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# GOOD MANUFACTURING PRACTICE (GMP) GUIDELINE IN PHARMACEUTICAL INDUSTRIES: IMPLEMENTATION AND ITS SIGNIFICANCE FROM THE VIEW OF PHARMACISTS

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## ABSTRACT

Good manufacturing practice or GMP are regulations governed by the US Food and Drug Administration under the authority of the Federal Food, Drug, and Cosmetic Act. These regulations require that manufacturers, processors, and packagers of drugs take appropriate proactive steps to ensure that their products are safe, pure, and effective. GMP is also sporadically referred to as "**cGMP**". The "c" stands for "current", reminding manufacturers that they have to employ technologies and systems that are up-to-date to cope with the regulations. Testing a small sample from a batch may not enough to ensure quality. So, it is significant that drugs are manufactured under controlled conditions to repeatedly meet consistent specifications required by the GMP regulations to assure that quality is built into the design and manufacturing process. We aimed to concentrate on the justification of the incorporation of GMP guidelines in the pharmaceutical industry from the perception of pharmacists.

**KEYWORDS:** Batch record, cross contamination, GMP, quality assurance, safety, testing.

## INTRODUCTION

Medicines are perhaps as old as Mankind and, the perception of their quality has unfolded gradually with the progression of time. Unpropitious experiences have aided the advancement of medicines regulations and management than the evolution of the knowledge base (Immel, 2001; Jain & Jain, 2017; J. D. Nally, 2007; J. Nally & Kieffer, 1998; Sharp, 1991).

People depend solely on doctors for prescriptions, and on pharmacists for dispensing. Pharmacists and doctors rely on the manufacturers who play central characters in assuring that the medicine is appropriate and safe. (Acquadro et al., 2003; Lund, 1994; Patel & Chotai, 2008; Salud & Organization, 2003; Scheme, 2009).

Drugs are not typical consumer commodities, and in most instances, choices concerning medication are not left to them. Therefore, the manufacture, distribution, and dispensing of medication also necessitates specialized expertise (Rägo & Santoso, 2008).

The production and distribution of pharmaceutical merchandise is a complicated, cross-border enterprise. Assuring their quality and safety is a significant global public health problem. For diverse causes, some manufactured drugs do not comply with regulations belonging to Good Manufacturing Practice (GMP). Correspondingly, hazardous medications or mediocre quality are accessing supply chains and being used to manage patients, not only nationally but also internationally(Brunner, 2004; Munro, 2017; Wada, Ozaki, Miyachi, Tanimoto, & Crump, 2021).

GMP is a collection of guidelines, codes, and regulations for the manufacture of medication, drug products, several medical devices, foods, and in-vitro and in-vivo diagnostic products. The Term "GMP" is recognized worldwide for the direction and superintendence of production and quality control testing of pharmaceuticals. Most requirements of GMP were put in place as responses to terrible events and to avoid future disasters. To achieve and maintain GMP compliance, one should know the pattern of the GMP. The present review highlights past, present, and future of GMP (Alici & Blomberg, 2010; Bretaudeau, Tremblais, Aubrit, Meichenin, & Arnaud, 2020; Ferdousi & Ahmed, 2009; Grob, Stocker, & Colwell, 2009; Haleem, Salem, Fatahallah, & Abdelfattah, 2015; Organization, 2011; Poli, Petroni, Pardini, Salvadori, & Menichetti, 2012; Robinson, 2003; Schedule, 1940, 2012)

**Quality Assurance**

The responsibilities of Quality Assurance department (QAD) are ever-increasing, as public awareness is far broader and focused now. (Manghani, 2011; Tauqeer, Myhr, & Gopinathan, 2019) Digitalization can affect the reputation of a corporation both positively and negatively. (Kemppainen & Liikkanen, 2017) As information is more accessible nowadays, any sort of issue may cause serious damage to the reputation of the corporation. (Rachinger, Rauter, Müller, Vorraber, & Schirgi, 2019) So, maintaining quality is a must for not just for legality, but also to sustain within the market. (Hind, 1995; Srinivasan, 2002) Digitalization also helps to execute plans sooner. (Kemppainen & Liikkanen, 2017) Because more access to information facilitates the minimization of risk factors and ensures immediate response. (Collins, 2003; Waddell & Mallen, 2001) Using computerized systems offers good functional response than the traditional systems. (Bouwman, Nikou, Molina-Castillo, & de Reuver, 2018) An enormous source of error in production is untrained personnel who don't know how to work different machines or the way to maintain the environment. Stronger QAD may help to make sure proper in-facility training for the workers.(Rondeau & Birdi, 2005) Specific trained teams should be developed to response to consumer feedbacks. (Serra, 2007) As QAD works to make impressions on both the regulatory bodies and the consumers, trained persons should be included to scale back professional errors. (Stewart & Waddell, 2003) Because the basic function of quality assurance department is documentation, regular checking and cross-checking must be the first duty of the workers. [40](Gouveia, Rijo, Gonçalo, & Reis, 2015).

