GOOD MANUFACTURING PRACTICES GUIDELINES FOR HOMOEOPATHIC PHARMACEUTICAL INDUSTRY

Directorate General of Drug Administration

Ministry of Health and Family Welfare

Govt. of the People's Republic of Bangladesh

2019

CONTENT

Preface

Homoeopathy is a system of medicine born in Europe in the last part of the eighteen century. The homoeopathic doctors used homoeopathic medicines, which are prepared following a well-defined procedure, starting from substances derived from the mineral, herbal and animal worlds. The techniques of preparation of these drugs include excipients, and the potentization of the product into different grades. In some cases, the dilutions are so high that it is almost impossible to find out molecule of the original raw materials.

With the constant increase in the use of homoeopathic & traditional medicines worldwide and the rapid expansion of the global market, the safety and quality of raw materials and finished homoeopathic products have become a major concern for health authorities, pharmaceutical industries and the public. The safety and efficacy of homoeopathic medicines largely depend on their quality.

Requirements and methods for quality control of finished homoeopathic products, particularly for combination/ mixing homoeopathic products are far more complex than for single drugs like Mother tincture & Liquid Potency Medicine. The quality of finished homoeopathic products is also influenced by the quality of the raw materials used.

The manufacturing process is one of the key steps where, quality control is required to ensure quality of medicinal products, including homoeo-pathic medicines. A good manufacturing practice (GMP) is one of the most important for this measure.

The use of homoeopathic medicines has spread more and more and nowadays it is widespread not only in European region but also in south Asian countries and north and South American countries. With the worldwide increase in the use of homoeopathic medicines and the rapid expansion of the global market, the safety

and the quality of homoeopathic medicines has become a major concern for health authorities, pharmaceutical industries and consumers. The safety of the homoeopathic medicines largely depends on their quality. Requirements and methods for the quality control of finished homoeopathic medicines are far more complex than for chemical drugs, particularly for the combined or mixed homoeopathic medicines. Furthermore, the quality of the homoeopathic medicines is influenced both by the quality of procedure used during their production and the quality of the raw material. Procedure used during their production and the quality of the raw material. Products which meet high quality standards are needed to allow the patient to make safe use of the homoeopathic medicines. Nowaday, this is more and more important because, as a consequence of market globalization, many of the raw materials and medicines used in the homoeopathic systems come from different countries.

There is no doubt that GMP is a key step in ensuring the safety and efficacy of homoeopathic medicines. However, meeting GMP requirements requires investment from manufactures and this may be especially difficult for small manufactures in developing countries. Investing the GMP may increase production costs, leading to an increase in the price of the final product. This will impact on the affordability of the medicines. Therefore, relevant national health authorities need to take this impact into consideration and take the appropriate measures to encourage and ensure that manufacturers are willing and able to improve their GMP. According to the experiences of some countries, giving a transition period to manufactures for them to improve the GMP is one good example. Therefore, these guidelines are only a reference and the national health authorities will, based on the guideline, further develop their own GMP requirements according to their circumstances, nature of drugs and the limitation of testing of high potency/dilution medicine.

Major General Md. Mahbubur Rahman
Director General

ABBREVIATIONS AND ACRONYMS

1. WHO : World Health Organization :
2. GMP : Good manufacturing practices
3. DRA : Drugs Regulatory Authorities
4. IDRA : Drugs Regulatory Authorities
5. DGDA : Directorate General of Drug Administration,
6. DA : Drug Administration
7. MOHFW : Ministry of Health and Family Welfare,
8. GOB : Government of People's Republic of Bangladesh
9. QC : Quality Control
10. QA : Quality Assurance
11. QO : Quality Operation
12. OOS : Out-of-Specification
13. PD : Product Development
14. PDD : Product Development Department
15. R&D : Research and Development
16. ICH : International Conference on Harmonisation (guide line)
17. PM : Packaging Materials
18. RM : Raw Materals
19. BP : British Pharmacopoeia
20. USP : United State Pharmacopeia
21. DHMS : Diploma in Homoeopathic Medicine & Surgery
22. BHMS : Bachelor of Homoeopathic Medicine & Surgery
23. BPR : Batch Processing Record, Batch Packing Record
24. BMR : Batch Manufacturing Record
25. S.S : Stainless Steel
26. Sq. ft : Square foot
27. TLC : Thin Layer Chromatography
28. UV : Ultra Vioet
29. IR : Infra Red
30. HPLC : High Performance Liquid Chromatography
31. SME : Small and Medium Enterprise
32. LAF : Laminar Air Flow
33. pH : Negative logarithm of Hydrogen Ion Concentration
34. LOD : Loss on drying
35. IPQC : In Process Quality Control
36. IPQA : In Process Quality Assurance
37. BHP : Bangladesh Homoeopathic Pharmacopeia
38. HPUS : Homoeopathic Pharmacopeia of United States
39. HPI : Homoeopathic Pharmacopeia of India
40. GHP : German Homoeopathic Pharmacopeia

GMP Guideline Preparation Committee

1. Major General Md. Mahbubur Rahman, Director General, The Directorate General of Drug Administration (DGDA)	President
2. Prof. Shahabuddin Kabir Chowdhury, Department of Pharmacy, Jahangirnagar University, Savar, Dhaka	Member
3. Md. Ruhul Amin, Director(C.C) Directorate General of Drug Administration, Dhaka	Member
4. Prof. Md. Abdur Rashid Department of Pharmaceutical Chemistry, Dhaka University, Dhaka	Member
5. Prof. Dr. Sitesh Chandra Bachar, Chairman, Department of Pharmacy Dhaka University, Dhaka	Member
6. Dr. Md. Al- Emran Ali Assistant Professor, Govt. Homoeopathic Medical College, Dhaka	Member
7. Hakim A.K. Mahbubur Rahman, Member Bangladesh Board of Unani and Ayurvedic Systems of Medicine, Dhaka	Member
8. Dr. Shopon Kumar Datta, Ayurvedic Specialist, Directorate General of Drug Administration, Dhaka	Member
9. Dr. Md. Babul Akter, Ayurvedic Specialist, Bangladesh Pharmaceuticals, (Ayurvedic), Dhaka	Member
10. Dr. Mamun Mia, Principal, Noor Majid Ayurvedic College (NMAC), Dhaka	Member
11. Dr. A.H.M. Kamruzzaman, Medical Officer(AMC), Director General of Health Services, Mohakhali, Dhaka	Member
12. Hakim Ferdous Wahid Principal, Tibbia Habiba College, Dhaka	Member
13. Md. Salahuddin Asst. Director Directorate General of Drug Administration, Dhaka	Member Secretary

WORKING COMMITTEE

1.	**Dr. S A M Reza-ur Rahim** Managing Director Maxfair & Company Ltd. Immediate Past President, Bangladesh Homoeopathic Medicine Manufacturing Association (BHMMA)	Convenor
2	**Dr. Md. Abdul Matin** Assistant Professor, Department of Materia Medica, Govt. Homoeopathic Medical College Mirpur-14, Dhaka-1206	Member
3	**Dr. Mahbub Hafiz** Immediate Past General Secretary Bangladesh Homoeopathic Medicine Manufacturing Association (BHMMA)	Member
4	**Dr. Md. Aminul Islam** Research/Production/ Quality Control Officer Research Cum Production Unit Govt. Homoeopathic Medical College Mirpur-14, Dhaka-1206	Member
5	**Dr. Md. Imrul Kayes** Homoeo Specialist, Directorate General of Drug Administration, Dhaka	Coopt Member
6	**Dr. Md. Al-Emran Ali** Assistant Professor Head of the Department of Materia Medica, Govt. Homoeopathic Medical College Mirpur-14, Dhaka-1206	Member secretary

INTRODUCTION

With the constant increase in the use of Unani, Ayurveda & Herbal medicines worldwide and the rapid expansion of the global market, the safety and quality of Unani, Ayurveda & Herbal materials and finished herbal products have become a major concern for health authorities, pharmaceutical industries and the public. The safety and efficacy of traditional medicines largely depend on their quality. Requirements and methods for quality control of finished products, traditional medicinal products particularly for combining/mixing herbal products, are far more complex than for chemical drugs. The quality of finished products is also influenced by the quality of the raw materials used.

