የኢትዮጵያ የምግብ፣ የመድኃኒትና የጤና ክብካቤ አስተዳደርና ቁጥጥር ባለሥልጣን

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

MEDICINE MANUFACTURING EATABLISHMENT DIRECTIVE

April, 2013

Table of Contents

Introduction

WHEREAS, it is necessary to protect public health through regulation of medicine manufacturer engaged in processing of active and inactive ingredient for further processing and distribution of medicines manufactured within their premises;

WHEREAS, regulatory provisions regarding the layout, design, location, construction, and maintenance of the premise; installation of equipments and utilities, personnel, and pre-approval and post approval inspection of manufacturer are important factor in the resulting safety, quality and efficacy of medicine to be produced;

WHEREAS, it is appropriate to suspend, revoke or take other administrative measures on the manufacturing certificate of competence of any manufacturer that is found operating contrary to this Directive and other applicable laws;

NOW, THEREFORE, this directive is issued by the Ethiopian Food, Medicine and Healthcare Administration and Control Authority in accordance with article 55(3) of the Food, Medicine and Healthcare Administration and Control Proclamation No. 661/2009.

Part One

General Provision

1. Short Title

This Directive may be cited as "Medicine Manufacturing Establishment Directive Number.12./2013"

2. Definitions

With due regard to the definition provided under the Food, Medicine and Healthcare Administration and Control Proclamation No. 661/2009, for the purposes of this directive

1. "Active Pharmaceutical Ingredient (API)" shall mean any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body;
2. "Air-handling unit (AHU)" shall mean a system that serves to condition the air and provide the required air movement within the manufacturing plant;
3. "Airlock" shall mean an enclosed space with two or more doors, which is interposed between two or more rooms for the purpose of controlling the airflow between these rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment;
4. "Authority" shall mean the Ethiopian Food, Medicine and Health Care Administration and Control Authority";
5. "Authorized person" shall mean the person recognized by the Authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the requirements of marketing authorization;

6. “Bulk product” shall mean any product that has completed all processing stages up to, but not including, final packaging;
7. “Calibration” shall mean the demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a traceable standard over an appropriate range of measurements. Limits for acceptance of the results of measuring shall be established;
8. “Clean area” shall mean an area (room) with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area;
9. “Commissioning” shall mean the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation;
10. “Controlled Area” shall mean an area constructed and operated in such a way that some attempt is made to control the introduction of potential contaminant and the consequences of accidental release of living organisms;
11. “Design condition” shall mean the design condition related to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system;
12. “Dosage form” shall mean a form of finished pharmaceutical product including tablet, capsule, injection, elixir or suppository;
13. “High Efficiency Particulate Air (HEPA) filter” shall mean retentive matrix designed to remove a defined percentage of particulate matter of a defined size;
14. “Pressure cascade” shall mean a process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure;
15. “Self-contained area” shall mean a premise which provides complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings;
16. “Non-sterile product” shall include tablets, capsules, dry powder for oral use, oral liquid, topical preparation, cosmetics and medical device;

17. “Sterile product” shall include finished pharmaceutical products such as small volume parenteral, large volume parenteral, ophthalmic preparations and invasive medical devices;
18. “Topical preparation” shall mean solution, usually aqueous but often containing other solvents, intended for topical application to the skin or to the oral mucosal surface;
19. “Capsule” shall mean a solid dosage form in which the drug substance is enclosed within either a hard or soft soluble container or shell.

3. Scope of Application

This Directive shall be applicable on all manufacturers of medicines.

4. Principles

1. It shall be mandatory for any person to engage in manufacturing medicine shall get Certificate of Competence from the Authority.
2. Certificate of Competence to be issued in accordance with article (1) of this article shall be given in compliance with this directive.
3. In case where manufacturer fails to continually observe applicable requirements after getting the Certificate of Competence the Authority shall take appropriate administrative measures.

Part Two

Medicines Manufacturing Certificate of Competence

5. General

1. It shall be mandatory to get a certificate of competence from the Authority to any person to engage in the manufacture of medicine.
2. An applicant with valid manufacturing certificate of competence and with successful completion of development, stability and process validation initiation

shall apply for a certificate of Good Manufacturing Practice (GMP) as per Annex II of this directive.

6. Application to get Certificate of Competence

1. At the same time as an applicant is strongly encouraged to read this directive before engaging in construction of the intended premises, it shall fulfil the requirement of this directive before starting the manufacture of medicine.
2. While engaging in the construction of the premise, the applicant shall consider requirements provided under the Good Manufacturing Practices Directive.
3. The application for Certificate of Competence shall be made to the Authority as per Annex I of this directive.
4. The application shall be accompanied with a sketch design of the proposed premise. Where appropriate, the sketch design, is required to comply with:

    a. Premises location suitability in accordance with Article 8 of this Directive;
    b. Premises design suitability in accordance with Articles 9-11 of this Directive;
    c. Material and personnel flow direction including controlled areas;
    d. Clean area classification;
    e. Equipment design and location;
    f. Source and quality of water including its design, treatment, storage, distribution and monitoring;
    g. Air Handling Unit (AHU) design; Heating, Ventilation and Air Conditioning (HVAC) component, air supply and exhaust system for each processing area and its suitability for the intended purpose;
    h. Quality control and laboratory testing;
    i. Waste management and treatment system; and
    j. Other requirements as described under Annex III of this Directive

5. The Authority through authorized inspection team shall verify if the sketch suits for the intended purpose and may approve, reject and/or propose an alternative to the submitted sketch design.

6. If the sketch is accepted, the applicant will be notified to continue with process of construction or renovation of the premises and upon completion shall inform the Authority for inspection. Where the sketch is rejected or need to be modified the applicant will be informed accordingly.
7. After approval is granted in accordance with sub-article (4) of this article, the inspectors will verify if all requirements laid out on the design have been met and suitably constructed. The inspectors shall use the inspection checklist provided under Annex III of this directive and give their observations and/or recommendation on the suitability of the premises.
8. The authorized person of the Authority shall evaluate and, as the case may be, recommend or decide after receiving duly filled application, premises inspection report and all other necessary documents from the inspectors.
9. The Authority may approve, reject or recommend corrections to the application by providing reason for its decision. Where the premises requirements have not been met, the applicant shall be informed to address the deficiencies.
10. Every applicant shall receive an official letter informing them on the status of their application within one week from the day the decision was made.
11. Applicants who are required to take corrective action shall carry out remedial measures before reconsideration of the premises.
12. Approved applicants will be required to procure raw materials from approved vendors and other reference materials related to the type of product and production line before starting manufacturing.
13. The Authority will issue approval to conduct manufacturing activity for lab-scale batches, pilot-scale batches, process validation batches, stability batches and other development exercise batches which are not intended for marketing purpose.

7. Premise

1. The premise shall be located, designed, constructed, adapted and maintained to suit the operation to be carried out.
2. The layout and design of premises shall 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 the product.

3. Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures shall be taken to avoid cross contamination and facilitate cleaning.
4. Premises shall be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.
5. Premises used for the manufacture of finished products shall be suitably designed and constructed to facilitate good sanitation.
6. Premises shall be carefully maintained, and it shall be ensured that repair and maintenance operations do not present any hazard to the quality of products.
7. Electrical supply, lighting, temperature, humidity and ventilation shall be appropriate such that they do not adversely affect, directly or indirectly, either the products during their manufacture and storage or the accurate functioning of equipment or safety and comfort of the operators.
8. The premise shall be designed and equipped so as to afford maximum protection against the entry of insects, vermin's, rodents, birds or other animals.
9. The premises shall have a sign board conspicuously displayed at the main entrance.

