FOOD AND DRUGS AUTHORITY

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Guideline on GMP Requirements for Drugs Manufacturing Facilities

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Document Revision History

SN.	Effective Date	Ver. No.	Description of Change (Section Revised)
1	01/12/2022	01	Initial issue
2	26/09/2024	02	i. General review of in line with new format for guideline. ii. Addition of the link to the landing page on the WHO's website for the current versions of the GMP related guidelines.

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Acknowledgements

It is acknowledged that, in the development of this, reference was made to the following sources:

- WHO good manufacturing practices (GMP): main principles for pharmaceutical products
- WHO (2007). WHO updated supplementary guidelines on good manufacturing practices (GMP) for herbal medicines.
- Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PIC/S Guidance on Classification of GMP Deficiencies
- The Public Health Act, 2012 (Act 851)

Executive Summary

This document is a guideline that prescribes how a GMP inspection of a drug manufacturing facility shall be carried out by the Food and Drugs Authority Ghana. It adopts WHO Technical Report Series (TRS) guidelines particularly the WHO TRS 986, Annex 2 and associated WHO supplementary guidelines and provides a high-level summary of the 17 elements of GMP as per the WHO Technical Report Series (TRS) guidelines particularly the WHO TRS 986, Annex 2. The guide for the classification of inspection findings have been adopted from the Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-Operation Scheme, PIC/S Guidance on Classification of GMP Deficiencies. Possible decisions and penalties emanating from the GMP inspection has also been covered in this guideline.

The guideline highlights the legal basis for the inspection activity provided for by the Ghana public Health Act, Act 851 of 2012 and the steps in the inspection process while indicating the responsibilities of the regulator and the inspected company where applicable.

The objective of this guideline is to serve as a guide to applicants and manufacturing facilities in the conduct of GMP inspections. It is also to increase transparency in the FDA's inspection activities and build confidence and accountability in the inspection process via public availability of information.

1. INTRODUCTION

The Food and Drugs Authority (FDA) is an agency of the Ministry of Health (MoH), mandated under the Public Health Act, 2012, Act 851 to ensure the quality, safety, and efficacy/performance of health products. The FDA executes this mandate through Registration, Inspections, Licensing, Surveillance and Clinical Trial activities.

To enhance the inspections and licensing functions of the FDA, this guideline is hereby made to provide information on the current codes of Good Manufacturing Practice (cGMP) requirements for drug manufacturing facilities.

Drugs manufacturing facilities shall therefore be subjected to pre-licensing and post-licensing inspections and are required to comply to the GMP requirements outlined in this guideline to ensure that their operations promote the production of quality, safe and efficacious drugs and to facilitate their licensing.

This Guideline is hereby promulgated for information, guidance, and strict adherence by all concerned.

1.1 Legal Basis

1.1.1 The following sections of the Public Health Act 2012, Act 851 mandates the Authority to carry out inspections and licensing of manufacturing facilities to achieve the desired safety, quality, and efficacy of the products for human and animal use regulated by the Authority.

- Section 115: Control of manufacturing
- Section 130: Registration of premises
- Section 131: Licences and permits.

1.1.2 Section 148 of The Public Health Act, 2012, Act 851 further mandates the Authority to issue guidelines and codes of practice in connection with products regulated by the Authority and persons in the industry and are required to comply. It is based on this legal provision that this guideline has been developed.

1.1.3 In accordance with Section 130(1) of the Public Health Act, 2012 (Act 851), the manufacturing of drugs shall not be carried out except in premises registered (licensed) by the Food and Drugs Authority (FDA) for that purpose.

1.1.4 Pursuant to Section 118(1), drugs manufactured by business entities in licensed facilities are required to be registered with the Authority before placing them on the Ghanaian market.

1.1.5 As per Section 115 of the Public Health Act 2012, Act 851, the manufacturing process in the facilities shall be carried out under the supervision of a person having appropriate knowledge and qualification in the product being manufactured.

1.2 Scope

1.2.1 This Guideline applies to all business entities duly registered by the Registrar-General Department with intention to manufacture drugs in Ghana and to continue manufacturing of same.

