GOOD MANUFACTURING PRACTICES

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This draft guideline is uploaded on the official website of DRAP dated 5th January, 2023 seeking comments and suggestions from stakeholders on the draft document. Stakeholders can submit their comments and suggestions within 15 days of uploading this document using prescribed format, (further information on comments submission can access on this link. Comments and suggestions can be forwarded via email to ajmal.sohail@dra.gov.pk, copying at hasan.afzaal@dra.gov.pk , or can be posted at mailing address, Additional Director, Quality Assurance & Lab Testing, Drug Regulatory Authority of Pakistan, 3rd floor TF Complex, 7th Mauve Area, G-9/4, Islamabad

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1. HISTORY

Although the Drugs (Licensing, Registering & Advertising) Rules, 1976 under the Drugs Act, 1976 provide detailed Good Manufacturing Practices (GMP) spread through its various rules and schedules; however, this is **the first edition** of a compiled GMP guidance document stipulating Drug Regulatory Authority of Pakistan's (DRAP) expectations on GMP from pharmaceutical & biological drugs manufacturers.

2. APPLICATION

This document is applicable to all the manufacturers of Pharmaceutical and Biological Drugs for complying with the GMP standards. It is also intended to serve the purpose of guidance to the regulators on the applicable GMP standards.

3. PURPOSE

This document is intended to provide guidance regarding Good Manufacturing Practices (GMP) for the manufacturing of pharmaceutical & biological drug in accordance with the Drugs (Licensing, Registering & Advertising) Rules, 1976, under the Drugs Act, 1976, the good manufacturing practices aim at ensuring that:

i. Products are consistently produced and controlled to the quality standards appropriate to their intended use
ii. Products are manufactured as required by the marketing authorization or product specification; and
iii. All those risks have been diminished that are inherent in any pharmaceutical / biological production operation, including contamination, cross contamination and mix ups (confusion) that cannot be detected completely through the testing of final products.

For the purposes of these guidelines, DRAP sets down the provision that the terms of current good manufacturing practices and good manufacturing practices are equivalent.

This document provides guidance on GMP requirements; however, it does not provide details on safety and environmental aspects of manufacturing processes since ensuring the applicability of aforementioned aspects are the responsibility of the manufacturers. Furthermore, requirements for registering a pharmaceutical or biological drug or health products are laid down in the respective rules, which shall be followed accordingly. This document does not, in any way, shall be deemed to be the only requirement for registration process of a therapeutic good.

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4. INTRODUCTION

Drug Regulatory Authority of Pakistan (DRAP) is mandated to implement the Good Manufacturing Practices (GMP) for manufacturing of pharmaceutical & biological drugs, and health products. Compliance to GMP is one of the requirements set forth for registering a drug in the country. Since the promulgation of The Drugs Act, 1976 and rules framed thereunder, GMP practices have been provided in various rules and schedules. This document compiles such rules and provisions and provides guidance to industry for implementation in light of international guidelines on GMP to comply with.

As GMP ensure establishing such systems that are capable of assuring design, monitoring, and control of manufacturing processes and facilities, the principles laid down in this document cover all the operations involved in the production of the drug, including processing, compounding, formulating, filling, packing, repacking, altering, ornamenting, finishing and labelling with a view to its storage, sale and distribution and related controls of pharmaceutical or biological drugs.

This guidance document covers the aspects of GMP as specified by Schedule B-II of The Drugs (Licensing, Registering & Advertising) Rules 1976, and are developed to give a harmonized approach to the industry for compliance with current GMP requirements.

5. BACKGROUND

Good Manufacturing Practices are essential for manufacturing of pharmaceutical and biological drugs, and health products. Before establishment of DRAP in 2012, Drug Control Organization was responsible to enforce GMP. DRAP Act 2012, Section 4 (c) has mandated Division of Quality Assurance & Laboratory Testing (QA&LT) for enforcement of current good manufacturing practices.

DRAP continuously worked on strengthening the GMP enforcement and implemented current good manufacturing practices in line with its function under DRAP Act 2012. For this purpose, cGMP committee constituted by the Authority in 2019 recommended implementation of the cGMP as per Pharmaceutical Inspection Cooperation/ Scheme (PIC/S) GMP guide in a stage wise manner which was approved by the Authority for implementation.

6. LEGAL FRAMEWORK

DRAP Act 2012 and The Drugs Act, 1976 stipulate basis for enforcement of such rules that aim at ensuring quality, safety, and efficacy of pharmaceutical & biological drugs. There are comprehensive provisions in the Schedule B-II of the Drugs (Licensing, Registering & Advertising), 1976 explaining requirements for good manufacturing practices. DRAP Act 2012, under its Section 7, empowers the Authority to implement current good manufacturing practices. Various Sections of the DRAP Act 2012 and Drug Act 1976, and different articles in the rules framed thereunder provides enabling provisions that specify requirements of good manufacturing practices to be followed by the manufacturers and registration holders of drug products.

6.1. For Licensing of a Pharmaceutical or Biopharmaceutical Manufacturer

Rule 20 (a) of the Drugs (Licensing, Registering & Advertising) Rules, 1976 provides that license holding permission to manufacture drugs shall comply with the requirements and the conditions in respect of goods practices in the manufacture and quality control of drug as specified in Schedule B-II.

6.2. For Registration of Pharmaceuticals & Biological Drugs

Rule 29 (02) of the Drugs (Licensing, Registering & Advertising) Rules, 1976 clearly mentions that *"The Registration Board may, before issuing a certificate of registration, cause the premises in which the manufacture is proposed to be conducted, to be inspected by itself or by its sub-committee or by a panel of Inspectors or experts appointed by it for the purpose, which may examine all portions of the premises and the plant and appliances, inspect the process of manufacture intended to be employed and the means to be employed for standardizing, if necessary, and testing the substances to be manufactured and enquire into the professional qualifications of the technical staff employed"*.