8. Premises location

1. The premises shall be located away from sites or activities that emit obnoxious materials like fumes and contaminants; open sewerage, malting and brewery industries or other offensive trades having direct or indirect impact on the quality, safety or efficacy of medicine.
2. The premises shall be located in such a way that it shall have no direct link to any other building engaged in other business activity and/or belonging to other business entity.

9. Premises design

1. General

a. The premise shall be carefully designed that repair and maintenance operations do not present any hazard to the quality of products and easy to be cleaned and, where applicable disinfected adequately with suitably designed drainage system.
b. The premise shall have an airtight ceilings and walls, coved edges, close fitting doors and sealed light fittings.
c. Interior surfaces of the premise (wall, floor and ceiling), where starting and primary packaging materials, intermediate or bulk products will exposed to the environment, shall be smooth, free from cracks and open joints, and shall not shed particulate matter and shall permit easy and effective cleaning and, if necessary, disinfection. This area shall be defined as clean area to meet at least grade D requirement with controlled room temperature and humidity.
d. The premises preferably be laid out in such a way that allows processing to take place in areas connected in a logical order corresponding to the sequence of the operations and to the designed cleanliness levels.
e. The surrounding shall be designed so as to minimise dust, soil and other contamination to enter the building.
f. Pipe work, light fittings, ventilation points and other services shall be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they shall be accessible from outside the manufacturing areas.
g. The unidirectional flow velocity of air shall be in such a way that it does not disrupt the sensitivity of balances in weighing areas and/or create air turbulence in the manufacturing area.
h. A room that is tested for an “operational” condition shall be able to be cleaned up to the “at-rest” clean area classification design after a short clean-up time which is generally of the order of 20 minutes.
i. Premises for the manufacture of products, where starting materials and finished products, utensils and equipment are exposed to the environment, shall be classified as “clean areas”.

2. Ancillary areas

a. Premise for changing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the users. Toilets and refreshment rooms shall not directly link with production or storage areas.
b. Rest and refreshment areas shall be separate from other areas but shall be accessible to the staff.
c. Maintenance workshops shall as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they shall be kept in rooms or lockers reserved for that use.

3. Storage areas

a. The premise where products and materials are stored shall be sited where the risk of contamination from the local environment or from other nearby activities is low. There shall be appropriate mapping design for the control of the room temperature and humidity.
b. The size or capacity of the working and storage areas shall permit the orderly and logical storage and flow of equipment and materials so as to minimise the risk of confusion between different stage products (starting material, packaging material, bulk product or their components) and of goods of different status (approved, rejected, returned, recalled) to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.
c. Premises for storage areas shall be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

4. Weighing areas

a. A dispensary or weighing and sampling booth shall be provided with unidirectional air flow for protection of the product and operator.

b. Premises for sampling and weighing of materials shall have the same cleanness as for the subsequent production area for both physical and microbiological environmental condition.

5. Production areas

a. In order to minimise the risk of a serious medical hazard due to cross contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins, biological preparations, oncologicals, steroids). There shall be self-contained dedicated processing area as may be determined through air handling, physical separation and separate material/personnel entry and exit.
b. The total manufacturing and processing area of the product shall be designed to suit the intended purpose to achieve the desired room temperature, humidity, equipment accommodation, operators comfort and safety to permit easy cleaning and material movement.
c. The premise in production areas shall be effectively ventilated with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate all to the products handled, to the operations undertaken within them and to the external environment.
d. Where materials and utensils are exposed to the environment, there shall be an evidence for the achievements of 'clean area' classification through the design of appropriate air filtration and air change rates. The 'clean area' status shall be attained where the air change rate is between 6 and 20 air change per hour.
e. Production area shall be maintained at a positive pressure relative to the outside to limit the ingress of contaminants.
f. Highly potent products shall be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.
g. Negative air pressure shall be encapsulated with surrounding areas with clean air supplies so that only clean air infiltrate in to the controlled areas.
h. Manufacturing cubicles and core processing areas generating dusts such as compression rooms shall maintained at negative pressure relative to the corridor.

i. Adjacent rooms of different grades shall have a minimum pressure differential of 5 to 15 Pascal's; with particular attention to the protection of the zone of greatest risk (e.g. clean area).

j. Too low pressure adjacent room pressure differentials shall be avoided in order to prevent flow reversals. Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used.

k. Doors shall open to the high pressure side, and be provided with self-closers. Door closer springs, if used, shall be designed to hold the door closed and prevent the pressure differential from pushing the door open. Sliding doors shall not be recommended.

l. Cubicles, or suites, in which products requiring low humidity are processed, shall have well-sealed walls and ceilings and shall also be separated from adjacent areas with higher humidity by means of suitable airlocks.

6. Quality control area

Premises for quality control laboratories shall be separated from production areas. This is particularly important for laboratories for the control of biological, microbiological and radioisotopes, which shall also be separated from each other.

7. Equipment

a. Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise 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.

b. The premises shall be provided with suitable equipment and facilities for proper storage, safety keeping and handling of products and health and safety measures for the staff in the event of emergency management.

8. Air system

a. The premise shall be equipped with appropriate air system and it shall be provided with suitable filters including:

   i. Primary filter type (e.g. ≥ EN779 G4) for normal housekeeping ,
   ii. Primary plus secondary filter (≥EN779G4+≥EN1822F8) for areas where materials and utensils are exposed to the environment operating on 100% fresh air,
   iii. Primary plus secondary plus tertiary filter type (e.g. EN779 G4+ ≥ EN1822 F8+≥ EN1822 H13) where there is potential risk of contamination, e.g. re-circulated air etc

b. Building structure shall be given special attention to accommodate the pressure cascade design.
c. Humidity control shall be achieved by removing moisture from the air, or adding moisture to the air, as relevant. When specifying relative humidity, the associated temperature shall also be specified.
d. Where the powders are not highly potent, final filters on a dust exhaust system shall be fine dust filters with a filter type of F9.
e. Where harmful substances such as penicillin, hormones, toxic powders and enzymes are manufactured, the final filters on the dust exhaust system shall be at least HEPA filters of H12 classification according to EN1822 filter standard.
f. For exhaust systems where the discharge contaminant is considered particularly hazardous, it may be necessary to install two banks of HEPA filters in series, to provide additional protection shall the first filter fail. The quality of exhaust air shall be monitored to see the filtration efficiency.
g. There shall be no failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan.
h. Depending on the airborne contaminants in the return-air system it may be acceptable to use re-circulated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus prevent cross contamination. The HEPA filters for this application shall have H13 classification in accordance with EN1822.

i. HEPA filters may not be required where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.
j. Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.
k. HEPA filters may be located in the air-handling unit or placed terminally.
l. Air containing dust from highly toxic processes shall never be re-circulated to the HVAC system.