WHO has committed to the development of a series of technical guidelines related to quality assurance and control of herbal medicines, as well as to updating existing guidelines.

The manufacturing process is one of the key steps where quality control is required to ensure quality of medicinal products, including herbal medicines. Good Manufacturing Practices (GMP) is one of the most important tools for this measure.

Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicines are prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products.

Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of Unani, Ayurveda & Herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.

GMP: An Overview

1. GMP

Good Manufacturing Practice (**GMP**) guidelines provide guidance for manufacturing, testing and quality assurance practice in order to ensure that a quality drug product is safe for human consumption. GMP guidelines are not prescriptive instructions on how to manufacture products. These are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. But mostly it is the company's responsibility to determine the most effective and efficient quality process. The Good Manufacturing Practice is prescribed here to ensure-

(i) the raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination;

(ii) the manufacturing processes it has been prescribed to maintain the standards;

(iii) to adopt adequate quality control measures;

(iv) the manufactured medicines which are released for sale are of acceptable quality;

(v) to achieve the above objectives, each licensed manufacturing unit shall evolve its methodology and procedures for manufacturing of medicines following prescribed processes which should be well documented as a manual, will keep for future reference and inspection when required..

2. Importance of GMP

Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, Homoeopathic medicines are mainly prepared from materials of plant, animal *and mineral/chemical* origin, which are often obtained from varied geographical and/or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of Homoeopathic medicines are often substantially different from those employed for conventional pharmaceutical products. Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the examples of contamination with toxic medicinal plants and/ or plant parts and the number and small quantity of defined active ingredients, the production and primary processing has a direct influence on the quality of Homoeopathic medicines. For this reason, application of GMPs in the manufacture of Homoeopathic medicines is an essential tool to assure their quality.

3. Basic Principles of GMP

Govt. of Bangladesh has included in drug policy that pharmaceutical companies must follow GMP procedures and have created their own GMP guidelines that correspond with their legislation. Basic concepts of all of these guidelines remain more or less similar to the ultimate goals of safeguarding the health of the patient as well as producing good quality medicine.

- Production operations must follow clearly defined procedures in accordance with *approved pharmacopeial* manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.
- All critical processes are validated to ensure consistency and compliance with specifications *but there are short coming in case of some products with high potencies.*
- Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.
- Instructions and procedures are written in clear and unambiguous language.
- Operators are trained to carry out and document procedures.
- Records are made manually or by instruments during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.
- Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
- A system is available for recalling any batch of drug from sale or supply.
- Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

3.1 Good practices in production

General

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

3.1.2. Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be recorded in writing by a designated person, with the involvement of the quality assurance department, when appropriate.

3.1.3. Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

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

3.1.5 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases it may be useful to record also the name of the previous product that has been processed.

3.1.6 Access to production premises should be restricted to authorized personnel.

3.1.7 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

3.1.8 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mixup).

Prevention of cross-contamination and bacterial contamination during production

3.1.9 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

3.1.10 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated..

Processing operations

3.1.11 Before any processing operation is started, steps should 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.

3.1.12 Any necessary in-process controls and environmental controls should be carried out and recorded.

3.1.13 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

3.1.14 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

3.1.15 Any significant deviation from the expected yield should be recorded and investigated.

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

3.1.17 Pipes used for conveying distilled or deionized/purified water and, where appropriate, other water pipes should be cleaned and stored according to written procedures.

3.1.18 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

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

Packaging operations

3.1.20 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

3.1.21 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

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

3.1.23. Normally, filling and sealing should be followed as quickly as possible by labelling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

3.1.24 The correct performance of any printing (e.g. of code numbers or manufacturing expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

3.1.25 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. When labels are attached manually, in-process control checks should be performed more frequently.

3.1.26 Printed or embossed (where applicable) information on packaging materials should be distinct and resistant to fading or erasing.

3.1.27 Regular on-line control of the product during packaging should include at least checks on:

a. the general appearance of the packages;
b. whether the packages are complete;
c. whether the correct products and packaging materials are used;
d. whether any overprinting is correct;
e. correct functioning of line monitors.
f. *Whether approved label, carton, insert, batch no., Mfg & Exp date are printed of relevant products are being used.*

Samples taken away from the packaging line should not be returned.

3.1.28 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.

3.1.29. Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

3.2 *Good practices in quality assurance and control*

3.2.1 Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory *with standard specifications*. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

3.2.2 The independence of quality control from production is considered fundamental.

3.2.3 Each manufacturer (the holder of a manufacturing authorization) should have a quality control function. The quality control function should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

a. adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
b. samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department;
c. qualification and validation must be performed;
d. records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
e. the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;
f. records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

g. no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization.

h. sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

3.2.4 Quality control as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

3.2.5 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

3.2.6 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

3.2.7 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

3.2.8 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

3.2.9 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

3.2.10 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

3.2.11 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

3.2.12 Each sample container should bear a label indicating:

a. the name of the sampled material;

b. the batch or lot number;
c. the number of the container from which the sample has been taken;
d. the number of the sample;
e. the signature of the person who has taken the sample;
f. the date of sampling.

3.2.13 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test requirements

Starting and packaging materials

3.2.14 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

3.2.15 An identity test should be conducted on a sample from each container of starting material

3.2.16 Each batch (lot) of printed packaging materials must be examined following receipt.

3.2.17 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier.

Certificates must contain at least the following information (*6*):

a. identification (name and address) of the issuing supplier;
b. signature of the competent official, and statement of his or her qualifications;
c. the name of the material tested;
d. the batch number of the material tested;
e. the specifications and methods used;
f. the test results obtained;
g. the date of testing.

In-process control

3.2.18. In-process control records should be maintained and form a part of the batch records.

Finished products

3.2.19. For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

3.2.20. Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch record review

3.2.21 Production and quality control 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 thoroughly 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 discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

3.2.22 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

Stability studies

3.2.23. Quality control section should evaluate the quality and stability of finished products and, when necessary, starting materials and intermediate products.

3.2.24. Quality control section should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

3.2.25. A written program for ongoing stability determination should be developed and implemented to include elements such as:

a. a complete description of the drug involved in the study;
b. the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
c. provision for the inclusion of a sufficient number of batches;
d. the testing schedule for each drug;
e. provision for special storage conditions;
f. provision for adequate sample retention;
g. a summary of all the data generated, including the evaluation and the conclusions of the study.

3.2.26. Stability should be determined prior to marketing and following any significant changes in processes, equipment , packaging materials, etc.

4. Research and Development

Research and development (R&D) is the work where pharmaceutical company innovates, introduces, and improves products and dosage forms. It is a series of investigative activities to improve existing products to lead to the development of new products. It is challenging venture for local and global market and development of novel homoeopathy medicines. The homoeopathy industries shall built up Research and Development section separate or as a part of Quality Control with required expert manpower and equipment, space and environment

The R & D personnel shall discharge the following functions diligently

4.1.1 Pre-formulation studies to check pharmacological actions and uses of ingredients.

4.2.2 Trials to assess efficiency and reproducibility of any formulation and develop self-explanatory methods and manufacturing processes

4.3.3 Stability studies both at accelerated conditions and at real time life following ICH guide line to check physical, chemical, and microbiological aspects of any formulation.

4.3.4 Determine shelf life of products and to ensure that all batches of the released products are maintaining within specification limits throughout their entire shelf life

4.3.5 Standardize processes for consistency and uniformity in product quality.

4.3.6 Technical Transference to production and quality operation division/department

4.3.7 Analytical method validation supported by the Quality Control Department.

4.3.8 Improvement of new and existing products for customer satisfaction, environmental change, technology change and other competitors.

4.3.9 Formulation and method development, re-formulation and method up gradation to achieve superior quality medicines at affordable prices by implementing efficient cost-effective measures and management system.