Amendment in rule 26 (1) of The Drugs (Licensing, Registering & Advertising) Rules, 1976 vide SRO 713(I)/2018 implements common technical document format for registration of pharmaceutical & biological drugs for human use in Pakistan which stipulates GMP report / certification of the manufacturer as a requirement.

Similarly, DRAP can take following actions in case of non-compliance to the GMP

6.3. Suspension/ Cancellation of Drug Manufacturing License

Central Licensing Board (CLB) holds the power of suspension/ cancellation of DML if it finds a manufacturer non-complaint to GMP requirements based on inspection reports of Federal Inspectors of Drugs/ Inspection Panel constituted by it, and/or on recommendations of Provincial Quality Control Boards.

6.4. Suspension/ Cancellation of Registration of Drugs

Registration Board of DRAP exercises this authority to suspend/ cancel the registration of a drug based on non-complaint GMP status of a manufacturer. Furthermore, registration is not granted if GMP requirements are not met. The Board may inspect any manufacturer or require reports from Division of Quality Assurance & Laboratory Testing (QA&LT). Furthermore, Provincial Quality Control Boards may also recommend any such actions to the Registration Board.

7. CONSIDERATIONS FOR IMPLEMENTATION

This guidance presents cGMP requirements that must be met as per the Drugs (Licensing, Registering & Advertising) Rules 1976. DRAP advises that it must be read in conjunction with the following to understand and implement current good manufacturing practices:

- ***Guide to Good Manufacturing Practices for Medicinal Products- Part I' published by Pharmaceutical Inspection Co-operation Scheme (PIC/S) (Doc. No. PE 009-15 01-May-2021).***

Along with the following annexes of 'Guide to Good Manufacturing Practices for Medicinal Products' published by Pharmaceutical Inspection Co-operation Scheme (PIC/S): -

Annex-1: Manufacture of sterile medicinal products
Annex-2B: Manufacture of biological medicinal substances and products for human use
Annex-8: Sampling of starting and packaging materials
Annex-9: Manufacture of liquids, creams and ointments
Annex-10: Manufacture of pressurised metered dose aerosol preparations for inhalation
Annex-11: Computerised systems
Annex-15: Qualification and validation
Annex-16: Qualified person and batch release
Annex-19: Reference and retention samples
Annex-20: Quality risk management

Manufacturers, licensed or new applicants, are also encouraged to implement following guidelines in addition to requirements laid down in this document:

- ***Pharmaceutical Development as per ICH Q08 guidelines***
- ***Quality Risk Management as per ICH Q09 guidelines***
- ***Pharmaceutical Quality Systems in accordance with ICH Q10 guidelines***

8. GENERAL CONDITIONS

SECTION-1

1. Responsibility of Licensee for Drug's fitness for use

The licensee shall assume the responsibility for the quality of the drugs manufactured by it to ensure that they are fit for their intended use and comply with the requirements of the DRAP Act, 2012 and Drug Act 1976 and rules framed thereunder and do not place patients at risk due to inadequate safety, quality, or efficacy.

To achieve the quality objective reliably, there shall be a comprehensively designed and correctly implemented system of quality assurance incorporating Good manufacturing practices, and Quality control.

It shall be fully documented, and its effectiveness monitored. All parts of the quality assurance system shall be adequately staffed with competent personnel, and shall have suitable and sufficient premises, equipment, and facilities.

The manufacturer must ensure: -

i. Independent Quality Assurance System has been established;
ii. All documentation is developed and maintained in a manner recommended by relevant standards of International Standard Organization (ISO) and Pharmaceutical Quality Systems, ICH Q10. Examples include but are not limited to SMF, VMP, Validation, SOPs, Protocols, BMRs, Product specification, In-process controls, Self-inspection, Product release etc;
iii. Validation activities are performed, and relevant records are generated.

SECTION-2

2. Pharmaceutical Quality System (Quality Assurance System)

The manufacturer shall have a system of quality assurance appropriate to the manufacture of drugs which shall ensure:

a) Drugs are designed and developed in a way that takes into accord the requirements of good manufacturing practices and other associated codes as may be notified from time to time.
b) Production and control operations are clearly specified in a written form and good manufacturing practices requirements are adopted and followed.
c) Managerial responsibilities are clearly specified in job description
d) Arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials.
e) All necessary controls on starting materials, intermediate products, and bulk products and other in process controls calibrations and validations are carried out.
f) The finished products are correctly processed and checked, according to the defined procedure.
g) Finished drugs are not sold or supplied before the authorized person(s) has certified that each production batch has been produced and controlled in accordance with the requirements of the good manufacturing practices and the relevant rules made under the Ordinance relevant to the production, control, and release of drugs as well as of conditions of registration.
h) Satisfactory arrangements exist to store in appropriate storage conditions.
i) There is procedure for self-inspection and or quality audit at appropriate intervals that regularly reviews the effectiveness and applicability of the quality assurance system and that such a procedure is followed; and
j) A system exists in the form of written Standard Operating Procedure according to which 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 recurrence and that system is followed.

Because of its immense importance for ensuring quality in the product that corresponds to its intended use, Pharmaceutical Quality System must be established. All applicants are advised to make arrangements that fulfil its requirements. During various types of inspections for checking of GMP compliance, DRAP will evaluate determination of Pharmaceutical Quality System's capability in terms of design of the system and implementation of good manufacturing practices by the manufacturer as well. Further guidance regarding following can be taken from 'Guide to Good Manufacturing Practices for Medicinal Products- Part I' published by Pharmaceutical Inspection Co-operation Scheme (PIC/S):

i. Pharmaceutical Quality System,
ii. Good Manufacturing Practices and
iii. Quality Risk Management

SECTION-3

3. Quality Control

3.1. Quality Control Department: -

Manufacturer shall maintain and satisfactorily run its quality control department, which is independent of other departments and under the authority of a person with the required qualifications and experience and with adequate facilities to ensure that all the quality control arrangements are effectively and reliably carried out.