The word "current" before GMP demands implementation of the newest technology to ensure premium quality. (F. and D. Administration, 2014; A. Shukla, Vishnoi, & Das, 2016; J. Shukla, 2019) Pharmaceutical companies should follow cGMPs in order that their products are manufactured maintaining the precise requirements like identity, quality, strength and purity. (Gouveia et al., 2015; N. Kumar & Ajeya, 2016) Some violation of federal regulations associated with cGMP may end in criminal penalties. (Abdellah, Noordin, & Ismail, 2015; Pinkerton & Pickar, 2016) So, in an excess of caution, companies should adopt practices, and risk management systems cautiously beyond cGMP regulations to beat legal barriers. (U. S. F. and D. Administration, 2015; Srinivasan, 2002).

Drug manufacturing should be regulated strictly because ensuring uniformity of products is mandatory to ensure proper dosing. (J. D. Nally, 2016; Serra, 2007) As a little portion of produced items are tested in quality analysis, it's considerably important that each product is manufactured maintaining an equivalent condition following an equivalent guideline. (He, Ung, Hu, & Wang, 2015) For this reason, GMP is much important in pharmaceutical industries. (Gouveia et al., 2015; He et al., 2015; "Introduction," n.d.; Marshall & Baylor, 2011; Srinivasan, 2002).

Sanitation and personal hygiene are parameters which are essential in pharmaceutical production. Cleaning of the whole facility before starting a new production is the primary requirement to avoid cross-contamination. Rest rooms, toilets, animal rooms should be far away from production floor. Air flow must be set in such a way that particles from other areas don't enter into the production area. Cleaning materials shouldn't affect the production or the equipment. If the containers imported from outside must be cleaned properly before use. Accidental contamination must be reported immediately to the supervisor. Regular health examinations must be conducted for the workers. Each employee should receive training on personal hygiene. All types of personal hygiene procedures must be applicable for employees as well as the allowed outsiders. Proper sanitation demands not only a clean facility, but also a clean surrounding and personnel. So, the main sources of contamination must be restricted strictly. (V. Kumar, Bist, Banyal, & Patial, 2019)

**Personnel hygiene**

1. Technical staff should supervise all the manufacture and testing procedure.
2. QC and QA must be experienced and qualified.
3. The workload must be in direct proportion of no of personnel employed.
4. The duties and responsibilities must be assigned by receiving appropriate training in production and QC lab.
5. Special protective attire must be distributed. (Muddukrishna et al., 2016)

**Quality control area**

1. The laboratories must be dependent of the production areas. For each biological, microbiological or physic-chemical analysis, separate areas should be provided.

2. Cleaning of the entire facility before starting a new production after one is the primary requirement to avoid cross-contamination.
3. Air flow must be set in such a way that particles from other areas don't enter into the production area.
4. Radioisotopes testing areas and air handling areas must be provided separately.
5. Regular supply of water must be controlled in appropriate quality for cleaning.

**Building and Premises**

(i) Must be compatible with manufacturing operations.
(ii) Working space must be provided adequately.
(iii) The risks of mix-up must be avoided.
(iv) Any types of contamination must be avoided.
(v) Pets, birds, rodents etc. must be prohibited from entering.
(vi) The production area as well as dispensing and interior space must be smooth, well lightened and free from cracks.
(vii) Rest rooms, toilets, animal rooms should be far away from production floor.

**Water system**

(i) Validated system must be provided for water treatment.
(ii) Potable water must be used for all operation to perform except cleaning and washing.
(iii) The storage tanks must be cleaned and controlled properly.

**Warehousing area**

1. Various categories of materials and products must stocked properly.
2. The area must be designed to ensure good storage condition.
3. The quarantine area must be restricted to authorized person.
4. Starting material and excipients must have separate sampling areas.

**Weighing areas**

(i) There should be separate weighing areas for raw materials and finished product.
(ii) Such areas generally a part of either storage or production area.

**Production areas**

1. Dedicated and self-contained facilities must be available in order to reduce the risk of serious medical hazards from cross contamination.
2. The manufacturing of certain highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products should not be run in the same facilities.
3. The manufacture of technical poisons such as pesticides and herbicides should not be done in premises used for the manufacture of pharmaceutical products.
4. Premises should preferably be furnished with in such a way as to allow the production to take place in areas connected in a rational order corresponding to the vital cleanliness level.
5. For the adequacy of working and in-process storage space there should be permission of orderly and logical position of equipment and materials to reduce the confusion between two pharmaceutical products or components as well as to avoid cross contamination.
6. Walls, floors, ceilings should be smooth and free from cracks and open joints should not shed particulate matter where starting and primary packaging materials and intermediate or bulk products are exposed.
7. Pipework, light lifting, ventilation points should be accessible from outside the manufacturing areas.
8. Drains should be of adequate size and designed and equipped to prevent back flow. Open channel should be avoided where possible but if they are necessary, they should be shallow to facilitate cleaning and disinfection(Myers, 1994)

**Storage area**

1. Should have enough capacity to properly store various categories of materials and products with proper separation and dissociation.
2. Should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Special storage conditions should be provided, controlled, monitored and recorded where appropriate.
3. Received and dispatched batches should be kept in separate places.
4. Rejected, recalled, or returned materials or products should be stored in separate area.
5. Only authorized personnel should have access to the 'quarantine status' marked areas.
6. Drugs and substances which present high risks of abuse and fire e.g., highly active radioactive materials, narcotics etc. should be stored in safe and secure areas.
7. Separate sampling area for starting materials should be provided. If unavailable, sampling performed in the storage area should be conducted such that contamination or cross-contamination is avoided.