Stability studies :

4.3.10. Research and Development section / Product Development Department (PDD) should evaluate the quality and stability of finished products and, when necessary, starting materials and intermediate products.

4.3.11. Research and Development section should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

4.3.12. A written program for ongoing stability determination should be developed and implemented to include elements such as:

a. a complete description of the drug involved in the study;
b. the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
c. provision for the inclusion of a sufficient number of batches;
d. the testing schedule for each drug;
e. provision for special storage conditions;
f. provision for adequate sample retention;
g. A summary of all the data generated, including the evaluation and the conclusions of the study.

4.3.13. Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc

GOOD MANUFACTURING PRACTICES (GMP) GUIDELINES

The Good Manufacturing Practices (GMP) are prescribed as follows in Part I and Part II to ensure:-

i) Raw materials used in the manufacture of drugs are authentic, of prescribed quality and are free from contamination;

ii) The manufacturing process is as has been prescribed to maintain the standards;

iii) Adequate quality control measures are adopted;

iv) The manufactured drug which is released for sale is of acceptable quality;

v) To achieve the objectives listed above, each licensee shall evolve methodology and procedures following the prescribed process of manufacture of drugs which should be documented as a manual and kept for reference and inspection. However, under Homeopathic Practitioner Ordinance 1983 registered homoeopathic doctors holding DHMS by Homoeopathy Board and BHMS by Directorate General of Health Services who prepare medicines on their own to dispense to their patients and not selling such drugs are exempted from the purview of Good Manufacturing Practices (GMP).

PART-1
GOOD MANUFACTURING PRACTICES

Factory Premises:
The manufacturing plant should have adequate space for:-

Receiving and storing raw materials;

Raw Materials store with Quarantine Area

(i) Manufacturing process area;

(ii) Quality control section;

(iii) Herbs Processing (Cutting/Chopping/Crushing/Sieving with dust control)

***Finished goods* store with Quarantine Area**

(i) Finished goods store;

(ii) Office;

(iii) Rejected goods/drugs store;

(iv) Packaging material store

1.1. General Requirements:

1.1.1 Location and surroundings.- The factory building for manufacture of Homeopathic medicines shall be so situated and shall have such construction as to avoid contamination from open sewerage, drain, public lavatory for any factory which produces disagreeable or obnoxious odour or fumes or excessive soot, dust and smoke.

1.1.2 Buildings.- The buildings used for factory shall be such as to permit production of drugs under hygienic conditions and should be free from cobwebs and insects/rodents. It should have adequate provision of light and ventilation. The floor and the walls should not be damp or moist. The premises used for manufacturing, processing, packaging and labeling will be in conformity with the provisions of the Factory Act. It shall be located so as to be:

(I) Compatible with other manufacturing operations that may be carried out in the same or adjacent premises.

(II) Adequately provided with working space to allow orderly and logical placement of equipment and materials to avoid the risk of mix up between different drugs or components thereof and control the possibility of cross contamination by other drugs or substances and avoid the risk of omission of any manufacturing or control step.

(III) Designed, constructed and maintained to prevent entry of insects and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks and permit easy cleaning and disinfection. The walls of the room in which the manufacturing operations are carried out shall be impervious to and be capable of being kept clean. The flooring shall be smooth and even and shall be such as not to permit retention or accumulation of dust or waste products.

(IV) Provide with proper drainage system in the processing area. The sanitary fittings and electrical fixtures in the manufacturing area shall be proper and safe.

(V) Furnace section could be covered with roof and proper ventilation, but sufficient care should be taken to prevent flies and dust.

(VI) There should be fire safety measures and proper exits should be there.

(VII) Drying Space:- There should be separate space for drying of raw materials, in process medicine or medicines require drying before packing. This space will be protected from files/insects/dust etc., by proper flooring, wire mesh window, glass panels or other materials.

(VIII) Herbs Crushing/Processing : There should a dedicated area/room for cleaning/ processing of herbs.

1.1.3 Water Supply- (i) The water used in manufacture shall be purified as per BP/USP and of potable quality.

(ii) Manufacturers must have own 2 stage water purification plant for production of all kinds of oral preparation.

Adequate provision of water for washing the premises shall be made.

1.1.4 Disposable of Waste.- From the manufacturing section and laboratories the waste water and the residues which might be prejudicial to the workers or public health shall be disposed off.

1.1.5 Container's Cleaning.- In factories where operations involving the use of containers such as glass bottles, vials and jars are conducted, there shall be adequate arrangements separated from the manufacturing operations for washing, cleaning and drying of such containers.

1.1.6 Stores.- Storage should have proper ventilation and shall be free from dampness. It should provide independent adequate space for storage of different types of materials, such as raw material, packaging material and finished products.

1.1.7.1 Raw Materials.-All raw materials procured for manufacturing will be stored in the raw materials store. The manufacture based on the experience and the characteristics of the particular raw materials used in Homeopathy System shall decide the use of appropriate containers which would protect the quality of raw materials as well as prevent it from damage due to dampness, microbiological contamination or rodent and insect infestation, etc. If certain raw materials require such controlled environmental conditions, the raw materials stores may be sub-divided with proper enclosures to provide such conditions by suitable combination. While designing such containers, cupboard or areas in the raw materials store, care may be taken to handle the following different categories of raw materials:-

1. *Plant origin*
2. *Animal origin*
3. *Mineral/Chemical origin*
4. *Sarcodes*
5. *Nosodes*
6. *Imponderibilia*
7. Excipients etc.

Each container used for raw material storage shall be properly identified with the label which indicates name of the raw material, source of supply and will also clearly state the status of raw material such as 'Quarantine, UNDER TEST' or 'APPROVED' or 'REJECTED'. The labels shall further indicate the identity of the particular supply in the form of Batch No. or Lot No. and the date of receipt of the consignment.

Raw materials to be kept under quarantine (as area to be marked) before necessary in raw material store.

Dispensing booth : Raw materials to be issued using dispensing booth.

All the raw materials shall be sampled and got tested either by the in-house- Homeopathic, (Quality control technical person) or by the laboratories approved by the Government and shall be used only on approval after verifying. The rejected raw materials should be removed from other raw material store and should be kept in separate room. Procedure of 'First in first out' should be adopted for raw materials wherever necessary. Records of the receipt, testing and approval or rejection and use of raw material shall be maintained.

Sampling booth : Sampling for test to be performed a sampling booth.

1.1.7.2 Packing Materials- All packaging materials such as bottles, jars, foils, labels, capsules etc. shall be stored properly. All containers and closure shall be adequately cleaned and dried before packing the products.

1.1.7.3 Finished Goods Stores.- The finished goods transferred from the production area after proper packaging shall be stored in the finished goods stores within an area marked "**Quarantine**". After the quality control laboratory and the experts have checked the correctness of finished goods with reference to its packing/labeling as well as finished product quality as prescribed, then it will be moved to "Approved Finished goods Stock" area. Only approved finished good shall be dispatched as per marketing requirements. Distribution records shall be maintained as required.

If any Homeopathy &Herbal drug needs special storage conditions, finished goods store shall provide necessary environmental requirements.

1.1.8 Working space. – The manufacturing area shall provide adequate space (manufacture and quality control) for orderly placement of equipment and material used in any of the operations for which these employed so as to facilitate easy and safe working space to minimize or to eliminate any risk of mix-up between different drugs, raw materials and to prevent the possibility of cross contamination of one drug by another drug that is manufactured, stored or handled in the same premises.

1.1.9 **HEALTH, CLOTHING, SANITATION AND HYGIENE OF WORKERS.**- All workers employed in the Factory shall be free from contagious diseases. The clothing of the workers shall consist of proper uniform suitable to the nature of work and the climate and shall be clean. The uniform shall also include cloth or synthetic covering for hands, feet and head mouth/nose wherever required. Adequate facilities for personal cleanliness such as clean towels, soap and scrubbing brushes shall be provided. Separate provision shall be made for lavatories to be used by men and women, and such lavatories shall be located at places separated from the processing rooms. Workers will also be provided facilities for changing their clothes& shoes and to keep their personal belongings.