3.2. Basic requirements: -

The Basic requirements for quality control have been elaborated in Schedule B-II under Rule 20 of the Drugs (Licensing, Registering & Advertising) Rules, 1976. It covers followings: -

i. Manufacturers shall ensure that adequate facilities, trained personnel, and approved procedures are available for carrying out quality control activities.

ii. Sampling, specifications and testing, documentation and release procedures that indicate that required testing has been performed and a mechanism to ensure that no drug or material is used or supplied without proper quality control release are essential parts of quality control.

iii. For GMP of quality control, manufacturer must ensure that adequate independent area with the arrangement to protect sensitive electronic equipment such as balances from vibrations, electric interference, accidental hazards has been provided.

3.3. Control Procedures: -

All control procedures must be established in accordance with the instructions given in the relevant written test procedures. The result shall be checked by the supervisor before the material or product is released or rejected.

Sampling plan, procedures, and tools must be clearly specified, maintained, and checked for meeting GMP requirements. Maximum retention time for samples shall be mentioned. Schedule B-II gives a comprehensive guideline on sampling as follows: -

i. The samples shall be representative of the batches of material from which they are taken and in accordance with the approved written procedure.

ii. Samples shall be taken in a manner to avoid contamination or other adverse effect on quality, and the containers that have been sampled shall be marked accordingly and carefully resealed after sampling.

iii. Samples shall be taken with care to guard against contamination or mix-up of or by, the material being sampled, all sampling equipment that comes into contact with the material shall be clean, and some particularly hazardous or potent materials may require special precautions.

iv. Samples shall be taken with equipment which shall be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment and labelled with requisite information to prevent cross contamination.

It is also mandatory that quality control of the manufacturer must demonstrate testing capabilities for raw and packaging materials, finished products, reprocessed products must be examined and tests shall be carried out. The quality control manager shall ensure that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameter

For starting materials, an identity test shall be conducted on a sample from each container or starting material. Furthermore, each batch (lot) of raw material, packaging materials, in process and/or finished products shall be examined following receipt. Laboratory determination of satisfactory conformity to its finished product specifications prior to release must be ensured for each batch of drug products.

Manufacturers shall ensure in their quality control laboratories that: -

i. All critical activities are carried out under the direct supervision of the competent technical staff;

ii. All personnel attached to quality control laboratory are given trainings on GMP on induction;

iii. The procedure followed for approval/rejection of raw materials, packaging materials, intermediate products and finished products are available

Manufacturers are required to implement procedures and maintain records of: -

i. Procurement, evaluation, storage, and maintenance of reference standards

ii. Preparation of working standards from reference standards

iii. Destruction of reference standards
iv. Sampling of

- Starting materials
- Primary packaging materials
- Secondary packaging materials
- In process materials
- Finished products
- Water analysis
- Wash water analysis
- Swab analysis
- Wash water analysis of cleaned garments

v. Approved specifications based on validation for the above
vi. Handling of Out of Specification (OOS)
vii. Review of test data and calculations performed during testing
viii. Procedures followed for issuance of certificate of analysis (CoA
ix. Procedures for storage of samples after testing
x. Procedures for retention of samples
xi. Procedures for safe removal of waste from the laboratory
xii. Reviews of defective product complaints including recording the quality defect and investigating it thoroughly
xiii. Quality audit by an independent specialist
xiv. Authorized person, after ensuring that specifications mentioned are in accordance with registration, releases the batch for sale or supply

In addition to above requirement, DRAP encourages the manufactures or applicants to follow Guide to Good Manufacturing Practices for Medicinal Products- Part I' published by Pharmaceutical Inspection Co-operation Scheme (PIC/S).

3.4.Product Recall: -

Manufacturer must establish a system that is capable of conducting effective and prompt recall across the supply chain whenever a quality defect has been proven or suspected in a drug product. Schedule B-II of Drugs (Licensing, Registering & Advertising) Rules 1976 provide that: -

i. A system of product recall must be established
ii. Responsible person for execution and coordination of recalls shall be designated

iii. Sufficient staff must be present to handle all aspects of the recall
iv. Written procedures with a system of regular update shall be available and implemented
v. All competent authorities shall be promptly informed regarding recall
vi. Distribution records of recalled or suspected product shall be available to the person responsible for recall
vii. Progress of the recall shall be recorded and a final report including reconciliation shall be issued
viii. Time to time evaluation of effectiveness of the arrangements for recall shall be performed
ix. Storage of recalled products in a segregated area is to be ensured

In addition to the above, DRAP's guidance document on 'Recall and Rapid Alerts of Defective Therapeutic Goods' shall be consulted for establishing effective and prompt recall arrangements. In case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the registration or product specification file, or any other serious quality problems), it is the responsibility of the manufacturer to timely inform DRAP about the initiation of recall.

Recall mechanism of the manufacturers or applicants intend to manufacture drugs shall be robust. Separate personal, with specific qualifications and experience having special trainings, may be assigned to coordinate recall activities.

Quality Assurance must have the access to all the information regarding recalls and recalled products. Details of distributors where product has been sent after release must be available with the head of quality assurance.

The communication on recall decision, response from each distributor, recalled quantity and reconciliation shall be maintained. Recall mechanisms of the manufacturers must be able to demonstrate that no product from recalled lot of the product has been sold anywhere after the initiation of a recall for that lot.

Further guidance can be taken from 'procedures for handling and investigating complaints including possible quality defects' and performing 'root cause analysis and corrective and preventive actions' in the PIC/S guide to GMP (Part-1).