9. Water system

a. Water production, storage and distribution systems shall be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. Water shall be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination (e.g. with dust and dirt).
b. Where appropriate, purified water shall be used and the purification method, or sequence of purification steps, shall be appropriate to the intended purpose. The following shall be considered when selecting the water treatment method:
    i. the water quality specification;
    ii. the yield or efficiency of the purification system;
    iii. feed-water quality and the variation over time (seasonal changes);
    iv. the reliability and robustness of the water-treatment equipment in operation;
    v. the availability of water-treatment equipment on the market; and
    vi. the ability to adequately support and maintain the water purification equipment; and the operation costs.
c. The design, configuration and layout of the water purification equipment, storage and distribution systems shall account the following physical considerations:
    i. the space available for the installation;
    ii. structural loadings on buildings;
    iii. the provision of adequate access for maintenance; and
    iv. the ability to safely handle regeneration and sanitization chemicals.

d. The grade of water used shall take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process, in particular:-

i. Highly Purified Water shall be used in the preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed, but the process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeia monographs for Water for Injection.

ii. Water for Injection shall be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections. Water for Injection shall also be used for the final rinse after cleaning of equipment and components that come into contact with injectable products as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

iii. When steam comes into contact with an injectable product in its final container, or equipment for preparing injectable products, it shall conform to the specification for Water for Injection when condensed.

e. Mechanisms for microbiological control and sanitization shall be considered and the following techniques shall be given due regard during the design of the water system:-

i. maintenance of flow through water-purification equipment at all times;
ii. control of temperature in the system by pipeline heat exchange or plant-room cooling to reduce the risk of microbial growth (guidance value <25 ℃);
iii. provision of ultraviolet disinfection;
iv. selection of water-treatment components that can be thermally sanitized; and/or
v. application of chemical sanitization (including agents such as ozone).

f. The materials that come into contact with Water for Pharmaceutical Use (WPU), including pipe work, valves and fittings, seals, diaphragms and instruments, shall be selected to satisfy the following objectives;

i. All materials used shall be compatible with the temperature and chemicals used by or in the system.

ii. All materials that come into contact with WPU shall be non-leaching at the range of working temperatures.

iii. The materials used to prevent the corrosive nature of Purified Water, HPW and WFI shall be appropriate, the method of jointing must be carefully controlled, and all fittings and components must be compatible with the pipe work used. With a view to achieve the same, appropriate sanitary specification plastics or stainless steel materials shall be used for WPU systems. When stainless steel is used it shall be at least grade 316L. The system shall be passivated after initial installation or after modification. When accelerated passivation is undertaken, the system shall be thoroughly cleaned first, and the passivation process shall be undertaken in accordance with a clearly defined documented procedure.

iv. The internal finish of the water system shall be smooth with surface roughness not greater than 0.8 micrometre arithmetical mean roughness (Ra) in order to prevent corrosion and microbiological contamination. When stainless steel is used, mechanical and electropolishing techniques may be employed to improve the resistance of the stainless steel material to surface corrosion.

v. System materials used for jointing of water system shall be able to be easily jointed by welding in a controlled manner. Welding shall be considered controlled, at least, when the operator is qualified; documentation of the welder set-up, work-session test pieces, logs of all welds and visual inspection of a defined proportion of welds are properly maintained.

vi. Where flanges or unions are used, they shall be of a hygienic or sanitary design. Appropriate checks shall be carried out to ensure that the correct seals are used and that they are fitted and tightened correctly.

vii. All system components shall be fully documented and be supported by original or certified copies of material certificates.

viii. Suitable materials that may be considered for sanitary elements of the system include 316 L (low carbon) stainless steel, polypropylene, polyvinylidenedifluoride and perfluoroalkoxy. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

g. Water treatment equipment, storage and distribution systems used for PW, HPW and WFI shall be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for sanitizing or sterilizing the system after intervention for maintenance or modification. The techniques employed shall be considered during the design of the system and their performance proven during the commissioning and qualification activities.

10. Premises for manufacture of non-sterile product

1. General

Any manufacturing premises layout for manufacturing of non-sterile dosage form shall contain physically segregated areas or cubicle designed for weighing and dispensing, preparation (milling, sifting, compaction where applicable), mixing, bulk formulation (e.g. compression, filling), intermediate and bulk product holding, packaging, quarantined and approved area.

2. Tablets

Tablets may be prepared by wet granulation, dry granulation (roll compaction or slugging), or direct compression and the layout of the premises shall always be designed to suit the selected manufacturing procedure, in particular:

a. Where wet granulation is involved there shall be a procedure for drying with segregated holding and drying area as applicable;
b. When there is an additional procedure such as granule sizing, milling, sieving, granule coating, polishing, tablet coating, tablet polishing there shall be adequately designed area or cubicles for such procedure; or
c. Where the product under consideration is found to be sensitive to moisture, heat and light; there shall be an adequately designed environmental monitoring system.

3. Capsules

The following are particulars to capsule manufacturing premises layout:

a. When soft gelatine capsules are used there shall be physically segregated processing area for gelatine preparation and melting with an adequate monitoring system for moisture and temperature.
b. The capsule filling area shall always be monitored for humidity and temperature preferably to meet the storage condition of the empty capsule and the product.

4. **Oral liquid and dry powder**

The following are particulars for oral liquid or dry powder manufacturing layout:

a. Where possible, preparation and mixing of the drug substance with other excipient shall be conducted in a closed vessel. Transfer of the final mix to the filling machine shall be through pipe fittings. Any pipes and vents shall be made of high standard or inert materials and shall permit easy cleaning.
b. The design shall allow easy cleaning and sanitization of the containers (vials, bottles, ampoules, etc).
c. The final rinse water for container shall at least be purified water.

d. When air, such as nitrogen, is used for purging or any other purpose the quality of the air as well as the efficiency of downstream filters shall be well designed and defined to meet the intended purpose.

5. **Topical Preparations**

The premises for topical preparation shall always be separated from other product processing lines for oral use.

6. **Medical Device**

The premises for manufacturing of medical device shall account the following consideration.

a. The manufacturing premises of medical device shall be self-contained and dedicated facility without any direct link with other products
b. The premises for the manufacture of high risk invasive medical device (class III and higher) shall be separated from the manufacturing premises of other devices. These premises shall at least meet either the premises for oral dosage form and/or sterile product manufacturing depending on the intended use of the device.

7. **Traditional Medicine**

The premises for the manufacturing and processing of any traditional medicine shall be conducted in self-contained and dedicated facility without any direct link with other products.

11. Premises for manufacture of sterile product

1. The manufacture of sterile products shall be carried out in clean areas to which entry shall be through airlocks.

2. Where airlocks are used, both airlock doors shall not be opened simultaneously. An interlocking system or a visual and/or audible warning system shall be operated to prevent the opening of more than one door at a time.
3. All exposed surfaces and premises of the manufacturing plant shall be smooth, impervious and unbroken.
4. Sinks and drains shall be prohibited in grade A/B areas used for aseptic manufacture.
5. The various operations of component preparation, product preparation and filling shall be carried out in separate areas within the clean area. The clean room classification shall be in accordance with applicable standard.
6. The sterility assurance level and efficiency of the selection of particular sterilization procedure shall be demonstrated through process validation and the design and procedure shall provide provision for 10^{-6} sterility assurance level and/or 3log reduction in Endotoxin in both material and component sterilization process.
7. For the manufacture of sterile medicinal products clean areas shall be classified in to 4 grades:

a. Grade A

High risk operations including filling zone, stopper bowls, open ampoules and vials making aseptic connections shall be carried out in Grade A areas. This shall be achieved by using laminar air flow work station which shall provide a homogeneous air speed in a range of 0.36 – 0.54m/s at the working position in open clean room applications. The maintenance of laminarity shall be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.

b. Grade B

For aseptic preparation and filling, this shall be the background environment for the grade A zone.

c. Grade C and D

This shall be the clean areas for carrying out less critical stages in the manufacture of sterile products.