1.1.10 Medical Services: The manufacturer shall also provide:-

(a) Adequate facilities for first aid;

(b) Medical examination of workers at the time of employment and periodical check up thereafter by a physician once a year, with particular attention being devoted to freedom form infections. Records thereof shall be maintained.

1.1.11 machinery and Equipment's.- For carrying out manufacturing depending on the size of operation and the nature of product manufactured, suitable equipment either manually operated or operated semi-automatically or fully automatic machinery shall be made available. These may include machines for use in the process of manufacture such as crushing, grinding powdering, boiling, mashing, burning, roasting, filtering, drying, processing, filling, packing, labeling etc. to ensure case in movement of workers and orderliness in operation a suitably adequate space will be ensured between two machines or rows of machines. These equipment's have to be properly installed and maintained with proper cleaning. List of equipment's and machinery recommended is indicated in Part II A.

Proper Standard Operational Procedures (SOPs) for cleaning, maintaining and performance of every machine should be laid down.

1.1.12 Batch manufacturing records.- The licensee shall maintain batch manufacturing record of each batch of Homeopathic drugs manufactured irrespective of the type of product manufactured (classical preparation or patent and proprietary medicines). Manufacturing records are required to provide and account of the list of raw materials and their quantities obtained from the store, tests conducted during the various stages of manufacture like taste, colour, physical characteristics and chemical tests as may be necessary or indicated in the approved homoeopathic pharmacopeia These tests may include any in-house or pharmacopoeial test adopted by the manufacturer in the raw material or in the process material and in the finished product. These records shall be duly signed by production and Quality control Personnel respectively. Details of transfer of manufactured drug to the finished products store including dates and quantity of drugs transferred along with record of testing of the finished product, if any, and packaging, records shall be maintained. Only after the manufactured drugs have been verified and accepted quality shall be allowed to be cleared for sale.

It should be essential to maintain the record of date, manpower, machine and equipment's used and to keep in process record of various steps.

1.1.13 Distribution Records.- Records of sales and distribution of each batch of Homeopathic Drugs shall be maintained in order to facilitate prompt and complete recall of the batch, if necessary. The duration of record keeping should be at least for 3 years.

1.1.14 Record of Market Complaints.- manufacturers shall maintain a register to record all reports of market complaints received regarding the products sold in the market. The manufacturer shall enter all data received on such market complaints, investigations carried out by the manufacturers regarding the complaint as well as any corrective action initiated to prevent recurrence of such market complaints shall also be recorded. The register shall also be available for inspection during any inspection of the premises.

Records of any adverse reaction resulting from the use of Homeopathic drugs shall also be maintained in a separate register by each manufacturer. The manufacturer shall investigate any of the adverse reaction to find if the same is due to any defect in the product, and whether such reactions are already reported in the literature or it is a new observation.

Quality Assurance/Quality Control

1.1.15 **Quality Assurance/Quality Control** - Every licensee should have quality assurance systems to assure the quality and required to provide facility for quality control section in his own premises. The test shall be as per the homoeopathic pharmacopocial standard. Where the tests are not available, the test should be performed according to the manufacturer's specification or other

information available. The ***Quality assurance*** department shall verify all the raw materials, monitor in process, quality checks and control the quality of finished product being released to finished goods store warehouse. Preferably for such Quality control/Quality Assurance there will be a separate qualified person. The quality control section shall have the following facilities: -

1) For identification of raw drugs, reference books and reference samples should be maintained.
2) Relevant requisition & testing batch record should be maintained for the various processes.
3) To verify the finished products, controlled samples of finished products of each batch will be kept for 5 years.
4) To supervise and monitor adequacy of conditions under which raw materials, semi -finished products and finished products are stored.
5) Keep record in establishing shelf life and storage requirements for the drugs.
6) Manufacturers who are manufacturing patent proprietary homoeopathic medicines shall provide their own specification and control reference in respect of such formulated drugs.
7) The standards for identity, purity and strength as given in respective pharmacopoeias of homoeopathic systems of medicines approved by Government of Bangladesh shall be complied with.
8) All raw materials will be monitored for fungal, bacterial contamination with a view to minimize such contamination.
9) Quality control section will have a minimum of:

    (i) One person with Pharmacy /Chemistry/ Botany (taxonomist)/Biochemistry/ Applied chemistry having 4 years honours degree from recognized Universityand one Registered DHMS/Registered BHMS as per Drug policy 2016.
    (ii) The manufacturing unit shall have a quality control section. Alternatively, these quality control provisions will be met by getting testing etc., from a recognized laboratory for Homeopathic, drugs. The manufacturing company will maintain all the record of various tests get done from outside recognized laboratory.
    (iii) List of equipment's recommended is *indicated in Part II.*

PART II

LIST OF MACHINERY, EQUIPMENT AND MINIMUM MANUFACTURING PREMISES REQUIRED FOR THE MANUFACTURE OF VARIOUS CATEGORIES OF HOMEOPATHIC MEDICINES.

Sl. No.	**Category of Medicine**	**Minimum space required for manufacturing**	**Machinery/ equipment recommended**
(1)	(2)	(3)	(4)
	Factory	**Min. *464.51* sq meter (5,000 sq ft)** covered area with separate cabins partitions for each activity. If Herbal medicines are manufactured in the same premises an additional separate area of 2000sq. ft will be required.	*Must have required machinery and equipment for the relevant products.*
1.	a) Mother Tincture & solutions section	Min. 55 sq. meter (592 sq. feet) For basic installations	The following equipment and facilities shall be provided:- (i) Macerators with lids (all made of stainless steel of grade 304 or neutral glass); (ii) Percolators (all made of stainless steel of grade 304); (iii) Filter press/Sparkler filter or suitable filtering device (all metal parts shall be of stainless steel); (iv) Mixing and Storage vessels.(Stainless steel of grade 304 (v) Portable stirrers (Rod, blades and screws shall be of stainless steel); (vi) Macerators and percolators for preparing mother solutions of materials of chemical origin. These shall be of material, which will not react with the chemicals, used and which do not bleach; and (vii) Filling and sealing machine. (viii) Water still/water purifier; (ix) Bottle washing machine Note : Herbs cleaning crushing/ sieving& processing to be done in separate area.
	b) Herbs cleaning crushing/ sieving & processing	Min. 15 sq. meter (160 sq. feet) For basic installations	01. Herbs cleaning machine 02. Dryer 03. Pulverizing machine 04. Grinding machine 05. Shifter machine (for sieving) 06. Blower machine 07. Dust collector
2.	Potentization Section	Min. 20 sq. meter (215 sq. feet) For basic installations	(i) Work benches with washable impervious tops; (ii) Facilities for orderly storage of different potencies and back-potencies of various drugs; (iii)Suitable devices for measuring and dispensing of potencies/back-potencies into the potentization phials; (iv) Potentiser with counter. Note –

			(a) The requirement of potentiser is not mandatory. The process may be done manually also with proper SOPs. Potentiser, if used, shall be properly validated and shall be calibrated every time before commencement of work for proper performance. (b) The manufacturer shall use back-potencies procured from Licensed manufacturer and the firm shall maintain proper records of purchase or shall prepare own back-potencies. Every container of potencies and back –potencies shall be kept properly labelled and there shall not be mix-up of different medicines and different potencies
3.	Tablet Processing (Trituration & Biochemic) Section	Min. 70 sq. meter (750 sq. feet) For basic installations *An area of 55 square meters shall be provided for basic installations. i) The area shall be suitably divided into cubicles to minimize cross contamination, mix-up etc. ii) Filling & packing & labeling in separate area.*	The following basic equipment and facilities shall be provided:- (i) Triturating Machine; (ii) Disintegrator; (iii) Mass Mixer; (iv) Granulator; (v) Tablets punching /Compression Machine; (vi) Kettle (steam or electrically heated) for preparing solutions; (vii) Driers for drying granules and tablets; (viii) Sieved separator (stainless steel); (ix) Multi mill (x) Balances;
4.	Capsule Section	Min. 20 sq. meter (215 sq. feet) For basic installations	The following basic equipment and facilities shall be provided:- (i) Mixer (ii) Encapsulation Medicine (Hand operated Semi Automatic/Automatic) (iv) Dryer (v) Dehumidifier (vi) Capsule polish machine (vii) Capsule sorting machine
5.	Blister Section	Min. 12 sq. meter (129 sq. feet) For basic installations	The following basic equipment and facilities shall be provided:- (i) Blister Packing Machine
6.	Liquid Combination section	Min. 25 sq. meter (270 sq. feet) For basic installations	The following basic equipment and facilities shall be provided:- i. Mixing and storage tanks. (stainless steel of grade 304); ii. Portable stirrer (Rod. Blades and screws shall be of stainless steel); iii. Filter press/Sparkler filter (all metal parts shall be of stainless steel); iv. Filling and sealing machine; v.) Labeling machine vi.) Distillation plant vii) Extraction vat viii) Transfer pump (1) Adequate number of workbenches shall be provided. (2) Visual inspection table shall be provided. This shall comprise of a colour contrast background with lamp for providing diffused light, mounted on a suitable table.