SECTION-4

4. Personnel

4.1. General: -

For conducting the intended operations, a manufacturer shall ensure presence of sufficient qualified personnel to fulfill all responsibilities required under the Drugs (Licensing, Registering & Advertising) Act, 1976. Placement of personnel shall be clearly mentioned in the organizational chart of the manufacturer. Following aspects must be complied with in order to ensure that GMP requirements are met:

4.2. Adequacy of Personnel to perform specific duties: -

Specific duties must be recorded in written and there shall be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP.

Individual responsibilities shall be clearly understood by the individual concerned. All personnel shall be aware of the principles of good manufacturing practices that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

Steps shall be taken to prevent unauthorized people from entering production, storage, and quality control areas and personnel who do not work in these areas shall not use them as a passageway.

4.3. Qualified Personnel: -

The head of the production and quality control department and quality assurance may have shared, or jointly exercised the following responsibilities relating to quality, namely:

i. The authorization of written procedures and other documents, including amendments;
ii. The monitoring and control of the manufacturing environment;
iii. Plant hygiene;
iv. Process validation and calibration of analytical apparatus;
v. Training, including the application and principles of quality assurance;
vi. The approval and monitoring of suppliers of materials;
vii. The approval and monitoring of contract manufacturers;

viii. The designation ad monitoring of storage conditions for materials and products;
ix. The retention of records;
x. The monitoring of compliance with good manufacturing practices requirements; and
The inspection, investigation, and taking of samples in order to monitor factors that may affect product quality.

The head of the production department may have the following responsibilities, namely:

i. To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
ii. To approve the instructions relating to production operations including the in-process controls, and to ensure their strict implementation;
iii. To ensure that the production records reevaluated and signed by a designated person before they are made available to the quality control department; to check the maintenance of the department, premises, and equipment
iv. To ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available; and
v. To ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

The head of the quality control department shall have the following responsibilities, namely: -

i. To approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products' to evaluate batch records'
ii. To ensure that all necessary testing is carried out;
iii. To approve sampling instructions, specifications, test methods, and other quality control procedures
iv. To approve and monitor analyses carried out under contract
v. To check the maintenance of the department, premises and equipment
vi. To ensure that the appropriate validation, including those of analytical procedures and calibrations of control equipment are done; and
vii. To ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Apart from their responsibilities as outlined above, their qualifications and experiences shall be in accordance with the DRAP's S.R.O. 1460(I)/ 2019 dated

27th November 2019. This S.R.O also stipulates the requirement of an independent head of quality assurance.

The head of the quality assurance department shall have the following responsibilities, namely: -

i. Establish the quality management system and procedures.
ii. Ensure that the quality control procedures are implemented during every step of the production process.
iii. Plan and conduct internal quality audits and facilitate proactive solutions by collecting and performing statistical analysis of quality data
iv. Establish and implement the Inspection and Testing Plan.
v. Take appropriate corrective actions on identified problems.
vi. Identify potential sources of error and suggest ways to eliminate them. (Preventive Actions)
vii. Continuous process improvement Devise procedures to inspect and report quality issues
viii. Keep records of quality reports, statistical reviews and relevant documentation

4.4.Training of Personnel

The training shall be provided in accordance with a written program for all the personnel whose duties require them to work in the production areas, as the case may be, in the control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

Besides basic training on the theory and practice of good manufacturing practices, newly recruited personnel shall receive training appropriate to the duties assigned to them., continuing training shall also be given, and its practical effectiveness shall be periodically assessed, training programs shall be available, approved by the head of either production or quality control, as appropriate, and training records shall be kept.

Personnel working in areas where contamination is a hazard, such as clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled, shall be given specific training.

The concept of quality assurance and all the measures capable of improving its understanding and implementation shall be fully discussed during the training sessions. Furthermore, evaluation of training must be performed, and records be

kept. Pharmaceutical and biological manufacturing operations are sensitive and therefore visitors or untrained personnel shall be discouraged entry into the production and quality control areas.

4.5.Personnel hygiene

All personnel prior to and during employment as may be appropriate, shall undergo health examinations and personnel conducting visual inspections shall also undergo periodic eye examinations.

All personnel shall be trained in the practices of personal hygiene, a high level of personal hygiene shall be observed by all those concerned with manufacturing processes, personnel shall be instructed particularly to wash their hands before entering production areas, and signs to this effect shall be pasted and instructions observed.

Any person down at any time to have an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle starting materials, packaging materials, in process materials, or drug products until the condition is no longer judged to be a risk.

All employees shall be instructed and encouraged to report to their immediate supervisor any conditions, relating to plant, equipment, or personnel, that they consider may adversely affect the products.

Direct contact shall be avoided between the operator's hands and starting materials, primary packaging materials, and intermediate or bulk product.

To ensure protection of the product from contamination, personnel shall war clean body coverings appropriate to the duties they perform, including appropriate hair cover, and used clothes, if re-usable, shall be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

Smoking eating, drinking, chewing and keeping plants, food, drink, smoking material, and personal medicine shall not be permitted in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.

SECTION-5

5. Good Practices in Manufacturing Processing

5.1. General responsibility of the licensee to review processes

Schedule B-II of Drugs (Licensing, Registering & Advertising) Rules 1976 provide in its section 5 that a licensee shall ensure that:

"All manufacturing processes which shall be defined are systematically reviewed in the light of experience and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications".

Under this section, manufacturers of drugs or applicants who intend to manufacturer drugs (in accordance with their scope) are expected to have documented procedures and implementation means to conduct a review of:

i. Starting materials including packaging materials
ii. Critical in-process controls
iii. Finished product results
iv. Investigation of failed batches
v. Deviations or non-conformances
vi. Effectiveness of resultant corrective and preventive actions taken
vii. All changes carried out to the processes or analytical methods
viii. Post-registration variations
ix. The results of the stability monitoring program and any adverse trends
x. All quality-related returns, complaints and recalls and the investigations performed at the time
xi. Adequacy of any other previous product process or equipment corrective actions,
xii. Post-marketing commitments
xiii. Any contractual arrangements
xiv. Management actions and the effectiveness of such procedures, specified by the management, verified during self-inspection.
xv. Risks to the quality of drug which can applied both proactively and retrospectively.