1.2.2 It applies to drug manufacturing entities whose products are marketed or intended to be marketed in Ghana.

1.2.3 Foreign manufacturing entities will be inspected to confirm compliance with this guideline on Good Manufacturing Practice (GMP) requirements for drugs manufacturing facilities

Note

a. GMP inspections of pharmaceutical facilities and food supplements shall be conducted in line with relevant WHO guidelines and their stated references. The latest versions of each guideline as revised by the WHO, as available shall be applicable in each case (see the link in [b] below).

b. The complete list and the current version of applicable WHO GMP guidelines are available on the WHO landing page https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/production

2. DEFINITIONS AND ABBREVIATIONS

2.1 Abbreviations

(a) CAPA: Corrective action and Preventive action
(b) EPA: Environmental Protection Agency
(c) GMP: Good manufacturing Practices
(d) QMS: Quality Management System
(e) QRM: Quality Risk Management
(f) WHO: World Health Organization

2.2 Definitions

The terms and their definitions used in the adopted WHO documents and guidelines that are widely used by the WHO Member States applies.

2.3 Authority: Food and Drugs Authority

2.4 Drugs: Drugs includes

(a) a substance referred to in a publication mentioned in the Fourth Schedule of the public Health Act 2012, Act 851
(b) a substance or mixture of substances prepared, sold or represented for use in
    (i) the diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the symptoms of it, in man or animal, or
    (ii) restoring, correcting or modifying organic functions in man or animal, and
(c) nutritional supplements.

2.5 Notification:

Changes to a manufacturing facility that could have minimal or no adverse effects on the overall safety, efficacy and quality of the finished product. Annual notification (AN) do not require prior acceptance but must be notified to FDA within 12 months following implementation of the change.

3. DRUGS GMP REQUIREMENTS

General Information

(a) As a general principle, manufacturers, and potential manufacturers of drugs that are intended to be marketed in Ghana are required to comply with all WHO Guidelines that are applicable to Good Manufacturing Practices (GMP) as adopted. The main principles can be found in the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty- eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986, Annex 2) titled "WHO good manufacturing practices for pharmaceutical products: main principles". The related guidelines and their references are as listed in Appendix I. The latest versions of each guideline as revised by the WHO shall be applicable in each case.

(b) Drugs manufacturing entities shall be inspected to confirm compliance to Good Manufacturing Practice (GMP) requirements spelt out in the documents referred to in 3(a) above.

(c) The primary objective of the GMP inspection is as follows:

(i) To determine if the procedures, equipment, and processes used by the manufacturer can be expected to consistently produce drugs that meet the specification/standard of the drugs being produced.

(ii) To verify that the production procedures and processes are carried out as described in the product dossier and quality manual summaries /site master file submitted to the FDA as part of the registration process.

(iii) To do an in-depth assessment of the drug manufacturing operations.

(d) The cGMP inspection will be risk-based and will be informed by factors such as product and process risk, the manufacturer's compliance history, risk associated with the use of the product, and relevant recalls carried out.

(e) The Authority will periodically conduct appropriate stakeholder meetings and trainings for manufacturers to enhance their level of compliance.

(f) The basic elements of the WHO good manufacturing practices for pharmaceutical products: main principles, as adapted is as follows:

(1) Pharmaceutical quality system
- Quality Risk Management
- Product Quality Review

(2) Good manufacturing practices for pharmaceutical products

(3) Sanitation and hygiene

(4) Qualification and validation

(5) Complaints

(6) Product recalls

(7) Contract production, analysis, and other activities
(8) Self-inspection, quality audits and suppliers' audits and approval
(9) Personnel
(10) Training
(11) Personal hygiene
(12) Premises
(13) Equipment
(14) Materials
(15) Documentation
(16) Good practices in production
(17) Good practices in quality control

(g) Additionally, all the supplementary WHO Technical Report Series documents related to GMP applies.

(h) The principles or key highlights of each of the WHO GMP elements are as specified or described below.