8. HEPA filters of aseptic area shall be located terminally.
9. The airborne particulate classification and monitoring for aseptic operations shall be designed in the layout of each room by indicating the frequency and method such as settle plates, volumetric air and surface sampling (e.g., swabs and contact plates).
10. The location of the settle plate shall be near to the exhaust air outlet and the number shall at least surpass the number of the exhaust unit by design.
11. The holding time of any sterilized materials, components and assemblies shall not be more than 24 hours in the design and holding shall be done under laminar air flow fitted with HEPA to meet class A/B design.
12. The handling of non-sterile material and component for the purpose such as terminal sterilization, washing may be conducted in lower grade areas as for non-sterile product (e.g. Grade D)

12. Personnel

1. The manufacturer shall have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual shall not be so extensive as to present any risk to the quality of product.
2. The manufacturer shall have an organisation chart. People in responsible positions shall have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities.
3. Key Personnel includes the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the authorised person(s) designated for the purpose (Quality Assurance Head), Head of engineering. Key posts shall be occupied by full-time personnel. The heads of Production and Quality Control shall be independent from each other.

4. Key personnel for Production, Quality Control and Quality Assurance shall be pharmacists and for engineering shall be an engineer specializing in their respective line of responsibility and with adequate relevant practical experience
5. Every personnel including the key personnel working in the pharmaceutical industry shall observe and maintain the following;
    a. High standard of personal hygiene
    b. Appropriate gowning and identification as per the required area cleanness
    c. Not to work under the influence of alcohol or illicit drugs
    d. Conduct himself/ herself under good and orderly behaviour
6. The key personnel shall be responsible for conducts of personnel working under their instructions and for any activities carried out in the premises.
7. The number of personnel working in particular area shall be adequately designed and indicated. Only the minimum number of personnel required shall be allocated in clean areas; this is particularly important during aseptic processing.

13. Pre-approval inspection

1. The purpose of pre-approval inspection shall be to issue 'Manufacturing Certificate of Competence as indicated in Annex IV of this Directive.
2. Prior to the conduct of official inspection, the applicant shall be required to fill the checklist in accordance with Annex III of this Directive.
3. The actual conduct of the site audit shall depend on the assessment of the outcome of the checklist completed by the applicant.
4. While pre-approval inspections shall be considered to be an important part of the application review and approval process, inspections might be carried out only in specific cases where noncompliance is possible.
5. An inspection team shall be established by the Authority for the conduct of the audit and the general principle of the audit shall be in accordance with the GMP Directive and Annex III of this directive.
6. Before any application is approved, it shall be necessary to determine whether the manufacturer of the product is in compliance with GMP and the application commitments. Pre-approval inspection shall be done with the objective to:

a. Evaluate the establishment's compliance with GMP requirements, particularly regarding proper environment, quality management, premises design and layout, personnel, facilities and equipment;
b. Evaluate the procedures and controls implemented in the manufacture of the product (pre-approval batches), to determine whether they are in conformity with the application commitments;
c. Audit the completeness and accuracy of the manufacturing and testing information submitted with the application, and of the conformity of pre-approval batches with planned commercial batches (process validation protocol); and
d. The collection of samples for the validation or verification of the analytical methods included in the application where applicable.

Part Three

Miscellaneous

14. Post approval inspection

1. The purpose of post approval inspection shall be to issue GMP certificate in accordance with Annex III of this Directive.
2. An inspection team established by the Authority shall conduct the audit in accordance with the GMP Directive.
3. Post-approval inspections shall be an integral part issuance and renewal of GMP certificate and marketing authorization. This inspection shall be considered to be a routine type inspection.
4. The inspection may be undertaken for a specific product and/or particular line of operation depending on a case by case basis.
5. Unless found to be necessary to be more frequent, every manufacturing premise shall be inspected every year as part of renewal of the GMP certificate.

15. Termination of manufacturing

1. The Authority may at any time suspend, revoke, vary any provisions of such registration licence and certificate or take other such other appropriate administrative measures as it may find necessary.
2. Any manufacturing certificate of competence and GMP certificate that has been suspended and/ or revoked may not be renewed except with the consent of the Authority if satisfied with the reasons given by the prior manufacturing certificate of competence holder.
3. If the proprietor wishes to close down his business because of any reason(s), he shall officially inform the Authority in advance.
4. A business that has been issued with a closure order shall surrender the manufacturing certificate of competence and GMP certificate to the Authority.
5. Businesses that have been issued with closure order shall be obliged to follow up and/or conduct proper product recall if deemed necessary as determined in the certificate of competence closure statement and conclusion.

16. Validity of manufacturing certificate of competence

1. Manufacturing certificate of competence shall be issued once and shall not be renewed.
2. Manufacturing certificate of competence shall remain valid provided that the following conditions are met:-
    a. Premises start to operate business within six (6) months following the approval or licensing;
    b. GMP certificate is renewed;
    c. The premises have been maintained and remained in conditions which led to its initial licensing; and
    d. There is no change of ownership, business name or location.
3. The GMP certificate shall be renewed every two year unless suspended, cancelled or revoked by the Authority.

17. Service fee

In order to get manufacturing certificate of premise applicable service fee shall be paid in accordance with the appropriate directive.

18. Notification for change of premises

1. Any change of location (shift of premises), trade name of the premises, ownership or any other change of registered premises, needs prior notification and approval by the Authority.
2. An intention to change location of registered premises shall be made in writings to the Authority before the change is made and the Authority shall notify the applicant on the procedure to be followed.

19. Effective date

This directive shall come in to effect as of Date April, 2013.

Yehulu Denekew

Director General

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

የኢትዮጵያ የምግብ፣ የመድኃኒትና የጤና ክብካቤ አስተዳደርና ቁጥጥር ባለሥልጣን

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

Annex I-Application Form for Manufacturing Premises Licensing

All the information required in this form shall be filled accurately and submitted with cover letter and copy of valid identification card to the Authority.

S/N	Application for Licensing of Manufacturing Premises	To be printed in the space provided
1	**Information on the applicant**	
	Name of the applicant	
	Postal address	
	City,Sub-city/Kifleketema	
	Particular name of the area	
	Telephone	
	E-mail and/or website	
2	**Name of business partner (if any)**	
3	**Type of application (mark as applicable**)	
		General product manufacturer ☐
		Sterile product manufacturer ☐
		Penicillin's and other ☐
		Other (specify)
5	**Information on the contact person**	
	Title of the contact person	Mr/Ms/Mrs/Dr/PhD
	Name of the contact person	

	Professional qualification	
	Address (Telephone, e-mail etc)	
	Professional registration number	
6	**Proposed name of the premises**(attach any official document, gazette etc)	
7	**Declaration by the applicant**	
	If my premise is permitted I shall keep it in hygienic condition and good state of maintenance as required under the act and regulations of Ethiopian Food, Medicine and health care Control Authority (EFMHACA) and in accordance with the National and International GMP requirement. I have not been convicted at any offence relating to any provision of Ethiopian Food, Medicine and health care Control Authority (EFMHACA) there under or any other written law related to the business being applied for within 12 months immediately preceding this application and have not been disqualified from holding a manufacturing certificate of competence and my permit is not suspended. Name_____ Signature_____ Date_____	
9	**To be completed by the Authority's Inspector**	
	I (name) Mr. /Mrs./Ms./Dr./Prof…….Inspector of the Authority hereby certify that, I have reviewed all pre-licensing information and/or inspected the above mentioned premises per attached inspection checklist and found that it (complies ☐ does not comply ☐) with standards prescribed for Licensing of premises National and International GMP Directive . I confirm that the following documents reviewed and complete as recommended by the Directive s. Premises and production design layout ☐ Pre-licensing Inspection checklist ☐ Qualification document ☐	
10	**Summary of Reason for non-compliance (if any):**	

11	**Nameof Inspector (Assessor) (s)** 1)_____ 2)_____3) _____ Signature 1)_____2)_____3)_____ Date _____
12	**For Official Use Only**
	Certificate of Competence Granted Not Granted
	Summary for Deniale of Certificate of Competence (where applicable)
	Certificate of Competence Number:
	Date of Registration:
	Signature of the Authority and Date:

የኢትዮጵያ የምግብ፣ የመድኃኒትና የጤና ክብካቤ አስተዳደርና ቁጥጥር ባለሥልጣን

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

Annex II-Application Form for GMP Certificate

The applicant holding valid manufacturing certificate of competence is required to provide completed application form with cover letter statement along with all required information stated in this Directive in order to obtain GMP certificate.