**Ancillary areas**

(i) Rest and refreshment place should be made in separate areas from other areas.
(ii) Facilities for changing clothes and for washing and toilet purposes should be easily accessible and enough for the peoples working there. Toilet should not in direct touch with the production and storage areas.
(iii) Maintenance workshops should be made as far as possible from manufacturing areas. If parts and tools are stored in production areas they should be kept in reserved room for this use or lockers.

(iv) Animal houses should be remote from other areas with separate entrance (animal access) and air handling facilities. (F. and D. Administration, 1997)

**Qualification & Validation**

Qualification and validation are much important processes that provide specificity, precision, reproducibility, recovery and stability to the products. (Geneva: PIC/S Secretariat, 2013)

**Organizing and Planning**

(i) All activities of qualification and validation must be conducted according to plans.
(ii) Following approved procedure, the activities of qualification and validation must solely be performed by trained personnel.
(iii) Pharmaceutical quality system must be reported by the qualification/validation personnel, although this may not crucial to be a quality assurance function. Quality oversight should be accurate over the life cycle of whole validation.
(iv) Planning must take a significant role for large and complex projects. Clarity should be enhanced by separate validation plans.
(v) The qualification / validation system must be defined by the VMP or equivalent document including the following reference: Qualification/Validation policy; Guidance developing on criteria of acceptance; existing documents references; summary of facilities, process on site, system, equipment and the qualification/validation; alter deviation management and control for qualification/validation;

**Validation**

Validation process is designed in such a way so that the quality, safety and efficacy of product requirements are met. As quality can't be tested for every product; equipment, process and personnel validation can only the quality problems. Quality risk assessment principles must be applied, with ongoing reviews taken regularly in place so that the operations don't exceed the validated state. Regulatory audits must be done for methods, equipment, utensils, components, and personnel. A highly skilled team should be formed to design the validation master plan and review the yearly activities. Sensitive instruments such as heat sensors, temperature and pressure controllers etc. should be calibrated properly. Using advanced technology in validation and calibration show better quality control results. Moreover, a combination of various professionals may improve the performance of validation department. (Huber, 2007)

In case of product complaint and feedback, all complaints and feedback related to the sold products should be reviewed according to standing procedure and action must be taken instantly. A specific team must be trained to handle complaints and take actions according to the principles. After proper investigation, if the complaint is justified, permission must be taken to recall the merchandise immediately to avoid further damage. After immediate action, the precise explanation for the defect must be hunted out and other batches must be thoroughly checked for similar lapses in quality. Appropriate follow-up actions must be maintained after the defect has been corrected. Keeping record of complaints may act as a reminder to not repeat this problem again. Authorities must be informed immediately if a manufacturer suspects faulty manufacturing, possible product deterioration, or other serious problems related to the quality of a product. Moreover, providing clear instruction with the merchandise may reduce complaint issues.("CFR - Code of Federal Regulations Title 21," n.d.)

**Product recall process**

There must be a written system to recall faulty products from the market. The authorized person must take all the responsibilities for the execution of recall. He/she must contain enough training and sufficient staff to handle the recall process. Recall must be performed following a regularly reviewed and updated, standard written procedure. There must be various time-framed plans according to the degree of emergency. Level of distribution is extremely important for product recalls. The cooperation of the retailers facilitates the recall process. Storage and elimination of recalled products must be performed maintaining specific written procedures. For straightforward recall process, all information related to the distribution (including, for exported products, those that have received samples for clinical tests and medical samples) must be easily accessible for the trained person. All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the merchandise because it is, or is suspected of being, defective. The recall process must be monitored closely to avoid unwanted difficulty. A final report must be submitted containing the pros and cons of the recall process. The effectiveness of the recall process must be monitored from time to time statistically and through personal feedback. (European commission, 2014; PIC/S, 2013; WHO, 2011)

The manufacturer must have competent and appropriately qualified personnel at his disposal in sufficient number. The duties of managerial and supervisory staff responsible for implementing and operating GMP shall be defined in job descriptions; their hierarchical relationships shall be defined in an organizational chart. (PIC/S, 2013a) Staff referred to in paragraph 2 shall be given sufficient authority to discharge their responsibilities correctly. Personnel shall receive initial and continuing training including the theory and application of the concept of QA and GMP practice. (J. Shukla, 2019) Internal audits and self-inspection should be conducted in an independent and detailed way by designated competent people. (European commission, 2014; European Commission, 2013; PIC/S, 2013b)

The training program designed for pharmaceutical industries should cover all important aspects of its function, for example,