7.	Ointment Section	Min. 20 sq. meter (215 sq. feet) For basic installations	The following basic equipment and facilities shall be provided:- (i) Mixing tanks(Stainless steel) (ii) Kettle (steam or electrically heated) for preparing solutions (iii) Suitable emulsifier (iv) Filling and sealing machine/crimping machine (v) Filtering equipment. (vi) Balance and weights.
8.	Ophthalmic Preparations section	Min. 20 sq. meter (215 sq. feet) For basic installations with asceptic filling	The following basic equipment and facilities shall be provided: (i) Hot air oven, electrically heated, with thermostatic control; (ii) Laminar Air Flow bench; (iii) Air Handling Unit with HEPA filters to provide filtered air and positive pressure to the section and air locks; (iv) Ointment mill/colloidal Mill; (v) Mixing and storage tanks.(stainless steel of grade 304); (vi) Pressure vessels, as may be needed; (vii) Sintered glass funnels, Seitz Filter/Filter candle; (viii) Vacuum pump; (ix) Filling machines for liquids ointments etc.; (x) Autoclaves with pressure and temperature gauges; and (xi) Necessary workbenches, visual inspection bench, etc.;
10	Containers and Closures Section	Min. 20 sq. meter (215 sq. feet) For basic installations	This area shall have the following facilities: (i) Washing tanks with suitable mechanical or hand operated brushes; (ii) Rinsing tanks. Purified water shall be used for rinsing; (iii) Closures washing/macerating tanks; (iv) Driers;
11.	Quality Control Department	Min. 38 sq. meter (410 sq. feet) For basic installations *A separate quality control division shall be provided in the premises. The section shall be under the control of an approved technical officer, independent of the manufacturing division and directly responsible to the management. The section shall be responsible for ensuring the quality of all raw materials, packing materials and finished goods*	The following equipment shall be provided:- (i) HPLC (ii) UV-Spectrophotometer (iii) Microscope of suitable magnification (iv) Dissecting microscope; (v) TLC apparatus; (vi) UV lamp viewer; (vii) Monopan Digital Electronic Balance; (viii) Hot air oven; (ix) Distillation apparatus; (x) Water Bath; (xi) Polarimeter; (xii) Refractometer; (xiii) Melting point apparatus; (xiv) P^H meter; (xv) Magnetic stirrer; (xvi) Table Centrifuge; (xvii) Muffle furnace/electric Bunsen;

			(xviii) Moisture determination apparatus; (xix) Rotary microtome/Section cutting facilities; (xx) Tablet Disintegration Machine. (xxi) Friability test apparatus (xxii) Hardness tester (xxiii) Glass wares for wet chemicals analysis (xxiv) Leak testing apparatus for strip/ blister (xxv) Standard Herbarium sheet. (xxvi) Stability Chamber (xxvii) Burate (xxviii) Mortar and pestle (xxix) Picnometer (xxx) Volumetric flask (xxxi) Test tube, Glass rode, beaker, pipette
12,	Microbiology Lab	Min. 15 sq. meter (160 sq. feet) For basic installations	(i) Oven (ii) Freeze (iii) Horizontal laminar air flow (iv) Autoclave (v) Incubator (vi) P^H meter (vii) Balance (viii) Colony counter (ix) Cooled incubator

Note: - The above requirements of machinery, equipment's, space, qualifications are made subject to the modification at the discretion of the Licensing Authority, if he is of the opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter then in the circumstances in a particular case.

I. PARTICULARS TO BE SHOWN IN MANUFACTURING RECORDS

A. Substances other than parenteral in preparation in general.

1. Serial number
2. Name of the product
3. Reference of Master Formula Records.
4. Lot/Batch Size.
5. Lot/Batch Number
6. Date of commencement of manufacture and date of completion of manufacture and assigned date of expiry.
7. Name of all ingredients, specifications quantities required for the lot/Batch size and quantities actually used. All weighing and measurements shall be carried out by a responsible person and initialed by him and shall be counter-checked and signed by the competent technical staff under whose personal supervision the ingredients are used for manufacture.
8. Control Numbers of raw materials used in the formulation.
9. Date, time and duration of mixing.
10. Details of environmental controls like room temperature, relative humidity.
11. Date of granulation, wherever applicable.
12. Theoretical weight and actual weight of granules/powder blend.
13. Records of in-processes controls (Periodically whenever necessary)
    - i Uniformity of mixing.
    - ii Moisture content of granules/powder in case of Tablet/Capsules.
    - iii pH of solution in case of liquid.
    - iv Weight variation of tablet.
    - v Disintegration time of tablet.
    - vi Hardness of tablet
    - vii Friability test of tablet
    - viii Leak test in case of strip packing.
    - ix Filled volume of liquids.
    - x Quantity of tablets/capsules in the final container.
    - xi Content of ointment in the filled containers.
14. Date of compression in case of Tablets/date of filling in case of capsules.

15. Date of sealing/coating polishing in case of tablets/capsules wherever applicable.
16. Reference to analytical Report number stating the result of test and analysis.
17. Separate records of the disposal of the rejected batches and of batches withdrawn from the market.
18. The theoretical yield and actual productions yield and packing particulars indicating the size and quantity of finished packing.
19. Specimen of label/strip, carton with batch coding information like Batch Number, date of manufacture, date of expiry, retail prices as applicable, stamped thereon and inserts used in the finished packing's.
20. Signature with date of competent technical staff responsible for the manufacture.
21. Counter-signature of the head of the testing units or other approved person-in-charge of testing for having verified the batch records and for having released and batch for sale and distribution, the quantity released and date of release.
22. Date of release of finished packing and quantity released for sale and distribution.
23. Quantity transferred to warehouse.

II. RECORDS OF RAW MATERIALS

Records in respect of each raw material shall be maintained indicating the date of receipt, invoice number, name and address of the manufacturer/supplier, batch number, quantity received, pack size, date of manufacture, date of expiry, if any, date of analysis and release/rejection by quantity control, analytical report number, with special remarks, if any, quantity issued, date of issue and the particulars of the name and batch numbers of products for the manufacture of which issued and the proper disposal of the stocks.

III. PARTICULARS TO BE RECORDED IN THE ANALYTICAL RECORDS.

A. TABLETS AND CAPSULES.

1. Analytical report number.
2. Name of the sample
3. Date of receipt of sample
4. Batch/Lot number
5. Protocols of tests applied.
    a) Description
    b) Identification
    c) Uniformity of weight
    d) Uniformity of diameter (if applicable).
    e) Disintegration test (time in minutes)
    f) Hardness
    g) Friability

Note: - Records regarding various test applied (including readings and calculations) should be maintained and necessary reference to these records should be entered in Col. 5 above whenever necessary.

6. Signature of the Analyst.
7. Opinion and signature of the approved Analyst.

Note: - Records regarding various test applied (including readings and calculations) should be maintained and necessary reference to these records should be entered **in 7 above**, wherever necessary.