Additionally, qualification status of equipment and facilities including heating, ventilation and air conditioning units (HVAC) must be reviewed.

DRAP understands that a product quality review process helps in ascertaining consistency in manufacturing processing for which process capability and process capability index are calculated. Therefore, a review program with special focus on statistical quality control and statistical process control must be developed for each drug product separately.

In order to implement this specific section, it is expected that manufacturers of drugs will perform annual product quality review (more guidance on the subject can be sought from 'Pharmaceutical Quality Systems" ICH Q-10).

SECTION-6

6. Materials

6.1. Materials General

All kinds of materials used in the GMP environment must be known and accounted for. Therefore, it is very important to establish a robust material handling system with clear written procedure that can trace, label, identify, store, and dispose of materials to be used for manufacturing purposes. Following principles of material management ensure that GMP requirements as stipulated by the Schedule B-II are met starting with:

i. All incoming materials and finished products shall be quarantined immediately after receipt or processing, until they are released for use or distribution.
ii. All materials and products shall be stored under the appropriate conditions established by the manufacturer and in an orderly manner to permit batch segregation and stock rotation by a first-in, first-out rule

It is the responsibility of an applicant intending to manufacture a drug or a manufacturer to ensure that adequate facilities, trained personnel, and approved procedures are available for sampling & testing of starting materials, packaging materials, intermediate, bulk, and finished products. Proper environmental controls and monitoring must be present for sensitive materials.

Retention samples and current specifications of materials is required, and a regular review shall be conducted with focus on those materials that have been acquired from new sources. A documented selection criterion, qualification, approval and maintenance of suppliers, for starting materials, packaging materials and intermediate, and/or bulk, where required is kept.

All the intermediate and bulk products, which have been purchased from a supplier to be used in manufacturing processing, must be treated as starting materials.

6.2.Starting Materials

Beginning with the purchase of starting materials to their use, following essentials must be ensured:

i. Specific staff, preferably a pharmacist, having thorough knowledge of the products and suppliers
ii. Ensuring that the starting materials have been purchased directly from the producer or only the established suppliers
iii. For each consignment, the containers shall be checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels, and containers shall be cleaned where necessary and labelled, if required, with the prescribed data
iv. Damage to containers and any other problem that might adversely affect the quality of a material shall be recorded and reported to the quality control department and investigated

If a delivery of material is made up of different batches, each batch shall be considered as separate for sampling, testing and release.

Starting materials in the storage area shall be appropriately labelled, and labels shall bear at least the following information, namely: -

i. The designated name of the product and the internal code reference where applicable
ii. The batch number(s) given by the supplier and on receipt by the manufacturer, if any.
iii. Where appropriate, the status of the contents such as on quarantine, on test, released, rejected returned, and recalled, and
iv. Where appropriate an expiry date or a date beyond which retesting is necessary. When fully computerized storage systems are used appropriate system shall be developed for the identification of above referred information.
v. There shall be appropriate procedures or measures to ensure the identity of the contents of each container of staring material, but bulk containers from which samples have been drawn shall be identified
vi. Only starting materials released by or quality control department and within their self-life shall be used
vii. Starting materials shall be dispensed only by designated persons, following a written procedure to ensure that the correct materials are accurately weighted or measured into clean and properly labeled containers
viii. Each dispensed material and its weight or volume shall be independently checked, and the check recorded
ix. Materials dispensed for each batch of the final product shall be kept together and conspicuously labeled as such

For all starting materials, supply chain and traceability records should be available with the manufacturer of the drugs. Testing of starting materials to be used in the manufacturing processing is the responsibility of the manufacturer of drug products. As a requirement, identification of each batch of starting materials must be performed by the finished product manufacturers with keeping proper trace of record of such tests performed.

6.3.Packaging Materials

Due to their immense importance for being in contact with the drug and presenting a unique identification, packaging materials shall be given due consideration in a GMP environment. Following essentials must be ensured:

i. The purchase, handling and control of primary and printed packaging materials shall be as for starting materials
ii. Particular attention shall be paid to printed packaging materials which shall be stored in secure conditions to exclude the possibility of unauthorized access, cut labels, and other loose printed materials shall be stored and transported in separate closed containers so as to avoid mix-ups and packaging materials shall be used for using only by designated personnel following an approved and documented procedure
iii. Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark
iv. Outdated or obsolete primary packaging material or printed packaging material shall be destroyed, and its disposal be recorded
v. All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity, and conformity with the packaging instructions

6.4.Intermediate and bulk products

Schedule B-II stipulates that every intermediate and bulk product, which is purchased by the manufacturer, shall be treated as a starting material on receipt. Labelling, handling, identity tests, quality control release, and dispensing must be carried out as mentioned in section 9.2.1 of this guideline. All such activities shall be performed as per written details and be recorded including independent checks on dispensed material's weight and volumes.

Appropriate storage conditions for intermediate and bulk products must be ensured in accordance with their physio-chemical properties. In general, good storage practices shall be followed for all kinds of materials. Where required, special storage conditions must be maintained with proper checks and monitoring for example temperature and humidity logs.