3.1 Pharmaceutical Quality System

The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization, and do not place patients at risk due to inadequate safety, quality, or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented pharmaceutical quality system (PQS) incorporating good manufacturing practice (GMP) and Quality Risk Management (QRM)

3.2 Good Manufacturing Practices (GMP) for Pharmaceutical Products

Licensed pharmaceutical products (marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities and verified to be GMP compliant. GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and QC. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

3.3 Sanitation And Hygiene

A high level of sanitation and hygiene should be practised in every aspect of the manufacture of medicines. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to

the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene.

3.4 Qualification and Validation

Each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their operation are controlled. The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan and documentary evidence should be provided for all qualification and validation activities carried out.

3.5 Complaints

All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.

3.6 Product Recalls

There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

3.7 Contract Production, Analysis and Other Activities

Contract production, analysis and any other activity covered by GMP must be correctly defined, agreed and controlled to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

3.8 Self-Inspection, Quality Audits and Suppliers' Audits and Approval

The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g., in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

3.9 Personnel

The establishment and maintenance of a satisfactory system of QA and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

3.10 Training

The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel.

3.11 Personal Hygiene

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

3.12 Premises

Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out

3.13 Equipment

Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

3.14 Materials

The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging). Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

3.15 Documentation

Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a medicine for sale; to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described below may be brought together, but they will usually be separate.

3.16 Good Practices in Production

Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

3.17 Good Practices in Quality Control

QC is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation which ensure that the necessary and relevant tests are 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 compliant with the requirements. QC is not confined to laboratory operations but may be involved in many decisions concerning the quality of the product. A strong quality control system must be in place to perform this function or role.

4. CLASSIFICATION OF GMP INSPECTION DEFICIENCIES

4.1 Deficiencies

Deficiencies identified following an inspection may be classified as critical, major or other. These shall be communicated to the company and a corrective and preventive action to address them would be required of the company inspected. There could also be comments.

4.2 Critical Deficiency

A “Critical” deficiency is a deficiency which has produced or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

A “Critical” deficiency also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.

4.2.1 A “Critical” deficiency may consist of several related deficiencies, none of which on its own may be “Critical”, but which may together represent a” Critical” deficiency, or systems’ failure where a risk of harm was identified and should be explained and reported as such.

4.2.2 A “Critical” deficiency is a serious situation that could result in regulatory action being considered.

4.2.3 Examples of deficiencies rated as “Critical” (in the absence of risk reducing factors) include the following where it can be reasonably expected that the definition in this guideline will be met.

(i) Lack of sterilisation validation (relevant to all sterile products).

(ii) Lack of adequate control measures resulting in an actual, or significant risk of, cross contamination above the level of the health-based exposure limit in subsequent products.

(iii) Evidence of gross pest infestation (relevant to all manufacturers).

(iv) Falsification or misrepresentation of analytical results or records (relevant to all manufacturers).

(v) Failure to ensure the quality and/or identity of starting materials (relevant to all manufacturers).

(vi) No master batch documents (relevant to all manufacturers).
(vii) Absence, falsification or misrepresentation of manufacturing and packaging records (relevant to all manufacturers).
(viii) Water system for sterile products not validated (for manufacturers of sterile products).
(ix) HVAC system for sterile products not validated (for manufacturers of sterile products).
(x) Grossly unsuitable premises so that there is a high or likely risk of contamination (relevant to all manufacturers).
(xi) No evidence that mandated recall processes have been complied with (relevant to all manufacturers)

4.3 Major Deficiency

A Major deficiency that is not a "Critical" deficiency, but which:

(i) has produced or may produce a product which does not comply with its Marketing Authorisation, Clinical Trial Authorisation, product specification, pharmacopoeia requirements or dossier;
(ii) does not ensure effective implementation of the required GMP control measures.
(iii) indicates a major deviation from the terms of the manufacturing authorisation;
(iv) indicates a failure to carry out satisfactory procedures for release of batches or failure of the authorised person to fulfil his/her duties;
(v) consists of several "Other" related deficiencies, none of which on its own may be "Major", but which may together represent a "Major" deficiency or systems failure and should be explained and reported as such.