S/N	Section II-Application for GMP Certificate	To be printed in the space provided
1	Information on the applicant	
	Name of the manufacturer	
	Cite, Sub city/Kifle Ketema	
	Particular name of the area	
	Postal address	
	Telephone	
	E-mail and/or website	
2	**Name of business partner (if any)**	
3	**Type of application** (mark one)	New ☐ Renewal ☐ Change of address ☐
4	Premises permitted for the purpose of (mark as applicable)	General product manufacturer ☐
		Sterile product manufacturer ☐
		Penicillin's and other ☐
		Other (specify)
5	**Information on the contact person**	
	Title of the contact person	Mr/Ms/Mrs/Dr/PhD

	Name of the contact person	
	Professional qualification	
	Address (Telephone, e-mail etc)	
	MOH registration number	
6	**Premises Certificate of Competence Number**	
7	**Existing GMP certificate number and date of expiry**(if any)	
10	**Declaration by the applicant**	
	If my premise is certified for GMP, I shall keep it in hygienic condition and good state of maintenance as required under the act and regulations of Ethiopian Food, Medicine and health care Control Authority (EFMHACA) and in accordance with the National and International GMP requirement. I have not been convicted at any offence relating to any provision of Ethiopian Food, Medicine and health care Control Authority (EFMHACA)there under or any other written law related to the business being applied for within 12 months immediately preceding this application and have not been disqualified from holding a manufacturing certificate of competence and my permit is not suspended. Name_____ Signature_____ Date_____Name_____ Signature_____ Date_____	
11	**To be completed by Authority's designated inspector**	
	I (name) Mr. /Mrs./Ms./Dr./Prof…….Inspector of the Authority hereby certify that, I have reviewed and inspected the above mentioned premises per attached inspection report and found that it (complies ☐ does not comply ☐) with the cGMP standards for manufacturing of pharmaceuticals . I confirm that in addition to the manufacturing site audit, the following documents were reviewed and found to be complete as recommended by the GMP Directive. Pre-licensing Inspection report ☐ Validation document ☐	

12	**Summary of reason for non-compliant**
13	**For Official Use Only**
	GMP certificate granted ☐ Not Granted ☐ Summary of reason for denial of the certificate
14	**GMP certificate number**
15	**Signature and Stamp of the Authority:**

የኢትዮጵያ የምግብ፣ የመድኃኒትና የጤና ክብካቤ አስተዳደርና ቁጥጥር ባለሥልጣን

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

Annex III-Inspection checklist of Manufacturing Premises

This form must be carefully completed and submitted to the Authority along with the application form provided as an annex I of this Directive for the purpose of registration of new premises and/or change in the location of premises or along with annex II of the application form for the purpose of GMP certificate. Normally, the checklist needs to be completed by the applicant at the time of pre-licensing and where applicable shall be completed by the inspector after licensing of the premises in order to issue the GMP certificate. By considering the type of product all the applicable section of the checklist shall be completed and/or properly justified at the time of GMP certificate application for the issuance of the GMP certificate. The operational procedure and activity of the checklist may not be applicable at the time of licensing application for the premises licensing.

S/N	Description	Notes/Observation/Response
1	**Office/Owner Address**	Name:
		Subcity/Kifleketema
		Particular area name
		Telephone
		E-mail:
2	**Physical address of the establishment**	Name:
		Sub city/Kifleketema
		Particular area name
		Telephone
		E-mail:

3	**Purpose of the establishment premises**	General product manufacturer ☐	
		Sterile product manufacturer ☐	
		Penicillin's and other ☐	
		Other (specify)	
		Compliance,√[1],X,~	Remark
4	**PERSONNEL**		
4.1.	Qualified and adequate personnel available?	☐☐☐	
4.2.	Organization chart available?	☐☐☐	
4.3.	Job description available?	☐☐☐	
4.4.	Responsibilities clearly defined?	☐☐☐	
	Key personnel		
4.5.	• Quality Assurance Head	☐☐☐	
	• Production Head	☐☐☐	
	• Quality Control Head	☐☐☐	
	• Engineer Head	☐☐☐	
4.6.	Are they independent from each other?	☐☐☐	
4.7.	Are joint functions clearly defined?	☐☐☐	
4.8.	Are the key personnel working full time?	☐☐☐	
	Training		
4.9.	Continuous training program for all staff?	☐☐☐	
4.10.	Induction training for all staff?	☐☐☐	
4.11.	External training courses for all staff?	☐☐☐	
5	**Hygiene**		
	Personnel Hygiene		
	Detailed written hygiene programs for		
5.1.	• Clothing?	☐☐☐	
5.2.	• Gloving?	☐☐☐	
5.3.	• Showering?	☐☐☐	
5.4.	• Behaviour in production areas?	☐☐☐	
	Medical examination		
5.5.	• On recruitment?	☐☐☐	
5.6	• Regular examination?	☐☐☐	

[1]√complete, x incomplete, ∞, partial

5.7.	Instructions for appropriate working clothes?	□□□	
5.8	Absence of food and drinks (chewing gum) in the working area?	□□□	
5.9.	Measures against contact with open product (e.g. gloves,etc)?	□□□	
5.10.	Change of clothes when entering and leaving the production?	□□□	
5.11.	Change rooms and toilets easily accessible?	□□□	
5.12.	Toilet and refreshment rooms adequately separated from production areas?	□□□	
5.13.	Workshops separate from production areas?	□□□	
5.14.	Laboratory animal rooms totally segregated from production room?	□□□	
6	**WAREHOUSE**		
	Rooms/Cubicles/Booths		
6.1.	Suitable for intended purpose?	□□□	
6.2.	• Adequate size?	□□□	
6.3.	• Clean?	□□□	
6.4.	Located and designed to exclude external contamination?	□□□	
6.5.	Maintenance work possible without contamination risk?	□□□	
6.6.	Appropriate lighting and air conditioning?	□□□	
6.7.	Controlled access for authorized person only?	□□□	
6.8.	Protection against entry of insects or other animals?	□□□	
	Rooms, Special requirement		
6.9.	Receiving bay available?	□□□	
6.10.	Segregation of material is sufficient?	□□□	
6.11.	Provision for different storage condition and mapping (T,RH)?	□□□	
6.12.	Protected receiving area?	□□□	
6.13.	Cleaning area for incoming material available?	□□□	
6.14.	Quarantine area sufficiently segregated with controlled access?	□□□	
6.15.	Separate, protected area for sampling?	□□□	
	Separate and safe storage area for		