6.5.Finished Pharmaceutical Products (FPPs)

Finished Pharmaceutical Products must be stored in a quarantine before final release of the whole lot/batch. Storage conditions after the release of FPPs must be maintained as determined by the manufacturer. Proper record and monitoring shall be in place. To release FPPs for sale and distribution into the market, manufacturers shall ensure that:

i. Analytical testing has been conducted and specifications are confirmed as per marketing authorization. These findings must be recorded and reported.
ii. Proper evaluation of FPPs as per documentation including dispensing of materials record, line clearances, closing of batch manufacturing records with results from in process controls, checking of specifications, quality control reports, reconciliations, and other necessary controls must be maintained and verified by quality assurance

6.6.Rejected or recovered materials

Rejected and recovered materials shall be:

i. clearly marked (labelled) as such
ii. stored separately in restricted areas
iii. may be returned to the supplier
iv. where appropriate, shall be reprocessed or destroyed while ensuring that such actions are approved by authorized persons and recorded

Any reprocessing of the rejected products can be accepted if the manufacturer has sufficient scientific evidence to confirm that quality of the final product has not been affected in the form of protocols, study report, process validation record, quality control reports and logs indicating Conducting of tests, and risk identification, assessment, and evaluation.

Manufacturer must ensure that:

i. Internal procedures for control of process parameters must be present. As per requirement of Schedule B-II, a reprocessed batch after meeting above criteria shall be given new batch number for identification.

ii. records of manufacturing processing must clearly indicate earlier steps taken on the rejected materials to ensure that the scientific and regulatory requirements have been met.

iii. introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture shall be authorized beforehand, this recovery shall be carried out in accordance with a defined procedure after evaluation of the risks involved including any possible effect on shelf-life and the recovery shall be recorded

iv. the need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, shall be considered by the quality control department.

6.7.Recalled and Returned Products

6.7.1. Recalled products

i. Recalled products shall be identified, clearly marked as such and stored separately in a secure area until a decision is taken on their fate.

ii. Storage area for such products must be segregated and access must be controlled to this area. All handling of recalled products must be documented in accordance with the written procedures. Furthermore, it is the responsibility of the manufacturer to inform all the concerned authorities in advance regarding intended product recall.

iii. Recall must be performed in line with the regulatory requirements. For this purpose, detailed requirements are given in the 'DRAP's Guidelines on Recalls and Rapid Alerts of Therapeutic Goods'.

6.7.2. Returned goods

i. Products returned from the market shall be destroyed unless it is certain that their quality is satisfactory, they may be considered for resale, relabeling, or bulking with a subsequent batch only after the quality control department in accordance with a written procedure has critically assessed them.

ii. The nature of the product, any special storage conditions, it requires, its condition and history, and the time elapsed since it was issued shall all be taken into account in this assessment, where any doubt arises over the quality of the product, it shall not be considered suitable for reissue or re-use,

although basic chemical reprocessing to recover the active ingredient may be possible, and any action taken shall be appropriately recorded.

6.8. Reagents and culture media

As a documented practice, all reagents and culture media shall be recorded upon receipt or preparation. Proper labeling practices must be adopted for all reagents and culture media with date of preparation, name of analyst and date of expiry mentioned conspicuously on the label. Specific procedures for handling guaranteed reagents; lab reagents and analytical reagents must be present and practiced.

Following provisions of Schedule B-II shall be applicable to reagents and culture media:

i. Reagents made up in the laboratory shall be prepared according to written procedures and appropriately labelled, the label shall indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions and the label shall be signed and dated by the person preparing the reagent.
ii. Both positive and negative controls shall be applied to verify the stability of culture media and the size of the inoculum used in positive controls shall be appropriate to the sensitivity required.

6.9. Reference standards

Reference standards may be available in the form of official reference standards and reference standards prepared by the producer shall be tested, released, and then stored in the same way as official standards, and they shall be kept under the responsibility of a designated person in a secured area.

Official reference standards shall be used only for the purpose described in the appropriate testing method submitted for registration purposes. All reference standards shall be stored and used in a manner that will not adversely affect their quality.

6.9.1. Working standards

Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization,

and all in-house reference standards shall be based on official reference standards, when available.

6.10. Waste Materials

6.10.1. Storage

Provision shall be made for the proper and safe storage of waste materials awaiting disposal, and toxic substances and flammable materials shall be stored in suitably designed and separate enclosed cupboards.

6.10.2. Disposal

Waste material shall not be allowed to accumulate, and it shall be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

6.10.3. Effluent Control

There shall be an effluent control system.

SECTION-7

7. Processing

7.1. Processing operations

7.1.1. General

Production operations must follow clearly defined procedures with the objective of obtaining products of the requisite quality.

7.1.2. Material handling

All handling of materials and products such as receipt and quarantine, sampling, storage, labeling dispensing, processing, packaging, and distribution shall be done in accordance with written procedures or instructions and, where necessary, recorded.

7.1.3. Avoiding deviation

Any deviation from instructions or procedures shall be avoided as far as possible and if deviations occur, they shall be approved in writing by a designated person, with the involvement of the quality control department.

7.1.4. Yield checks

Check on yields and re-conciliation of quantities shall be carried out as necessary to ensure that yields are within acceptable limits.

7.1.5. Avoiding mix-ups

Operations on different products shall not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

7.1.6. Labelling

At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms used shall be labelled or otherwise identified with an indication of the product or material being processed and its strengths, where applicable, and the batch number, and where applicable this indication shall also mention the stage of production.

7.1.7. Un-authorized entry prohibited

Access to the production premises shall be restricted to authorize personnel.

7.1.8. In-process controls

In process controls are mostly performed within the production are and they shall not carry any risk for the quality of the product.

7.2. Prevention of Cross-Contamination and Bacterial Contamination in Production

7.2.1. Precautions against dust

When dry materials and products are used in production, special precautions shall be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.