(i) Every single personnel involved in production must be trained properly.
(ii) Newly recruited personnel should be given appropriate, duty-specific training besides basic training on GMP. Its practical effectiveness should be periodically assessed and training records should be kept.
(iii) The concept of quality assurance and other relevant terms should be made clear during the training session.
(iv) Specific training should be given to the personnel working in contamination hazard areas where toxic, highly active, radioactive, infectious or sensitizing materials are handled.
(v) There should have restriction on the entry of visitors or untrained personnel into the production and quality control areas. If this is unavoidable personal protective clothing (apron, gloves, face mask, head protective cap/face shield, shoe cover, goggles etc.) should be given to them before entry as well as they should be given relevant advance information particularly about personal hygiene.
(vi) Qualified consultant and contract stuff should be provided.

For ease of conducting the aforementioned, trainees should have a basic idea of pharmacotherapy, should know the importance of personal health and hygiene, cleanliness, company's key manufacturing activities, importance of validation, role of production, QAD, Quality Control and engineering, problem of rejected batch, principles of GMP, effects of GMP violation etc.(European commission, 2014; European Commission, 2013; PIC/S, 2013b; US FDA, 2020a; WHO, 2011b)

**When it comes to personal hygiene, the possible findings include,**

1. All personnel should undergo health examination prior to and during employment. Everyone should be free from tuberculosis, skin and other communicable or contagious disease.
2. Personnel hygiene should be taught in practice to all, especially those who are directly concerned with manufacturing processes.
3. Any person with a visible illness or an open wound that may adversely affect the quality of products should not be allowed to handle starting materials, in-process materials, packaging materials or drug products until his condition is judged safe.
4. To prevent contamination personnel should wear clean body covering, face covering, hair covering, shoe appropriate to the duties they perform. Used cloths, caps, masks if reusable should be stored in separate containers until properly cleaned and if necessary, sterilized.
5. Operators should not directly touch starting materials, primary packaging materials and intermediate and bulk products. Wearing gloves is a must.
6. There should be strict prohibition of eating, smoking, drinking, chewing and keeping plants, food, drink, smoking material in production, laboratory and storage areas or any other areas where they might adversely influence product quality.
7. Personal hygiene including the use of protective clothing should be applied to all whoever entering the production area whether they are temporary or full-time employees or non-employees.
8. Penicillin sensitivity of the employees involved in the handling of beta-lactam antibiotics, must be tested before employment and personnel handling, sex hormones, cytotoxic substances and other potent drugs must be periodically examined for adverse effects. (WHO, 2011b)

**In case of premises,**

1. Premises should be located on a place where contamination from surrounding environment (e.g., air, earth and water pollutant) as well as from nearby activities which could adversely affect the product quality couldn't take place. (US FDA, 2001)
2. There is a risk of cross contamination where dust is generated (e.g., during sampling, weighing, mixing, packaging of powders) so appropriate measure should be taken to avoid cross-contamination
3. Premises should be cleaned and when needed disinfected according to detail written procedure. Record should be maintained.
4. Water supply, electrical supply, temperature, humidity, lighting should be compatible and they should not directly or indirectly affect the pharmaceutical products.
5. Premises should be planned, constructed and equipped to give maximum protection against weather, flood, ground seepage as well as insects, birds, rodent, vermin. There should be an effective procedure to control pest and rodent.
6. The condition of building should be reviewed periodically and repaired if necessary. All premises including production areas, laboratories, stores, passage way, canteen should be maintained in a clean and tidy condition.
7. Steps should be taken in order to prevent the access of unauthorized person in production, storage and quality control areas. The use of the production area as a general traffic for personnel and materials or for storage must be avoided.
8. Defined areas for materials receiving, incoming goods quarantine, starting materials storage, weighing and dispensing, processing, equipment washing, equipment storage, storage of bulk products, packaging, and quarantine storage before the final release of finished products, product shipping and control laboratory are required.

(European Commission, 2014a; PIC/S, 2013c; WHO, 2011c)

**Weighing areas**

(i) There should be a separate weighing area for the weighing of starting materials and the estimation of yield by weigh.
(ii) Generally a part of either storage or production area.

**Production areas**

1. Dedicated and self-contained facilities must be available in order to reduce the risk of serious medical hazard due to cross contamination e.g., production of particular pharmaceutical products such as extremely sensitizing materials (e.g., penicillin, amoxicillin) or biological preparations (live microorganism).
2. The manufacturing of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products should not be run in the same facilities.
3. The manufacture of technical poisons such as pesticides and herbicides should not be done in premises used for the manufacture of pharmaceutical products.
4. Premises should preferably be furnished with in such a way as to allow the production to take place in areas connected in a rational order corresponding to the vital cleanliness level.
5. For the adequacy of working and in-process storage space there should be permission of orderly and logical position of equipment and materials to reduce the confusion between two pharmaceutical products or components as well as to avoid cross contamination.
6. Walls, floors, ceilings should be smooth and free from cracks and open joints should not shed particulate matter where starting and primary packaging materials and intermediate or bulk products are exposed.
7. Pipework, light lifting, ventilation point should be accessible from outside the manufacturing areas.
8. Drains should be of adequate size and designed and equipped to prevent back flow. Open channel should be avoided where possible but if they are necessary, they should be shallow to facilitate cleaning and disinfection.
9. Effective ventilation with air control facilities should be provided in production areas appropriate to the products handled, to the operation undertaken and to the external environment.
10. Production areas should be well lit, particularly where visual online controls are carried out.