6.16.	• Rejected material?	□□□	
6.17.	• Returned goods?	□□□	
6.18.	• Recalled goods?	□□□	
6.19.	Separate and safe storage of highly active, toxic, or dangerous substance?	□□□	
6.20.	Safe storage of controlled substance (narcotics & psycho tropics)?	□□□	
6.21.	Safe storage of printed packaging materials?	□□□	
6.22.	Security measurement against theft?	□□□	
6.23.	Smoke detectors?	□□□	
6.24.	Fire extinguishing system?	□□□	
	Procedure and activity:		
6.25	Reception, Sampling and labelling written procedure available?	□□□	
6.26	Sampling procedure available?	□□□	
6.27	Cleaning of incoming containers?	□□□	
6.28	Investigation and corrective action for damaged container?	□□□	
6.29	FIFO/FEFO procedure?	□□□	
6.30	Incoming goods conformity with approved supplier list?	□□□	
	Labelling of incoming containers with		
6.31	• Internal name and code?	□□□	
6.32	• Allocated batch number?	□□□	
6.33	• Status labelling (quarantine, approved etc)	□□□	
6.34	• Expiry date or re-test date?	□□□	
6.35	Identity test for each incoming container?	□□□	
6.36	Marking of sampled container?	□□□	
6.37	Retention of reference sample?	□□□	
6.38	Safe storage of printed packaging material?	□□□	
6.39	Lot tracing of all packaging materials?	□□□	
6.40	Destruction of excess packaging material?	□□□	
7	**Dispensing**		
	Rooms/Cubicles		
	Suitable for the intended use?	□□□	
7.1	• Adequate size	□□□	

7.2	• Clean	□□□	
7.3	Designed and located to exclude contaminants?	□□□	
7.4	Proper maintenance?	□□□	
7.5	Maintenance possible without contamination risk?	□□□	
7.6	Appropriate lighting and air conditioning?	□□□	
7.7	Protection against the entry of insects and other animals?	□□□	
7.8	Controlled access for authorized person only	□□□	
7.9	Meets the same standard as subsequent processing area?	□□□	
	Procedure and activity		
7.10	Program for regular calibration of balance?	□□□	
7.11	Only materials for subsequent production?	□□□	
7.13	Only one materials at a time?	□□□	
7.14	Labelling of dispensed material?	□□□	
7.15	Only released material dispensed?	□□□	
7.16	Cleaning procedure between dispensed materials?	□□□	
7.17	Log book of dispensing?	□□□	
7.18	Procedure to prevent mix ups during transfer to production?	□□□	
8	**Non-sterile Manufacturing (solid, dry powder, medical device etc)**		
	Production line and unit operation activity		
	• Granulation	□□□	
	• Compression	□□□	
	• Encapsulation	□□□	
	• Coating	□□□	
	• Visual Inspection	□□□	
	• Other, specify	□□□	
	Rooms/cubicle, general		
	Suitable for the intended purpose?	□□□	
8.1	• Adequate size?	□□□	
8.2	• Clean?	□□□	
8.3	Designed and located to exclude contaminants?	□□□	
8.4	Proper maintenance	□□□	
8.5	Maintenance work possible without contamination risk?	□□□	

8.6	Appropriate lighting and air conditioning?	□□□	
8.7	Recording of temperature and humidity?	□□□	
8.8	Protection against entry of insects or other animals?	□□□	
8.9	Controlled access for authorized personnel only?	□□□	
	Rooms/cubicle, special requirement		
8.10	Separate manufacturing area for penicillin's, cephalosporins, or highly sensitizing substances?	□□□	
8.11	Only for processing particular product (e.g. pharmaceuticals, Food, Traditional medicine, medical device)	□□□	
8.12	Logical flow of materials?	□□□	
8.13	Walls, floors and ceiling smooth surface and free of cracks?	□□□	
8.14	Easy cleaning possible?	□□□	
8.15	Adequate drains with traps and grilles?	□□□	
8.16	Appropriate air handling system?	□□□	
	Air pressure gradient from room/cubicle →Corridor		
	Classification according to GMP Directive		
8.17	Appropriate dust extraction system?	□□□	
8.18	Appropriate lighting?	□□□	
8.19	Separate rest and refreshment rooms?	□□□	
8.20	Changing rooms designed to avoid contamination?	□□□	
	Equipment		
8.21	Suitable for the intended use?	□□□	
8.22	Well maintained?	□□□	
8.23	Written and/or validated cleaning procedures?	□□□	
8.24	Maintenance without contamination risk?	□□□	
8.25	Material make up for equipment in contact with the product?	□□□	
8.26	Calibration procedure?	□□□	
8.27	Calibration records?	□□□	
8.28	Contents and flow direction marked on pipes?	□□□	
8.29	Pipes for distilled and demineralised water regularly monitored and sanitized?	□□□	

8.30	Status labelling of not functioning equipment?	□□□	
8.31	Equipment cleanliness status?	□□□	
8.32	Equipment ID, name?	□□□	
	Procedure and activity		
8.33	Written procedure available for all manufacturing steps	□□□	
8.34	Are all manufacturing steps recorded with actual parameters?	□□□	
8.35	Check of each single container of the starting materials (contents, weight, identity)	□□□	
8.36	Only one batch of product processed at a time?	□□□	
8.37	Limit for yield	□□□	
8.38	Protection against contaminant (e.g. microbial, etc)	□□□	
8.39	Appropriate measure against generation of dust (e.g. closed system)	□□□	
	Correct labelling of containers, materials, equipment, rooms with		
8.40	• Product name and batch number	□□□	
8.41	• Quarantine status	□□□	
8.42	Deviations from standard procedures recorded and appropriate corrective measures taken?	□□□	
8.43	Special procedure for production of penicillin's, hormones etc?	□□□	
	• Self-contained dedicated facility?	□□□	
	• Campaign production?	□□□	
	• Special monitoring	□□□	
	• Validated decontamination procedure?	□□□	
8.44	Line clearance?	□□□	
8.45	Investigation of deviation in the yield?	□□□	
8.46	Validated procedure when reworking of rejected batches?	□□□	
8.47	Detailed procedure for the addition of previous bathes?	□□□	
8.48	Special release procedure for those batches?	□□□	
8.49	Use protective clothing (hair cover, shoes, masks, gloves?	□□□	
	In Process Control		
8.50	Who performs IPC		
8.51	Type of tests		

8.52	Frequency of tests		
	Validation		
8.53	Validation master plan?	□□□	
8.54	Validation protocol?	□□□	
8.55	Re-validation plan for changes in		
8.56	Process?	□□□	
8.57	Starting materials?	□□□	
8.58	Equipment?	□□□	
8.59	Annual product review and retrospective validation plan?	□□□	
9	**Liquids Manufacturing**		
	Operation carried out in this line		
	• Dispensing	□□□	
	• Syrups and suspension	□□□	
	• Drops	□□□	
	• Ointment manufacture	□□□	
	• Ointment filling	□□□	
	• Ampoule solution manufacture	□□□	
	• Sterile or aseptic ampoule filling	□□□	
	Sterile freeze drying	□□□	
	Sterile powder filling	□□□	
	Rooms/Cubicles, general		
9.1	Suitable for the intended use?	□□□	
9.2	• Adequate size?	□□□	
9.3	• Clean?	□□□	
9.4	Designed and located to exclude external contamination?	□□□	
9.5	Proper maintenance?	□□□	
9.6	Maintenance work possible without contamination risk?	□□□	
9.7	Appropriate lighting and air conditioning?	□□□	
9.8	Recording of temperature and humidity?	□□□	
9.9	Protection against the entry of insects and other animals?	□□□	
9.10	Controlled access for authorized person only?	□□□	
	Rooms/Cubicles, special requirement		
9.11	Separate manufacturing area for penicillin's, cephalosporin's, highly sensitizing substance	□□□	

