological, microbiological and radioisotopes, which should also be separated from each other. Sufficient space should be

given to avoid mix-ups and cross-contamination Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

Ancillary areas

Rest and refreshment rooms should be separate from other areas. Maintenance workshops should as far as possible is separated from production areas Animal houses should be well isolated from other areas, with separate entrance and air handling facilities.

Equipment

Manufacturing equipment should be designed, located and maintained to suit its intended purpose. Repair and maintenance operations should not present any hazard to the quality of the products. Washing and cleaning equipment should be chosen and used in order not to be a source of contamination. Production equipment should not present any hazard to the products. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods.

Master Formula Records

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

Documentation

The manufacturing records relating to manufacture of sterile products shall indicate the following details:-

1) Serial number of the Batch Manufacturing Record.
2) Name of the product
3) Reference to Master Formula Record.
4) Batch/Lot number
5) Batch/Lot size.
6) Date of commencement of manufacture and date of completion of manufacture.
7) Date of manufacture and assigned date of expiry.
8) Date of each step in manufacturing.
9) Names of all ingredients with the grade given by the quality control department.

10) Quality of all ingredients.
11) Control reference numbers for all ingredients.
12) Time and duration of blending, mixing, etc. whenever applicable.
13) pH of solution whenever applicable.
14) Filter integrity testing records
15) Temperature and humidity records whenever applicable
16) Records of plate-counts whenever applicable.
17) Results of pyrogen and/or bacterial endotoxin & toxicity.
18) Results of weight or volume of drug filled in containers.
19) Bulk sterility in case of aseptically filled products.
20) Leak test records.
21) Inspection records.
22) Sterilization records including autoclave leakage test records, load details, date, duration, temperature, pressure, etc.
23) Container washing records.
24) Total number of containers filled.
25) Total numbers of containers rejected at each stage
26) Theoretical yield, permissible yield, actual yield and variation thereof.
27) Clarification for variation in yield beyond permissible yield.
28) Reference numbers of relevant analytical reports.
29) Details of reprocessing, if any.
30) Name of all operators carrying out different activities.
31) Environmental monitoring records.
32) Specimens of printed packaging materials.
33) Records of destruction of rejected containers printed packaging and testing.
34) Signature of competent technical staff responsible for manufacture and testing.

Result of the tests relating to sterility, pyroxenes, and Bacterial end toxins shall be maintained in the analytical records. Validation details and simulation trail records shall be maintained Separately, Records of environmental monitoring like temperature, humidity, microbilogical data, etc. shall be maintained. Records of periodic servicing of HEPA filters, sterilizers and other periodic maintenance of facilities and equipment carried out also be maintained. Separate facilities shall be provided for filling-cum-sealing of Small Volume Parenterals in glass containers and/or plastic containers, It is advisable to provide separate facilities for

manufacture of Large Volume Parenterals in glass containers and / or plastic containers. For manufacture of Large Volume Parenterals in plastic containers, it is advisable to install automatic (with all operations) Form–Fill-Seal machines having one continuous operation.

CONCLUSION

GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company 'responsibility to determine the most effective and efficient quality process. Regulated country like EU does not have separate GMP guidelines for tablets but they have general rules, whereas ROW country like India has separate GMP guidelines for tablet manufacturing. In general, there are a number of similarities in terms of the content of the US and EC documents. The EC Guide is give with more detailed where it has common ground with the US c GMP and, in addition, covers topics not considered in the latter. EU used Guide to Good Manufacturing Practice in assessing applications for Manufacturing authorizations and as a basis for inspection of "manufacturers of medicinal products." Hence understanding the similarities and differences among GMP requirements for the tablet manufacturing & general requirement which are used in tablet manufacturing by the regulated countries shall benefit the pharmaceutical companies of both ROW countries & Regulated countries.

REFERENCE

1. Entralblatt fur Bakteriologie, Mikrobiologie und Hygiene. Serie B, Umwelthygiene, Krankenhaushygiene, Arbeitshygiene, Praventive Medizin, 01 Apr, 1989; 187(4-6): 546-556.
2. Brief History of the GMPs for Pharmaceuticals, Barbar K. Immel, Pharmaceutical Technology, July, 2001; 44–52.
3. The 1941 Supfathiazole Disaster and the birth of Good manufacturing practices, John P Swann, pharmacy in history, 1999; 41(1): 16-25.
4. Patel K. T., Chotai N. P. Pharmaceutical GMP: past, present, and future – a review. Pharmazie, 2008; (63)4.
5. Poluzzi, E., Raschi, E., Motola, D., Moretti, U., De Ponti, F., Antimicrobials and the risk of torsades de pointes: the contribution from data mining of the us fda adverse event reporting system. Drug Saf, 2010; 33: 303–314.

6. Tian-Tian He, Carolina Oi Lam Ung, Hao Hu, Yi-Tao Wang, Good manufacturing practice (GMP) regulation of herbal medicine in comparative research: China GMP, cGMP, WHO-GMP, PIC/S and EU-GMP, European Journal of Integrative Medicine, 2015; 7(1): 55-66.
7. Sethi S.P., Veral E.A., Shapiro H.J., Emelianova O., Mattel, Inc.: global manufacturing principles (GMP)–a life-cycle analysis of a company-based code of conduct in the toy industry, Journal of Business Ethics, 2011; 99(4): 483-517.
8. S. P. Sethi and B. B. Bhalla A New Perspective on International Social Regulation of Business: An Evaluation of the Compliance status of the International Code of Marketing of Breast-Milk Substitutes. Journal of Socio-Economics, 1993; 22(2): 141–158.
9. ICCA's 2nd International Conference on "Globalization and the Good Corporation," 2007; 26–28.
10. Sethi, S. P., M. L. Weidenbaum and P. F. McCleary: A Case Study of Independent Monitoring of U.S. Overseas Production: Mattel Independent Monitoring Council For Global Manufacturing Principles (MIMCO) - Audit Report 1999. Global Focus, 2000; 12(1): 137-152.
11. Wagner A, Platzgummer M, Kreismayr G, et.al. GMP Production of Liposomes—A New Industrial Approach Journal of Liposome Research, 2006; 16(3): 311-319.
12. Jain S.K., Jain R.K., Evolution of GMP in Pharmaceutical Industry, Research J. Pharm. and Tech., 2017; 10(2): 501-506.
13. The 1941 Supfathiazole Disaster and the birth of Good manufacturing practices, John P Swann, pharmacy in history, 1999; 41(1): 16-25.
14. Remington, the Science and Practice of Pharmacy, 21st Edition, 1: 18-19.
15. A Brief History of the GMPs for Pharmaceuticals, Barbar K. Immel, Pharmaceutical Technology, July, 2001; 44–52.
16. Cusato S., Gameiro A.H., et.al. Assessing the costs involved in the implementation of GMP and HACCP in a small dairy factory, Quality Assurance and Safety of Crops & Foods, June, 2014; 6(2): 135-139.
17. Bata, D., Drosinos, E.H., Athanasopoulos, P. and Spathis, P., Cost of GHP improvement and HACCP adoption of an airline catering company. Food Control, 2006; 17: 414-419.
18. Motarjemi, Y. and Käferstein, F., Food safety, hazard analysis and critical control point and the increase in foodborne diseases: a paradox? Food Control, 1999; 10: 325-333.
19. Suwanrangsi, S., HACCP implementation in the Thai fisheries industry. Food Control, 2000; 11: 377-382.