7.2.2. Measures against contamination

Contamination of a starting material or of a product by another material or product shall also be avoided and similarly, cross-examination shall be avoided by appropriate technical or organizational measures, as may be necessary by production segregated areas, namely:

i. Conducting production in segregated areas;
ii. Providing appropriate airlock, pressure differentials and dust extraction;
iii. Minimizing the risk of contamination caused by re-circulation or re-entry of untreated or insufficiently treated air;
iv. Wearing and keeping protective clothing in areas where products with special risk of cross-contamination re processed;
v. Using, cleaning and decontamination procedures of known effectiveness, as in-effective cleaning of equipment is a common source of cross-contamination;
vi. Encourage using a ‘closed system" of production;
vii. Testing for residues where necessary;
viii. Using cleanliness status labels on equipment, showing the name of the previous product.

7.2.3. Cross-contamination checks

Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to standard operation procedures.

7.2.4. Microbiological monitoring

Production areas where susceptible products are processed shall undergo periodic microbiological monitoring and the bio-burden shall be kept within the specified limits.

7.3. Processing operations, intermediate and bulk products

7.3.1. Pre-processing cleanliness checks

Before any processing operation is started, steps shall be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels, or documents not required for the current operation.

7.3.2. In-process controls

Necessary in-process controls and environmental controls shall be carried out and recorded.

7.3.3. Defective equipment

Means shall be instituted for indicating failures of equipment or of services, such as water or gas, to equipment. Defective equipment shall be withdrawn from use until the defect has been rectified.

7.3.4. Cleaning containers

Containers for filling shall be cleaned before filing and attention shall be given to avoiding and removing any contaminants such as glass fragments and metal particles. Production equipment shall be cleaned according to detailed written procedures and stored only under clean and dry conditions.

7.3.5. Yield deviations

Any significant deviation from expected yield shall be recorded and investigated.

7.3.6. Product pipelines

Checks shall be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one are to another are connected in a correct manner.

7.3.7. Water pipes

Pipes used for conveying distilled or deionized water (we may write "purified water" instead) and, where appropriate, other water pipes shall be sanitized according to written procedures that detail the action and limits for microbiological contamination and the measures to be taken.

7.3.8. Equipment Calibration

Measuring, weighing, recording control equipment and instruments shall be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning instruments shall be checked daily or prior to use for performing analytical tests and the date of calibration and the date when re-calibration is due shall be clearly indicated.

7.3.9. Repair and maintenance

Repair and maintenance operations shall not present any hazard to the quality of the products.

7.4. Packaging operations

7.4.1. Avoiding mix-ups

When the program for packaging operations is being set up particular attention shall be given to minimizing the risk of cross-contamination, mix-up, or substitutions, and different products shall not be packed in close proximity unless there is physical segregation or the use of electronic surveillance.

7.4.2. Pre-packaging checks

Before packaging operations are begun, steps shall be taken to ensure that the work area, packing lines, printing machines, and other equipment are

clean and free from any products, materials, or documents previously used and not required for the current operation, and the line clearance shall be performed according to an appropriate checklist and recorded.

7.4.3. Labeling of packaging line

The name and batch number of the product being handled shall be displayed at each packaging station or line.

7.4.4. Process continuity

Normally, filling and sealing shall be followed as quickly as possible by labeling and if labeling is delayed, appropriate procedures shall be applied to ensure that no mix-up or mislabeling can occur.

7.4.5. Printing operation checks

The correct performance of any printing, mode numbers or expiry dates, done separately or in the course of the packaging shall be checked and recorded, and attention shall be paid to printing by hand which shall be re-checked at regular intervals.

7.4.6. Label verification

Special care shall be taken when cut labels are used and when over-printing is carried out off-line and in hand-packaging operations, roll-feed labels are normally preferable to cut labels in helping to avoid mix-up. On-line verification of all labels by automated electronic means can be helpful in preventing mix-up, but checks shall be made to ensure that electronic code readers, label counters, or similar devices are operating correctly.

7.4.7. Fast colour printing on labels

Printed and embossed information on packaging materials shall be distinct and resistant to fading or erasing.

7.4.8. On-line packaging checks

On-line control of the product during packaging shall include at least check on: -

i. The general appearance of the packages;
ii. Whether the packages are complete;
iii. Whether the correct products and packaging materials are used;
iv. Whether any over-printing is correct;
v. The correct functioning of line monitors; and
vi. Samples taken from the packaging line shall not be returned unless inspection is done in close the packaging proximity of line.

7.4.9. Product re-introduction on packaging line

Products that have been involved in an un-usual event during packaging shall be re-introduced into the process only after special inspection, investigation, and approval by authorized personnel and a detailed record shall be kept of this operation.

7.4.10. Discrepancies to be investigated

Any significant or un-usual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated and satisfactorily accounted for before release.

7.4.11. Destruction of un-used packaging materials

Upon completion of a packaging operation, un-used batch-coded packaging materials shall be destroyed and the destruction recorded, and a documented procedure shall be followed if encoded printed materials are returned to stock.

SECTION-8

8. Sanitation and hygiene

8.1. General

A high level of sanitation and hygiene shall be practiced in every aspect of the manufacture of drug products, the scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, product for cleaning and disinfection, and anything that could become a source of contamination to the product, and potential sources of contamination shall be eliminated through an integrated comprehensive program of sanitation and hygiene (For sanitation and hygiene please also refer to Section 5 of Schedule B and Section 4.9 of Schedule B-II).

SECTION-9

9. Validation

9.1. General

Validation studies shall be conducted in accordance with pre-defined protocols. A written report summarizing recorded results and conclusions shall be prepared and stored. Processes and procedures shall be established on the basis of a validation study and undergo periodic re-validation to ensure that they remain capable of achieving the intended results, and particular attention shall be accorded to the validation of processing, testing and cleaning procedures.

9.2. Process Validation to be performed as per written procedures

9.2.1. Validation of critical processes

Critical processes shall be validated, prospectively or retrospectively.

9.2.2. Validation of new master formula

When any new master formula or method of preparation is adopted, steps shall be taken to demonstrate its stability for routine processing, and, the defined process, using the materials and equipment specified, shall be shown to yield a product consistently of the required quality.