9.12	Only for processing of particular product (e.g. pharmaceuticals, Food, Traditional Medicine)	□□□	
9.13	Logical flow of materials	□□□	
9.14	Walls, floors, ceilings smooth and free from cracks?	□□□	
9.15	Easy cleaning possible	□□□	
9.16	Adequate drains with traps and grilles	□□□	
9.17	Air pressure gradient from cubicles → corridor		
9.18	Classification according to GMP Directive		
9.19	Appropriate lighting?	□□□	
9.20	Separate rest and refreshment rooms?	□□□	
9.21	Change rooms designed with an air lock with interlocking?	□□□	
	Equipment		
9.22	Suitable for intended use	□□□	
9.23	Well maintained?	□□□	
9.24	Tanks, containers, pipe work, and pumps designed for easy cleaning and sanitation (dead legs)?	□□□	
9.25	Written cleaning procedure?	□□□	
9.26	Maintenance without contamination risk?	□□□	
9.27	Calibration procedure?	□□□	
9.28	Calibration records?	□□□	
9.29	Contents and flow directions marked on pipes?	□□□	
9.30	Pipes for distilled and demineralised water sanitization procedure?	□□□	
9.31	Status labelling for not functioning equipment?	□□□	
9.32	Status of cleanliness indicated?	□□□	
9.33	Equipment ID, Name?	□□□	
	Procedures and Activity		
9.34	Written procedure and/or report for all manufacturing steps?	□□□	
9.35	Manufacturing procedures and observation record?	□□□	
9.36	Starting material test (contents, weight, and identity)?	□□□	
9.37	Limits for yields?	□□□	
9.38	Only one batch of one product processed at a time?	□□□	

9.39	Correct labelling of containers, materials, equipment and rooms with:	□□□	
9.40	• Product name and batch number	□□□	
9.41	• Status	□□□	
9.42	Procedure for handling OOS and investigation?	□□□	
9.50	Special procedure for penicillin's, hormones etc?	□□□	
9.51	• Dedicated self-contained premises?	□□□	
9.52	• Campaign production?	□□□	
9.53	• Special monitoring?	□□□	
9.54	• Validated cleaning procedure?	□□□	
9.55	Line clearance procedure before start of next batch?	□□□	
9.56	Hold time validation if not packaged and filled immediately (if >30days for non-sterile product)?	□□□	
9.57	Re-working of rejected batches?	□□□	
9.58	• Validated procedure?	□□□	
9.59	• Detailed procedure for the previous batches?	□□□	
9.60	• Special release procedure for those batches?	□□□	
9.61	Use of protective clothing (hair cover, shoes, masks, gloves)?	□□□	
9.62	Clothing regulation for visitors?	□□□	
	Water		
9.63	Loop system for purified water?	□□□	
9.64	Prevention of microbial proliferation of purified water?	□□□	
9.65	Loop system for water for injection?	□□□	
9.66	Storage temperature of water for injection:		
9.67	Loop system constructed to avoid dead legs?	□□□	
9.68	Regular microbial monitoring?	□□□	
9.69	Regular end toxin control?	□□□	
	Special requirement for sterile and aseptic processing:		
	Rooms and Equipment		
9.70	Material and personnel entry through air lock?	□□□	
9.71	Air lock with appropriate interlocking?	□□□	
9.72	Area classification for products to be sterilized:		
9.73	• Solution preparation class C	□□□	

9.74	• Filling under LAF in class C	□□□	
9.75	Classification for aseptic processing	□□□	
9.76	• Handling of starting materials that to be sterile filtered: Class C	□□□	
9.77	• Handling of sterile starting material: Class A/B background	□□□	
9.78	• Handling and filling of sterilized bulk product in class A/B background?	□□□	
9.79	Holding time of bulk product to be sterilized not more that 24hrs?	□□□	
9.80	Hold time of sterilized bulk product under LAF for not more than 24hrs?	□□□	
9.81	All rooms easy to clean and disinfect?	□□□	
9.82	Doors, windows, frames, lighting, etc. without edges?	□□□	
9.83	If suspended ceilings, sealed?	□□□	
9.84	Traps constructed to avoid microbial contamination?	□□□	
9.85	Change room appropriately constructed?	□□□	
9.86	Over pressure gradient from cleanest area to others?	□□□	
9.87	AHU validation and regular revalidation procedure?	□□□	
9.88	Pressure gradient control?	□□□	
9.89	Warning system in air supply failure?	□□□	
9.90	Do conveyer belts leave sterile areas?	□□□	
9.91	Recording of pressure gradient?	□□□	
9.92	Maintenance work outside from clean areas possible?	□□□	
9.93	Cleaning and disinfection after maintenance works?	□□□	
9.94	Regular revalidation of all equipment and systems?	□□□	
9.95	Water prepared, circulated and stored without microbial contamination?	□□□	
9.96	Cleaning and disinfection SOPs?	□□□	
9.97	Microbial monitoring of cleaning and disinfection agents?	□□□	
9.98	Microbial monitoring program of production areas?	□□□	
	Personnel and Hygiene		
9.99	Minimal number of personnel in clean areas?	□□□	
9.100	Special and regular training?	□□□	

9.101	Regular medical examination?	□□□	
9.102	Appropriate clean room clothes (material, design)?	□□□	
0.103	Protective clothe?	□□□	
9.104	Prohibition of cosmetics, jewellery and watches?	□□□	
9.105	New clean room clothing for each working cycle?	□□□	
9.106	Washing and sterilization of clothes?	□□□	
	Procedure and activities		
9.107	Media fill validation interval (at least every six month)	□□□	
	Monitoring of water system		
9.108	• Microbiological	□□□	
9.109	• Chemical	□□□	
9.110	• Particles	□□□	
9.111	• Endotoxins	□□□	
9.112	Microbiological monitoring of starting materials?	□□□	
9.113	Defined maximum storage time for sterilized equipment and under LAF?	□□□	
9.114	Material transfer to clean areas through double door autoclave?	□□□	
	Sterilization process		
9.115	All process validated?	□□□	
9.116	Sterilized and not sterilized material clearly segregated?	□□□	
	Trays and boxes clearly labelled with		
9.117	Product name and code	□□□	
	Batch number	□□□	
	Status: sterilized or not sterilized	□□□	
	Sterilizer		
9.118	• Record of temperature, pressure, and time?	□□□	
9.119	• Coldest point determined?	□□□	
9.200	• Independent counter check probe?	□□□	
9.201	• Heat up time for each product determined?	□□□	
9.202	• Sterile cooling media?	□□□	
9.203	• Clean steam for steamauthoclaves?	□□□	
9.204	• Circulated air with over pressure?	□□□	
9.205	• Re-circulated air: sterile filtered?	□□□	

9.206	• Ethylene oxide autoclaves: humidity, temperature and time record?	□□□	
9.207	• Ethylene oxide: use of bio indicators?	□□□	
	Filtration		
9.208	Double filtration?	□□□	
9.209	Final filter of pore size of 0.22µ	□□□	
9.210	Integrity testing of filters immediately after use?	□□□	
9.211	Filter integrity test result part of batch record?	□□□	
9.222	Optical control of each single container of ampoules, vials and infusion?	□□□	
	In Process Control		
9.223	Written IPC procedure and SOP?	□□□	
	Particle testing of:		
9.225	• Rooms	□□□	
9.226	• Primary packaging materials	□□□	
9.227	• System of warning and action limits	□□□	
	Microbiological monitoring of	□□□	
9.228	• Rooms	□□□	
9.229	• Personnel	□□□	
9.300	• Equipment	□□□	
9.301	Endotoxin monitoring of water and packaging materials?	□□□	
9.302	Calibration of equipment?	□□□	
9.303	Regular revalidation of equipment?	□□□	
10	**Packaging (Primary)**		
	Operations carried out	□□□	
	• Blistering	□□□	
	• Foil packaging	□□□	
	• Filling in to tablet glasses	□□□	
	• Effervescent packaging	□□□	
	• Powder filling	□□□	
	• Syrups/drops filling	□□□	
	• Ointment filling	□□□	
	• Other (please specify)	□□□	