**Storage area**

1. Should have enough capacity to properly store various categories of materials and products with proper separation and dissociation.
2. Should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Special storage condition should be provided, controlled, monitored and recorded where appropriate.
3. Receiving and dispatched batches should be in separate places.
4. Rejected, recalled, or returned materials or products should be in separate area.
5. Only authorized personnel should have access to the 'quarantine status' marked storage areas.
6. Explosive drugs and substances which presents high risks of abuse and fire e.g., highly active radioactive materials, narcotics, other dangerous drugs should be stored in safe and secure areas.
7. Separate sampling area for starting materials should be provided. If there is no separate area and sampling is performed in the storage area it should be conducted in such a way so that it can avoid contamination or cross-contamination.
8. Printed packaging materials and labels need safe and secure storage.

**Quality control areas**

(i) Quality control area should be separated from production areas. Particularly where biological, microbiological, or radioisotope test methods are employed should be separated from each other.
(ii) Control laboratories should be designed to appropriate for the operations carried out them. Sufficient space should be given to avoid mix-up and cross-contamination. Adequate suitable storage space for samples and records should be given.
(iii) To protect sensitive instruments from vibration, electrical interference and humidity there may be need a separate room.
(iv) Laboratories handling particular substances e.g., radioactive or biological samples need special provision.

**Ancillary areas**

(i) Rest and refreshment place should be made in separate areas from other areas.
(ii) Facilities for changing clothes and for washing and toilet purposes should be easily accessible and sufficient for the workforce. Toilet should not in direct touch with the production and storage areas.
(iii) Maintenance workshops should be made as far as possible from manufacturing areas. If parts and tools are stored in production areas they should be kept in reserved room for this use or lockers.
(iv) Animal houses should be remote from other areas with separate entrance (animal access) and air handling facilities. (PIC/S, 2013c)

**In terms of equipment**

1. Manufacturing equipment should be designed, planned, located and maintain appropriate for its intended purpose. (Ramakrishna, Tian, Wang, Liao, & Teo, 2015)
2. Repair and maintenance operations should not be the cause of any hazard to the quality of the products.

3. Equipment should be designed as to clean easily and thoroughly. It should be cleaned according to detail and written procedure and after that should keep and store in a dry, clean condition.
4. It should keep in head that washing equipment should be chosen and used in order not to be a source of contamination.
5. The parts of production equipment's that come into direct contact with the product should be non-reactive, non-additive and non-absorptive to protect the quality of the product.
6. Measuring equipment e.g., balances of an appropriate range and precision should be available for production and control operations. (PIC/S, 2021a)
7. Measuring, weighing, recording, and control equipment should be calibrated and checked periodically by appropriate method. Records of such tests should be kept.
8. Fixed pipework should be clearly labeled to indicate the flow and contents.
9. According to written procedure distilled, deionized and where appropriate other water pipes should be sanitized.
10. Defective equipment should be removed from production and quality control areas and if not possible to remove at least it should mark as 'defective'. (European Commission, 2014a; PIC/S, 2013c; WHO, 2011c)

**In the material part**

- Materials which are used for cleaning, lubrication of equipment and pest control should not come into direct contact with the product. If possible, such materials should be of a suitable grade e.g., food grade to reduce health risk.
- All incoming materials and finished products should be quarantined as soon as possible after receiving or processing until they are released for use or distribution.
- Materials and products should be reserved as per the suitable condition inaugurated by their manufacturer and in an orderly style, to permit batch segregation and stock rotation by a first-expire, first-out rule.
- Water used in the manufacturing operation of pharmaceutical products should be appropriate for their intended use. (US FDA, 2020b)

**Starting materials**

- The purchase of starting materials should be done by experienced staffs who have a thorough knowledge about the products and suppliers.
- If possible, starting materials should be purchased directly from the producer or at least from approved supplier. It is also recommended that specification made by the manufacturer should be discussed with the suppliers including the control of the starting materials, handling, labeling, packaging requirement as well as complains and rejection procedures.
- For every consignment the containers should be checked at least for supplier's labels, delivery note, integrity of package and seal an ensure the consignment is correspond to the order.
- Containers should be cleaned if necessary and labeled, if required with the prescribed information. Original label should not be lost where additional label is required.
- If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing, and release.
- Damage to any container or any other problem might affect adversely the quality of the product. If any such case is found, the QCD should know and investigate the matter.
- Only designated personnel should dispense starting materials following a written procedure and ensure that correct materials are measured and handled into clean and properly labeled containers.
- Each dispensed material for each batch should be weighed and volume independently.