8. Signature of the Analyst.
9. Opinion and signature of the approved Analyst.

B. FOR OTHER DRUGS

1. Analytical report number.
2. Name of the sample.
3. Batch/Lot number.
4. Date of receipt of sample.
5. Protocol of tests applied.
    i Description.
    ii Identification.
    iii Any other tests.
    iv Results of Assay.

Note :- Particulars regarding various tests applied (including readings and calculations) shall be maintained and necessary reference to these records shall be entered in Column 5 above, wherever necessary.

6. Signature of Analyst.
7. Opinion and signature of the approved Analyst.

C. **RAW MATERIALS**

l. Serial number,
2. Name of the materials.
3. Name of the manufacturer/supplier.
4. Quantity received.
5. Invoice/Challan number and date.
6. Protocols of test s applied.

Note: - Particulars regarding various tests applied (including readings and calculations) shall be maintained and necessary reference to these records shall be entered in Column 6 above, wherever necessary.

D. **CONTAINER, PACKING MATERIALS ETC.**

1. Serial number.
2. Name of the item.
3. Name of the manufacturer/supplier.
4. Quantity received.
5. Invoice/Challan number and date 6, Results of tests applied.

Note:- Particulars regarding various tests applied shall be maintained and necessary reference to these records shall be entered in column 6 above.

7. Remarks.
8. signature of the examiner.

Note: - The foregoing provisions represent the minimum requirements to be complied with by the licensee. The Licensing Authority, may however, direct the nature of records to be maintained by the licensee for such products as are not covered by the categories described above.

2. The Licensing Authority may permit the licensee to maintain records in such manner as are considered satisfactory, provided the basic requirements laid down above are complied with.
3. The Licensing Authority may at its discretion direct the licensee to maintain records for such additional particulars as it may consider necessary in the circumstances of a particular case.

I. Particulars to be shown in the manufacturing Records:

1. Serial number.
2. Name of the product.
3. Lot/Batch size.

4. Lot/Batch number
5. Date of commencement of manufacture and date when manufacture was completed.
6. Names of all ingredients, quantities required for the lot/batch size, quantities actually used.
7. Control reference numbers in respect of raw materials used in formulation.
8. Reference to analytical report number.
9. Actual production and packing particulars indicating the size and quantity of finished packing.
10. Date of release finished packing for distribution sale.
11. Signature of the expert staff responsible for the manufacture.

II. Records of Raw Materials

Records in respect of each raw material shall be maintained indicating the quantity received, control reference number, the quantity issued from time to time, the names and batch numbers of the products for the manufacture of which the said quantity of raw material has been issued and the particulars relating to the proper disposal of the stocks.

EXPIRY DATE

Expiry date of homoeopathic medicines depends on nature of following drugs.

a. Liquid potency/ attenuation (dilution)
b. Mother tincture/solutions
c. Solid potency; Trituration & Biochemic /cells salts
d. Combination liquid preparation
e. Combination tablets.
f. Ointment/Cream (external use)
g. Eye /Ears Drops.

Liquid potency/ attenuation

1. Usually liquid potency medicine have higher strength of Ethyl Alcohol (80-90%) as such these kind of drugs do not require expiry date i.e., Expiry date is not applicable (N/A).

2. Mother tincture : In mother tincture varied strength of ethyl alcohol depending on the herbs/ minerals/chemicals as such expiry date of such product may be ascertained after stability test or with reference to imported European and USA registered homoeopathic mother tincture/solutions.

3. Biochemic/Homoeopathic tablets; are manufactured with more than 95% lactose so incase of the solid potency (Trituration), Bio-chemic, Bio-chemic combination medicine expiry date

can be ascertained by stability test or self life of lactose used (certificate of analysis) or with reference to imported European and USA registered Homoeopathic Biochmeic Medicine

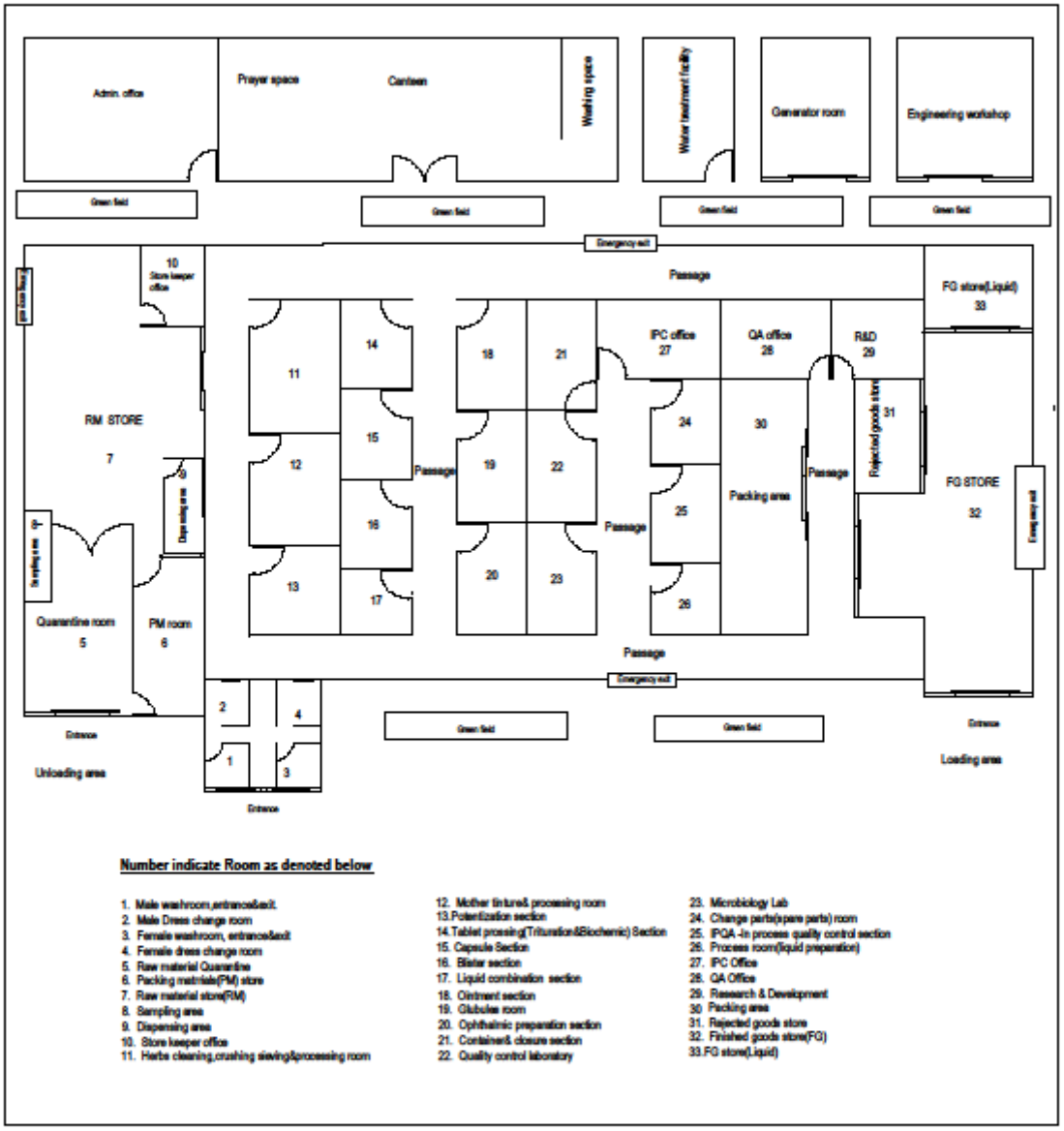
4. Ointment/Cream : There must be expiry date in the products, it can be ascertained by stability test or with reference to imported European and USA registered Homoeopathic ointment, cream, get etc..

5. Eye/Ear Drops (sterile production) : These product must have expiry date which should be ascertained by stability test or with reference to imported European and USA registered Homoeopathic Eye drops/Ear drops.