9.2.3. Validation of equipment and materials

Significant amendments to the manufacturing process, including any change in equipment or materials that may affect product quality and or the reproducibility of the process shall be validated.

SECTION-10

10. Documents

10.1. General

10.1.1. Maintenance of documents

Documents, as required under these rules, shall be meticulously maintained and regularly reviewed and kept up to date, and when a document has been revised, a system shall exist to prevent inadvertent use of the superseded version.

10.1.2. Records of action

Records shall be made or completed when any action is taken and in such a way that all significant activities, concerning the manufacture of pharmaceutical products are traceable. The batch record shall be retained for at least one year after the expiry date of the finished product.

10.1.3. Documentation systems

Data may be recorded by electronic data processing systems or by photographic or other reliable means. Master formulate and detailed standard operating procedures relating to the system in use shall be available and the accuracy of the records shall be checked and if documentation is handled by electronic data-processing method, only authorized persons shall be able to enter or modify data in the computer, and there shall be a record of changes, and deletions, access shall be restricted by passwords or their means and the entry of critical data shall be independently checked and data shall also be readily available.

10.1.4. Status identification

Labels applied to containers, equipment, or premises shall be unambiguous and in the company's agreed format. The labels of different colours may also be used in addition to the working to indicate the status such as "quarantined," "accepted," "rejected," or "clear."

10.1.5. Product labelling

All finished products shall be labeled in accordance with the Drugs (Labelling and Packing) Rules 1986.

10.1.6. Reference standards identification

For reference standards, the label or accompanying documents shall indicate concentration, date of manufacture, expiry, date, and storage conditions, where appropriate.

10.1.7. Specification approvals

Each specification shall be approved and maintained by the quality control unit.

10.1.8. Revision of specification

Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia or the Drugs (Specifications) Rules 1978.

10.1.9. Packaging material specification

Packaging material shall conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains.

10.1.10. Starting material re-assays

Documents describing testing procedures shall state the required frequency for re-assaying each starting material, as determined by its stability.

10.2. Specifications for Intermediate and Bulk Products

Specifications for intermediate and bulk products shall be available if these are purchased or dispatched, of if data obtained from intermediate products are used in the evaluation of the finished product, and the specifications shall be similar to specifications for starting materials or for finished products.

10.3. Batch processing records

10.3.1. General

A batch processing record shall be kept for each batch processed based on the relevant parts of the currently approved master formula and the method of preparation of such records shall be designed to avoid transcription errors.

10.3.2. Checking work station

Before any processing begins, a check shall be made that the equipment and work station are clear of previous products, documents, or materials

not required for the planned process, and that the equipment is clean and suitable for use, and this check shall be recorded.

10.3.3. Recording process operation

During processing, the following information shall be recorded at the time each action is taken, and after completion the record shall be dated and signed by the person responsible for the processing operations, namely:-

i. The name of the product;
ii. The number of the batch being manufactured;
iii. Date and times of commencement of significant intermediate stages and of completion of production;
iv. The name of person responsible for each stage of production;
v. The initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. Weighing);
vi. The batch number and or analytical control number and the quantity of each starting material actually weighed including the batch number and amount of any recovered or reprocessed material added;
vii. Any relevant processing operation or event and the major equipment used
viii. the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
ix. the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanation for significant deviations from the expected yield; and
x. Notes on special problems including details, with signed authorization for any deviation from the master formula.

10.4. Batch packaging records

10.4.1. General

A batch packaging record shall be kept for each batch or part batch processed based on the relevant parts of the packaging instructions, and the method of preparing such records shall be designed to avoid transcription errors.

10.4.2. Pre-packing line checks

Before any packaging operation begins, checks shall be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks shall be recorded.

10.4.3. Recording of packaging operation

The following information shall be recorded at the time each action is taken, and the date and the person responsible shall be clearly identified by signature or electronic password, namely:

i. The name of the product, the batch number, and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product obtained, the quantity actually obtained, and the reconciliation;
ii. the date(s) and time(s) of the packaging operation
iii. the name of the responsible person carrying out the packaging operation;
iv. the initials of the operators of the different significant steps;
v. the checks made for identity and conformity with the packaging instructions, including the results of in-process controls
vi. Details of the packaging operations carried out, including reference to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product un-packed or a record or returning product that has not been packaged to the storage area.
vii. Whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date, and any additional overprinting;
viii. Notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person; and
ix. the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained to permit and adequate reconciliation.

10.4.4. Recording batch numbers

Batch-number allocation shall be immediately recorded in a logbook, and the record shall include date of allocation, product identity, and size of batch.

10.4.5. Analytical records

Analysis records shall include at least the following namely

i. the name of the material or product and, where applicable, dosage form
ii. the batch number and, where appropriate, the manufacturer and/or supplier
iii. References to the relevant specifications and testing procedures;
iv. test results, including observations and calculations, and reference to any specifications (limits);
v. dates of testing;
vi. the initials of the persons who performed the testing;
vii. the initials of the persons who verified the testing and the calculations, where appropriate; and
viii. A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

10.4.6. Finished product release procedure

Written release and rejection procedures shall be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

10.4.7. Recording batch distribution

Records shall be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

10.4.8. Standard operating procedures

Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached shall be available at the premises for:

i. Equipment assembly and validation
ii. Analytical apparatus and calibration
iii. Maintenance, cleaning, and sanitization;

iv. Personnel matters including qualification, training, clothing, and hygiene
v. Environmental monitoring
vi. Pest control
vii. Complaints;
viii. Recalls; and
ix. Returns

10.4.9. Equipment logbooks

Logbooks shall be kept with major and critical equipment as identified by the licensee and shall record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations including dates and the identity of the people who carried out these operations.

10.4.10. Equipment utilization record

The use of major and critical equipment and the areas where products have been processed shall be appropriately recorded in chronological order.