**Packaging materials**

- The purchase, handling, control of primary and printed packaging materials should be same for starting materials.
- Special attention should be paid to printed packaging materials; they should be stored in secure condition to safe from unauthorized access. Roll feed labels should be used wherever possible. To avoid mix up cut labels and other loose printed materials should be stored and transport in separate closed containers. Only designated personnel should handle packaging materials following and approved and designated process.
- Each delivery or batch of printed or packaging materials should have specific reference number or identification mark.
- Outdated packaging materials or printed packaging materials should destroy and its disposal should be recorded.
- Packaging department should check all products and packaging material's quantity, identity, conformity according to the packaging instruction. (Huber, 2007)

**Intermediate and bulk product**

- Intermediate and bulk products should be preserved under appropriate conditions.
- Purchase of intermediate and bulk products should be handled on receipt as though they were starting materials.

**Finished products**

- Until final release finished products should be held in quarantine, after which they should be stored as usable stock under conditions established by the manufacturer.

- The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, "Good practices in quality control". (US FDA, 2020b)

**Rejected, recovered, reprocessed and reworked materials**

- Restricted areas should be provided for rejected materials and products as well they should be clearly marked. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Authorized personnel should take action and record it.
- Exceptional process is needed for the reworking or recovery of rejected products. It is permitted only if it is done in accordance with a defined and authorized procedure and if the quality of the final product is not affected and if the specifications are met after evaluation of the risks involved. A record of reworking should be kept. A new batch number is required for a reworked batch.
- The introduction of all or part of earlier batches, following to the required quality standards, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with an established written strategy after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be documented.
- The need for additional testing of any finished product that has been reprocessed reworked or into which a recovered product has been incorporated, should be considered by the QC department.

**Recalled products**

Recalled products should be identified and stored separately as soon as possible in a secure area until a decision is taken on their fate.

**Returned goods**

Products returned from the market should be destroyed unless it is certain that their quality is satisfactory and acceptable; in such cases they may be considered for resale or relabeling, or alternative action taken only after they have been critically assessed by the QC function in accordance with a written procedure. It should not be considered suitable for reissue or reuse if any doubt arises over the quality of the product. Any action taken should be correctly recorded.

**Reagents and culture media**

(i) Following written procedure reagents should be made up in the laboratory and appropriately labeled. The label should show the standardization factor, shelf-life, concentration, the date when standardization is due, and the storage conditions. The label should be signed and dated by the designated person preparing the reagent.

(ii) Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the required sensitivity.

**Reference standards**

(i) Official reference standards should be used only for the purpose described in the appropriate monograph.

(ii) Producer should prepare reference standards and test, release and store in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area; otherwise, it will cause a danger.

(iii) All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals.

(iv) All reference standards should be stored and manipulated in a manner that will not adversely affect their quality. (European Commission, 2005; PIC/S, 2021b)

**Miscellaneous**

Documents should be planned, prepared, reviewed and distributed with care. They should comply with the relevant parts of the production and marketing authorizations. Documents should be approved, signed and dated by the designated responsible persons. Without authorization and approval no document should change. Data may be recorded by electronic data processing systems or by photographic or other reliable means(Myers, 1994) Master formulae and detailed SOPs relating to the system in use should be available and the precision of the records should be checked. Only authorized persons should be able to enter or modify data in the computer system where documentation is handled by electronic data-processing methods, and there should be a record of changes and deletions; access should be restricted and the entry of critical data should be separately checked. Batch records stored electronically have to be protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is especially important that, during the period of retention, the data are readily available. (European Commission, 2010, 2011; PIC/S, 2021c; WHO, 2011d)

**Documents required**

***Label***

All finished medicines should be identified by labeling, as required by the national legislation, bearing at least the following information:

- The name of the medicines
- A list of the active ingredients (if applicable, with the INN), showing the amount of each present and a statement of the net contents (e.g., number of dosage units, weight, and volume);
- The batch number assigned by the manufacturer;
- the expiry date in an uncoded form;
- Any special storage conditions or handling precautions if necessary;
- Directions for use, and warnings and precautions that may be necessary;

- The information of the manufacturer (name and address) or the company or the person responsible for placing the product on the market.

**Specifications and testing procedures**

(i) Testing procedures described in documents should be validated in the context of available facilities and equipment before they are accepted for routine testing.

(ii) There should be precisely authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; they should also be available for intermediate or bulk products if required. Specifications for water, solvents and reagents used in production should be included.

**Specifications for starting and packaging materials**

Specifications for starting, primary and printed packaging materials should provide a description of the materials if required, including:

- The designated name (where necessary, the INN) and internal code reference;
- The reference, if available, to a pharmacopeial monograph;
- Qualitative and quantitative requirements with acceptable limits.
- According to the company's practice other data may be added to the specification, such as:
- The supplier and the original manufacturer of the materials;
- A copy of printed materials; Directions for sampling and testing;
- Storage conditions, precautions and use;
- The maximum period of storage before reexamination.

Packaging material should conform to specifications, and should not be incompatible with the material and/or with the medicines it contains. The material should be examined for compliance with the specification, and for defects as well as for the accuracy of identity markings.