4.3.1 Examples of deficiencies rated as "Major" (in the absence of risk reducing factors) include the following:

(i) Lack of validation of critical processes (applicable to all medicines, but could be "Critical" for low dose/high potency products, particularly sterilization processes for sterile products)
(ii) No or grossly inadequate air filtration to minimise airborne contaminants (applicable to all medicines manufacturers - could be "Critical" if possible, contaminants are a safety concern and "Critical" for sterile medicines)
(iii) Missing or ineffective control measures to provide adequate confidence that cross contamination will be controlled within the health-based exposure limit in subsequent products. (Would be "Critical" if resulting cross contamination has or is likely to exceed the health -based exposure limit)
(iv) Damage (holes, cracks, peeling paint) to walls/ceilings in manufacturing areas where product is exposed in non-sterile areas.
(v) Design of manufacturing area that does not permit effective cleaning
(vi) Insufficient manufacturing space that could lead to mix-ups

(vii) No raw material sampling area for medicine manufacturers (could be classed as "Other" if adequate precautions are taken)
(viii) Sanitary fittings not used on liquid/cream manufacturing equipment
(ix) Stored equipment not protected from contamination.
(x) Individuals in charge of QC/production not qualified by education, competency training and experience.
(xi) Inadequate initial and ongoing training and/or no training records
(xii) Cleaning procedures not documented and/or no cleaning records
(xiii) Production equipment cleaning procedures not validated
(xiv) Reduced QC testing of raw materials without data to certify suppliers
(xv) Incomplete testing of raw materials
(xvi) Test methods not validated.
(xvii) Complex production processes for non-critical products not validated.
(xviii) Unapproved/undocumented changes to master batch or equivalent documents
(xix) Deviations from instructions not approved.
(xx) No or inadequate internal inspection program.
(xxi) No proper release for supply procedure
(xxii) Product reworked without proper approval
(xxiii) No system/procedures for handling complaints or returned goods
(xxiv) Inadequate testing of packaging materials
(xxv) No ongoing stability program and/or stability data for all products not available
(xxvi) Insufficient lighting in production or inspection areas
(xxvii) Containers from which samples have been taken not identified.
(xxviii) The temperature of critical temperature-controlled storage areas not monitored and alarmed.
(xxix) Inadequate change control system
(xxx) Inadequate deviation system
(xxxi) No investigation into alarms and temperature excursions for deviations from storage or transport requirements

4.4 Other Deficiency

Other deficiency is a deficiency that is not classified as either "Critical" or "Major" but indicates a departure from Good Manufacturing Practice (GMP).

4.4.1 A deficiency may be judged as "Other" because there is insufficient information to classify it as "Critical" or "Major".

4.5 Comment

One-off minor discrepancies are usually not formally considered deficiencies but are brought to the attention of the manufacturer as comments.

5. DECISIONS AND PENALTIES

5.1 Decisions

The Authority shall take any or multiples of the underlisted decisions following the outcomes of a GMP inspection:

(a) Issue manufacturing license or GMP certificate to the facility found to be substantially compliant with this guideline.
(b) Refuse to issue a manufacturing license or GMP certificate to a facility that does not sufficiently meet the requirements of this guideline.
(c) Cause the suspension of manufacturing activities in the facility or a production line in the facility.
(d) Cause the detention and or seizure of manufactured batches observed to be capable of posing adverse health effects to users.
(e) Cause the suspension of importation of products into Ghana.
(f) Sample and test at the cost of the manufacturer, manufactured products suspected to be capable of causing adverse health effects because of observed deficiency(ies).
(g) Monitor more closely the manufacturing activities of the facility including sampling and testing of each batch before release to the market.
(h) Cause the suspension, withdrawal, or revocation of an existing manufacturing license or GMP certificate.
(i) Any other as directed.

5.2 The list of GMP compliant facilities shall be published on the FDA website and reviewed periodically.

5.3 Penalties

5.3.1 The Authority shall impose an administrative fine in accordance with the approved fees and charges Act applicable to the FDA if the facility contravenes GMP requirements thereby exposing consumers to safety hazards.

Other penalties such as legal actions as applicable, as provided for in section 129 and other related sections of the Public Health Act, 2012, Act 851, may be imposed if this guideline is contravened.