NOTE 1: The Licensing Authority may permit the licensee to maintain records in such manner as is considered satisfactory, provided the basic requirements laid down above are complied with.

NOTE 2: The licensing Authority may direct the licensee to maintain records for such additional particulars, as it may consider necessary in the circumstances of a particular case

A MODEL LAYOUT FOR HOMEOPATHIC MEDICINE MANUFACTURING FACTORY



A Typical General Factory Layout for Homoeopathy Manufacturing Plant (Not to scale)

For Homoeopathic Pharmaceutical Industries

CHECKLIST OF GMP INSPECTION FOR DRUG INSPECTORS

Sl. No	Areas/Activities to be Audited	Observations	
		Document Review	Remark
1.	**GENERAL**		
	- Name and address of Unit - MFG.Lic No. - Telephone - Fax: - Email: - Names and designation of the inspection team:		
2.	**PERSONAL**		
	Name of In charge a) production b) quality control		
	Number of Production Supervisors/Asstt. Mfg./Chemist		
	Number of Analysts		
	Have all personal received GMP Training?		
	Is Training Documented?		
	What is the periodicity of the training?		
3.	**FACTORY PREMISES**		
	Does manufacturing unit have adequate space for a) Receiving and storing raw material. b) Manufacturing process areas. c) Quality control section. d) Finished goods store. e) Office f) Rejected goods/drugs store.		
4.	**LOCATION AND SURROUNDINGS**		
	Is the establishment located away from environmentally polluted		

	areas?		
	Is the establishment located away from areas adjacent to open sewerage, drain/public lavatory or any factory which produces excessive, disagreeable odour.		
	Are sewage, trash and other effluent disposal provided?		
5.	**BUILDINGS**		
	Do the internal design and layout of establishment permit good hygiene practices including protection from cross- contamination?		
	Are surfaces of walls, partitions and floors made of impervious materials and capable of being kept clean?		
	Do walls and partitions have smooth surface?		
	Are floors constructed to allow adequate cleaning and drainage?		
	Are doors, windows, ceiling and overhead fixtures constructed and finished to minimize build up of dirt, condensation and shedding of particles and easy to clean?		
	Are working surfaces that come into direct contact with drugs of sound condition, durable and easy to clean, maintain and disinfect? a) Any open drain blocked sewer or public lavatory nearby? b) Are any products other than drugs manufactured in the same building?		
	Is there adequate space for equipment, material and movement of personal and materials?		
	Is there any programme/system to check of birds, rodents and insects?		
	Are lightening and ventilation adequate?		
	Are facilities for changing street clothes, footwear, washing and toilets adequately and satisfactorily maintained?		
	Is the space for drying of raw		

	materials satisfactory?		
6.	**WATER SUPPLY**		
	Is there adequate supply of potable water?		
	Does the potable water meet the specifications published HPI specifications?		
	Is only potable water Used in HOMOEOPATHIC medicines?		
7.	**DISPOSAL OF WASTE**		
	Are drainage and water disposal systems designed, constructed and maintained in such a way as to avoid contamination of HOMOEOPATHIC products?		
	Are the waste water and residues disposed of after suitable treatment as per guidelines of pollution control authorities?		
	Are the arrangements for the following adequate? a) Disposal of solid/semi solid waste b) Disposal of sewage c) Disposal of Liquid laboratory waste? d) Disposal of Management of gaseous pollutants?		
	Is efficient treatment plant in existence / if yes, give comment on it?		
	Are fume hoods of adequate design in existence and used wherever necessary?		
8.	**CLEANING OF CONTAINERS**		
	Is there proper arrangement for washing, cleaning and drying of containers? Is this area separated from manufacturing area?		
9.	**STORES**		
	Is there independent adequate space for storage of different types of		

	materials such as raw material, packaging material and finished products?		
	Are HOMOEOPATHIC medicine storage facilities designed and constructed to - Permit adequate maintenance and cleaning? - Avoid pest menace and harbourage? - Enable drugs to be effectively protected from contamination? - Provided the necessary environment to prevent spoilage?		
	Are storage facilities deigned, constructed and maintained to ensure that malicious or accidental contamination of HOMOEOPATHIC medicines with harmful materials is prevented?		
10.	**RAW MATERIALS STORES**		
	Are raw materials or ingredients checked for parasites, undesirable microorganisms, pesticide or decomposed or extraneous substances		
	Are raw materials or ingredients inspected and tested before processing?		
	Are raw materials or ingredients subjected to effective stock rotation?		
	Is the area adequate?		
	Are the ventilation and lighting of stores adequate?		
	Is the Raw Material store segregated for different types of Raw Material? - Raw materials of metallic origin - Raw materials of mineral origin - Raw materials of animal source - Fresh herbs - Dry herbs or plant parts - Excipients etc. - Volatile oils/perfumes and flavours		

	- Plant extracts and exudates/resins - Others		
	Is special area with special condition provided for special Raw Materials?		
	Are there labels for material of different status i.e. quarantine, tested and releases for use and rejected?		
	Are these labels of different colours?		
	Are labels on containers of RM to be used in manufacture checked with regard to identity, quantity and QA approval? If not give details/		
	Is there the following information on the labels? - Name of material - Batch number - Analysis number - Date of release/rejection? - Date of testing? - Date of expiry?		
	Is the sampling performed by quality control personal?		
	Are there sampling procedures?		
	Are the containers provided for storage of raw material suitable to preserve the quality?		
	Is exterior storage available for : Solvent storage area? Inflammable material storage area? Whether safety measures provided have been assessed by regulatory agency if any? Is SOP‘s available for handling of these materials? Are SOP‘s for cleaning of containers and closures available before packing of products?		
	Is the weighing area segregated?		
	Are lighting and ventilation adequate?		
	Is the area clean?		
	Do the personal wear appropriate clothing?		
	Is there danger of cross contamination during weighing?		
	Are the scales and balance calibrated regularly and records maintained?		
	Are the containers of the raw		

	materials to be weighed, cleaned before opening?		
	After weighing, are these containers sealed?		
	Are the raw materials for each batch, after weighing properly identified and checked? Are adequately clean and dried equipment used for dispensing materials from the containers?		
	Is FIFO principle adopted?		
11	**PACKING MATERIALS**		
	Is the area adequate with reference to packing material?		
	Are the containers and closures adequately cleared and checked?		
12.	**FINISHED GOODS STORES**		
	Is the area adequate with reference to materials stored?		
	Are lighting and ventilation adequate?		
	Are there inventory records to show:		
	Quantities		
	Batch number		
	Date of receipt		
	Have the distribution records been maintained?		
	Do distribution records provide sufficient information for drug recall purpose?		
	Is there segregation area for retrieved good?		
	Are records available for the retrieved goods?		
	Is there any marked quarantine area?		
	Is there space for special storage conditions (environmental condition), if required?		
13.	**WORKING SPACE**		
	Is space adequate as per manufacturing operations?		
	Is machinery along with working manual orderly placed with adequate		

	space?		
	Are there adequate precautions to check cross contamination?		
14.	**HEALTH ,CLOTHING, SANITATION AND HYGIENE OF WORKERS**		
	Are workers free from contagious disease?		
	Are workers properly uniformed?		
	Are there separate lavatories for men and women?		
	Is there provision for changing their cloth and to keep personal belongings?		
	Are adequate facilities like wash-basin with running water hand drier & clean towels, etc., available for personal hygiene before entering into production area?		
	Are personnel instructed to observe personal hygiene?		
	Are hygiene instructions displayed in change rooms and strategic locations?		
	Is the sanitation system monitored for effectiveness?		
	Is the sanitation system periodically verified by inspections? Is microbiological sampling of environment and HOMOEOPATHIC drugs contact surfaces carried out?		
	Is the sanitation system regularly reviewed and adapted to reflect changed circumstances?		
15	**MEDICAL SERVICES**		
	Is medical file of each worker maintained separately?		
	Is recruitment of an employee preceded by medical examinations?		
	What is the periodicity of subsequent medical examinations?		
	Is an employee whose state of health is doubtful immediately removed from work site until he is fully recovered?		