**Specifications for intermediate and bulk products:**

Specifications for intermediate and bulk products should be designed and followed. The specifications should be similar to specifications for starting materials or for finished products, as needed.

**Specifications for finished products:**

Specifications for finished products should include:

The designated name of the product and the code reference, where applicable; (b) the designated name(s) of the active ingredient(s) (if required, with the INN(s));

a. The formula or a reference to the formula;
b. The shelf life
c. Directions for sampling, handling, testing or a reference to procedures;
d. The qualitative and quantitative requirements, with acceptable limits;
e. The storage conditions and precautions, where necessary;
f. A description of the dosage form and details of packaging;

**Master formulae**

A formally authorized master formula should keep for each product and batch size to be manufactured.

The master formula should include:

- Name of the product, with a product reference code relating to its specification;
- A description of the dosage form with strength of the product and batch size;
- List of all starting materials to be used (if applicable with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material;
- An explanation of the expected final yield with the acceptable limits, and of relevant intermediate yields, if required;
- An explanation of the processing location and the principal equipment to be used;
- Methods, or reference to the methods, how to prepare and operate the critical equipment, e.g., cleaning (especially after a change in product or materials), calibrating, sterilizing, assembling, use;
- Step-wise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures) with detail;
- he directions for any in-process controls with their limits;
- If necessary, the precondition for storage of the products, including the container, the labeling, the handling and any special storage conditions;
- Any special precautions to be observed. (Committee for Proprietary Medicinal Products (CPMP), 2001; European Commission, 2018; PIC/S, 2007, 2013a)

**Packaging instructions**

Formally authorized packaging instructions should keep for each product, pack size and type. These should normally include, or make reference to:

(i) The name of the product

(ii) A brief description of its pharmaceutical form, strength, where applicable and method of application;

(iii) The pack size exhibiting in terms of the number, weight or volume of the product; (WHO, 2006)

**Batch processing records**

A batch processing record should be maintained for each batch processed. It is usually prepared based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to stay away from errors. (Copying or validated computer programs are suggested. Transcribing from approved documents should be avoided.) (Chaudhari, Yadav, Verma, & Singh, 2014; A. Shukla et al., 2016)

**Standard operating procedures and records:**
SOPs and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- Equipment assembly and validation;
- Analytical apparatus and calibration;
- Personnel matters e.g., qualification, training, clothing and hygiene;
- Maintenance, cleaning and sanitization
- Environmental monitoring;
- Pest control;
- Complaints;
- Recalls;
- Returns

**To maintain good practice in production**
Some handling and manipulation of materials and products should be done with written procedures according to the directions - Cleaning, Sampling, Testing, Quarantine, Processing, Storage, Labeling, Dispensing, Packaging, Distribution, Packaging.

(i) Handling and manipulation of materials and products, such as receipt and cleaning, sampling, testing, quarantine, processing, storage, labeling, dispensing, packaging and distribution should be done in accordance with written procedures or directions and if necessary, should be recorded by responsible personnel. (Bhargav, Parveen, Prajapati, & Yadav, 2020)

(ii) Deviation from directions or procedures should be avoided as far as possible. If deviations happen, they should be in accordance with an approved process. Deviation should be authorized by designated person in a written way, with the involvement of the QC department, when required. (Woo, Wolfgang, & Batista, 2008)

**Prevention of cross-contamination and bacterial contamination during production**

(i) When dry materials and products are used in production, generation and dissemination of dust happen; so special precautions should be taken to prevent the generation and dissemination of dust.

(ii) Contamination of a starting material or of a product by another material or product must be avoided. Risk of cross-contamination accidentally occurs from the uncontrolled or unavoidable release of dust, gases, particles, sprays, vapors or products in process, from residues on equipment, from intruding insects, and from operators skin, clothing, etc. The seriousness of this risk varies with the type of contaminant and of the product being contaminated. Among them most hazardous contaminants are highly sensitizing materials, biological preparations such as living microorganisms, cytotoxic substances, certain hormones, and other highly active materials. Products in which contamination is likely to be most significant are those administered directly into the blood by injection or applied to open lesion and those given in large doses and/or over a long time. (Godinho Filho, Marchesini, Riezebos, Vandaele, & Ganga, 2017)

New requirements for prevention of cross contamination: GMP regulations and guidance can be altered, but recently it is required toxicological evaluation of products which is used in non-dedicated facilities has been provided. The level of cross contamination. (U. S. F. and D. Administration, 2018)

**Quality control of starting materials, intermediate, bulk and finished products can be reviewed as**

(i) All tests should follow the directions given in the relevant written test procedure for each material or product. Supervisor should check the result before the material or product is released or rejected. (Khan, 1990)

(ii) In accordance with the approved written procedure Samples should be representative of the batches of material from which they are taken. (European Commission, 2014b; PIC/S, 2013a; WHO, 2011e)

**Test requirements**
**Starting and packaging materials**

(i) The QC manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters before releasing a starting or packaging material for use.