16.	**MACHINERY AND EQUIPMENT**		
	Is manually operated or semi-operated or automatic machines are used for Crushing, grinding, powdering, boiling, mashing, burning, roasting, filtering, drying, filling, labelling and packing ?		
	Are equipment and containers coming into contact with HOMOEOPATHIC drugs designed such that they can be adequately cleaned, disinfected and maintained?		
	Are equipment made of nontoxic materials?		
	Are equipment used to cook, heat, treat, cool, store designed to achieve the required temperature as rapidly as necessary?		
	Are equipments used to cook, heat, treat, cool, store designed to monitor and control the required temperature?		
	Are containers for waste suitably identified?		
	Are containers for waste closable to prevent malicious or accidental contamination of HOMOEOPATHIC Medicines?		
	Is the equipment adequate for intended use?		
	Is it constructed in such a way that lubricants, coolant, etc. cannot contaminate the drug product?		
	Does the equipment permit cleaning and maintenance?		
	Does the equipment show its status i.e. clean, dirty, batch contents?		
	Do all apparatus/equipment bear appropriate labels to identify the product for which the equipment is used, its batch no., date of manufacturing etc.		
	Are SOPS available for cleaning maintenance and sanitation of major equipment?		
	Are log books maintained for cleaning maintenance and sanitation of major equipment?		

	Are SOP‘s readily available to operators		
	If automatic electronic or mechanical equipment is used ,are there: • Written programs for calibration/inspection • Checks to ensure that may changes are made only by authorized persons/ Are suitable closures or lids available to protect the changes in properties of material exposed to outside atmosphere?		
17.	**BATCH MANUFACTURING RECORDS**		
	Are appropriate records of processing, production and distribution kept?		
	Are SOP’s available for the following - Receipt of raw material and other components? - Quarantine and storage? - Quality control system and approval/rejection - Release of production - In process testing and control - Finished product? - Storage of finished product? - Distribution - Returned goods - Recalls and complaints - Cleaning and maintenance? - Quality control of water - For reworking of non-conforming batches in existence? If yes, check)		
	Are there additional documents like log books, notebooks or other similar records available to show execution of various functions?		

	Are there records of receipts of materials and do these have following information? (goods Receipt Note-GRN) - Receiving GRN documents number? - Date of receipt? - Supplier? - Manufacturer? - Manufacture‘s batch number? - Type and size of containers? - Number of containers and conditions?		
	Are specifications available for all materials?		
	Are they dated authorized?		
	Are test methods validated?		
	Are periodic reviews of specification carried out to ensure compliance with new /revised National/international pharmacopoeia?		
	Are these records of stock and issue of raw materials and do these have following information: - Opening balance? - Date of receipt? - Quantity received? - Name and batch number assigned by the manufacturer? - Invoice number, date name and address of supplier? - Analysis receipt no. and date? - Date of expiry ,if any? - Name and batch number of product for manufacture for which issued? - Balance? - Signature of issuing person?	`	
	Are there master formulation records for each drug product being produced?		
	Is there a separate master production documents for each dosage form/batch size?		
	Are these master production records signed and dated by competent person?		

	Is a batch production record prepared for every batch produced?		
	Is it reproduction of the appropriate master production documents or it has all critical information about the batch?		
	Are batch records retained for at least one year after expiry date?		
	Has it been checked for accuracy, signed and dated by a responsible person?		
	Are the records maintained by QC for all the tests carried out? **Do these records include:** - The name of the product - Number of the batch being manufactured? - Issue slip with lab ref. No - Job cards? - Graphs, chart, spectra, etc? - List of major equipment used? - In-process testing reports? - Calculations of yield? - Notes on deviations with signed authorization? - Signature of individuals of who performed the tests? - Material returns to store slip? - Lab report of final product? - Review of results for any raw material issued under ‒positive Recall‖? - Signature of the designated person responsible for the review of records for accuracy and compliance with established standards?		
	Are other associated records available?		
	Is documentation available readily for examination?		
	Are batch production records capable of giving complete history of the batch right from the raw material stage to the distribution of finished products?		
18	**Records And Registers**		
	Are records of sale and distribution		

	of each batch of HOMOEOPATHIC drugs maintained? Are records maintained for a period of one year after the expiry of a batch or for three years whichever is later?		
19.	**QUALITY CONTROL**		
	What is the QC area?		
	Has Quality Control section minimum of: a) One person with Degree qualification in Homoeopathy; b)One chemist with Bachelor in Science or Pharmacy or Pharmacy (Homoeopathy) and; c)One Botanist (Pharmacognosist) with bachelor in Science (medical) or Pharmacy or Pharmacy (Homoeopathy)?		
	Are master control procedures signed and stated by authorised persons?		
	Do these control procedure include specifications, test procedure or other control procedure for:		
	- Raw materials		
	- In process materials		
	- Packaging and labelling materials?		
	- Finished products?		
	Are the procedure in written form and readily available to QC personnel for acceptance of reprocessed material?		
	Are the procedure in written form and readily available for acceptance of reprocessed material?		
	Do these control procedure include specifications test procured or other control procedure for :		
	- Raw material		
	- In process material		
	- Packaging and labelling materials		
	- Finished products?		
	Are samples collected by QC personal		
	Is there special room for		

	microbiological and sterility testing?		
	Is the environment of room controlled?		
	Are only materials, containers and appliance necessary for the job in hand stored in the vicinity of the manufacturing areas and are these properly labelled with name of the product, batch no. date etc.?		
	Are all raw materials, containers, closures, label and printed packaging material approved and released by QC for use in manufacture of drugs products		
	Are in-process controls carried out by QC personnel?		
	Are semi-finished products tested for appropriate tests when necessary?		
	Is bulk finished product tested for established specifications before packing?		
	Is every finished product tested for established specifications before release for sale?		
	Does the QC maintain records of all the tests carried out?		
	Does the QC review all production and control records to ensure compliance with established written procedure before a batch of the product is released for sale?		
	Reference standards: a) Are reference standards (R.S) available? b) Are these RS or working standards (WS)? c) Are WS standardised against RS or CRS? d) Are RS stored properly (at appropriate temperature under dehumidified conditions)? e) Are records of R.S and their standard maintained?		
	Are samples in sufficient quantity for testing twice retained of starting materials and finished products for future examination, in case of need?		
	Are quality control procedures validated?		

	Is written programs available for stability including the following:		
	- Sample storage condition		
	- Room temperature?		
	- Sample size and test intervals?		
	- Reliable and specific test methods?		
	- Testing in the same containers closure system in which it is marketed?		
	- Date and expiration date if any?		
	- Established of in-house specification?		-
	- Does the firm provided the equipment as recommended in Part II C ?		
20	**REQUIREMENT FOR STERILE PRODUCT**		
	A. Manufacturing areas		
	- Is there separate manufacturing area		
	- Are their air locks for entry?		
	- Is there dust free and ventilated for air supply		
	B. Precautions against contaminations and mix.		
	- Are manufacturing operations being carried out in a separate block of adequately isolated building		
	- Is there appropriate pressure differential in the process area.		
	- Is suitable exhaust system provided?		

	- For aseptic manufacturing proper air supply (filtered through HEPA) provided?		

Reference:

1. National Drug Policy – 2016
2. THE DRUGS (CONTROL) ORDINANCE, 1982
3. WHO guidelines on good manufacturing practices (GMP) for herbal medicines
4. GUIDELINES FOR INSPECTION OF GMP COMPLIANCE BY HOMOEOPATHIC DRUG INDRUSTY, Ministry of AYUSH (Drug Control Cell), Government of India
5. The Homoeopathic Pharmacopoeia of the United State
6. Homoeopathic Pharmacopoeia of Bangladesh
7. Safety issues in the preparation of homoeopathic medicines, world health organization.
8. MHRA, The homoeopathic registration scheme, guidance for manufacturers and suppliers. MHRA Guidance Note No. 17