(ii) An identity test should be conducted on a sample from each container of starting material. It is allowable to sample only a little portion of the containers where a validated method has been established to confirm that no single container of starting material has been wrongly labeled.

**Batch record review**

(i) Before transfer to the authorized person QC records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be carefully investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or deviation. A written record of the investigation should be created and should include the conclusion and follow-up action.

(ii) Retention samples from each batch of finished product should be maintained for at least one year after the expiry date. Finished products should be kept in their final packaging and stored under the recommended conditions carefully. If large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be preserved for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases and water) should be retained for a minimum of two years if their stability grants. Retention samples of materials and products

should be of a size sufficient to allow at least two full reexaminations.

**Advantage**

- It ensures the production of better-quality product
- Because of Maintaining GMP guideline nowadays drugs are becoming safer, basically for the thymine and sulfonamide incident, People are becoming conscious, and so drug are safer now.
- The safety security of personnel (hygiene) is also maintaining strictly.
- Contamination is a serious issue, previously before the establishment of GMP slight or major contamination was very common issue.
- Now quality control is also strictly maintained.
- One of the most significant contributions of GMP can be stated that, the calibration of the calibrating apparatus periodically. As if the celebration apparatus itself has become erroneous then ultimately everything will come faulty.
- In process quality control is another significant contribution, as any production, if found erroneous, can be immediately stopped, and the error taken care of or the batch discarded, saving the time, effort and money of the whole process. (WHO, 2010)
- Documentation process make production more secured. Proper documentation makes identification of mistakes easier.
- Training session for the personnel is also providing security, as previously at has been observed that many unpleasant incidents took place du to the inexperience if personnel.
- FIFO is now ensuring the manufactured drug will be reached to hand of consumer before finishing self-life.
- Product recalls are also enhancing the safety (US FDA, 2010; WHO, 1999)

**Disadvantage**

1. The structural establishment required for GMP approval is highly expensive, which may appear as an extra burden for developing countries like Bangladesh.
2. For GMP maintenance highly skilled personnel is required which is not easily available.
3. Industrial establishment as per GMP guidelines is time-consuming.
4. The incorporation of GMP regulations enhances the time required for approval.
5. Industrialists belonging to corrupt countries may not get approval easily, due to the corruption of top management even though their establishment and preparation may comply with GMP guidelines.
6. GMP regulations may change depending on some devastating outcome of previous lack. But changing the establishment will be tedious.
7. In Bangladesh the interest against Bank loans is too high. So, entrepreneurs used to prefer to the most easily accessible market where low investment is required as taking huge lone is difficult for the interest rate.

**Recommendation**

(II) Individual GMP requirements for solid, liquid, ophthalmic, parenteral and tropical product should strictly be maintained.

(III) Only pharmacists should get appointed in production and quality control, as others may fail to comprehend the seriousness of a botched-up production. (Abou-El-Enein et al., 2013)

**Current GMP practice in Bangladesh**

Bangladesh's pharmaceutical industry was heavily reliant on import-dependent MNCs after independence. However, following the establishment of the "National Drug Policy" and the "Drug (Control) Ordinance, 1982," local businesses experienced a significant increase. A few pharma firms experienced enormous growth in the following decades, and they reinvested their profits for a faster return. The Bangladeshi pharmaceutical industry is now heading towards self-sufficiency to meet local demand, with an annual growth rate of around 10%. (Mohiuddin, 2018) According to the DGDA (Drug Regulatory Authority of Bangladesh), there are 282 Allopathic, 204 Ayurvedic, 71 Homeopathic and biochemic, 37 Herbal, 281 Unani, drug manufacturing companies in Bangladesh. Additionally, the industry has 30,558 generics of Allopathic medicine, 4,500 registered Ayurvedic drugs, 592 registered Herbal drug, 2,387 registered Homeopathic & biochemic drugs, and 7,255 registered Unani Drugs now in the market.

According to the National Drug Policy (2005), the WHO's existing Good Manufacturing Practices (GMP) must be strictly followed, and manufacturing units should be inspected by the DGDA on a regular basis. As a result of these outcomes, many companies have received international accreditation from various national regulatory agencies, including the FDA and the UK-MHRA [Appendix A]. During the 2019-2020 fiscal year. Bangladesh's pharmaceutical industries export medication to 149 countries [Appendix B], with the total pharmaceutical market's annual export value estimated to be around 172 million USD [Appendix C]. The COVID-19 pandemic has globally interrupted local and global economy, Bangladesh is trying to overcome the situation by providing quality medicines all over the world.

**CONCLUSION**

GMP describes a set of principles and procedures that help ensure that therapeutic goods are of a high quality. GMP was introduced as a way to reduce the regulatory burden on industry while maintaining assurance that the suitability of manufacturing processes and quality control procedures are appropriate. Again, the problem cannot be solved by tighter regulations alone. Continuous and professional auditing is essential to overcome the challenge of meeting stringent requirements of GMP. GMP is doing the right thing

when nobody is watching but it will reflect in the final product being right. In matter of GMP, swim with the current and in matter of Quality stand like a rock!

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