	Rooms/Cubicles		
10.1	Suitable for the intended purpose?	□□□	
10.2	• Adequate size?	□□□	
10.3	• Clean?	□□□	
10.4	Designed and located to prevent contamination?	□□□	
10.5	Proper maintenance?	□□□	
10.6	Maintenance possible without contamination?	□□□	
10.7	Appropriate lighting and air conditioning?	□□□	
10.8	Controlled access for authorized personnel only?	□□□	
10.9	Proper segregation of packaging lines?	□□□	
	Packaging procedure and activity		
10.10	Only one product packaged per line at one time?	□□□	
10.11	Line clearance checklist before starting another product?	□□□	
10.12	Labelling of the packaging line (product name and code)?	□□□	
10.13	Material checklist delivered to the line (quantity, identity, conformity with order)?	□□□	
10.14	Cleaning of primary packing materials?	□□□	
10.15	Immediate labelling after filling?	□□□	
10.16	Checking of all printing process (code, expiry date)?	□□□	
10.17	Special safety measures for off-line printing?	□□□	
10.18	Control of printing devices (code reader, counter, etc)?	□□□	
10.19	Printings clear and permanent?	□□□	
10.20	Balancing of printed packaging materials and bulk?	□□□	
20.21	Destruction of left over coded material?	□□□	
20.22	Quarantine of finished product before release?	□□□	
20.23	Appropriate storage after release?	□□□	
	In process Control		
10.24	Check on identity of bulk and packaging materials?	□□□	
	Regular checks on:		
10.25	• Aspect of the packages	□□□	
	• Completeness	□□□	
	• Conformity of quantity and quality of materials with order	□□□	
	• Correct imprint	□□□	

	• Correct function of control devices	□□□	
	Are the following IPC performed:	□□□	
	• Leakage	□□□	
	• Release torque of screw caps	□□□	
11	**Documentation**		
	Specifications		
11.1	Specifications for raw/packaging materials?	□□□	
	Do specification include:		
11.2	• Internal name and code	□□□	
11.3	• Name of supplier and/or manufacturer	□□□	
11.4	• Reference sample (printed packaging materials)	□□□	
11.5	• Sampling procedure?	□□□	
11.6	• Qualitative/quantitative parameter with limit?	□□□	
11.7	• Storage conditions?	□□□	
11.8	• Maximum storage period?	□□□	
	Good receiving?		
11.9	Written procedure for the reception of materials?	□□□	
	Do records receipt include:		
11.10	• Product name on labels and delivery note?	□□□	
11.11	• Internal name and code?	□□□	
11.12	• Receiving date?	□□□	
11.13	• Name of supplier and/or manufacturer?	□□□	
11.14	• Batch number of supplier?	□□□	
11.15	• Total quantity and number of containers?	□□□	
11.16	• Allocated internal code	□□□	
11.17	SOPs for labelling, quarantine and storage of all incoming materials?	□□□	
	Sampling SOPs include		
11.18	• Authorized sampling personnel?	□□□	
11.19	• Method, equipment and quantities?	□□□	
11.20	• Safety measure	□□□	
	Master formulae		
11.21	Are master formulae for each product and batch size available?	□□□	

	The master formula include		
11.22	• Product name and code?	□□□	
11.23	• Description of dosage form, strength and batch size?	□□□	
11.24	• Composition of product (active and excipient) with name, code and weight?	□□□	
11.25	• Yields with limits?	□□□	
	Does the working procedure include:		
11.26	• The production line?	□□□	
11.27	• Equipment to be used?	□□□	
11.28	• Reference to methods for cleaning, assembling, and calibration of machines?	□□□	
11.29	• Detailed stepwise manufacturing instruction?	□□□	
11.30	• IPCs to be performed with limits?	□□□	
11.31	• Precautions to be followed?	□□□	
11.32	Are batch records kept for each batch processed?	□□□	
	Do the batch record include:		
11.33	• Protocol of line clearance	□□□	
11.34	• Name of the product and batch number?	□□□	
11.35	• Date and time of start and end of production?	□□□	
11.36	• Name and initials of responsible workers for each step?	□□□	
11.37	• Batch and analytical number and actual weight of all starting materials?	□□□	
11.38	• Equipment used?	□□□	
11.39	• Results of IPCs with initials of person who carries them out?	□□□	
11.40	• Yields of the relevant manufacturing steps?	□□□	
11.41	• Detailed notes on problems and process deviations?	□□□	
11.42	Procedure and records for reprocessing of batches	□□□	
11.43	Packaging instructions for each product, package size, and presentation?	□□□	

	Do the packaging instruction record include:		
11.44	• Product name?	□□□	
11.45	• Description of dosage form and strength?	□□□	
11.46	• Package size?	□□□	
11.47	• List of all packaging materials with code for a standard batch size?	□□□	
11.48	• Sample of printed packaging materials?	□□□	
11.49	• Special precautions?	□□□	
11.50	• Description of the process and equipment?	□□□	
11.51	• IPCs to be performed with sampling instruction?	□□□	
11.52	Are packaging batch records kept for each batch or per batch	□□□	
	Do the packaging record include:	□□□	
11.53	• Protocol of line clearance?	□□□	
11.54	• Name of the product?	□□□	
11.55	• Date and time when operation performed?	□□□	
11.56	• Name of the responsible person?	□□□	
11.57	• Initials of workers carrying out operations?	□□□	
11.58	• Notes on identity checks and conformity with packaging instructions?	□□□	
11.59	• Results of IPCs?	□□□	
11.60	• Details of operations and equipment used?	□□□	
11.61	• Samples of printed packaging materials with codes (MFD, EXP, Batch number, etc)	□□□	
11.62	• Record of problems and process deviations?	□□□	
11.63	• Quantities of packaging materials delivered, used, destroyed or returned?	□□□	
11.64	• Number of packs consumed?	□□□	
	Testing		
11.65	Do the written testing procedure include:		
11.66	• Testing methods?	□□□	
11.67	• Equipment for testing?	□□□	
11.68	Tests documented?	□□□	
	Others		

11.69	Procedure for release and rejection of materials and finished product?	□□□	
11.70	Final release by authorized person?	□□□	
11.71	Records about distribution of each batch?	□□□	
11.72	Procedure and protocol about	□□□	
11.73	• Validation?	□□□	
11.74	• Set up and calibration of equipment?	□□□	
11.75	• Maintenance, cleaning and disinfection?	□□□	
11.76	• Testing records?	□□□	
11.77	• Environmental monitoring of production areas?	□□□	
11.78	• Pest control?	□□□	
11.79	• Complaints?	□□□	
11.80	• Recalls?	□□□	
11.81	• Returned goods?	□□□	
11.82	Instruction for used of manufacturing and testing equipment?	□□□	
11.83	Log books for major equipment including date and name of persons who performed:	□□□	
11.84	• Validation?	□□□	
11.85	• Calibration?	□□□	
11.86	• Maintenance, cleaning and repair works?	□□□	
12	**QUALITY CONTROL**		
	General requirement		
12.1	Independent QC department available	□□□	
12.2	Head of QC well qualified and sufficiently experienced?	□□□	
12.3	Qualified personnel available?	□□□	
12.4	Organization charts available?	□□□	
12.5	Job description available?	□□□	
12.6	Responsibilities clearly defined?	□□□	
12.7	Continuous training for QC personnel?	□□□	
12.8	Initial job training for all employees?	□□□	
12.9	Training records?	□□□	
12.10	QC personnel admitted to the production rooms for sampling etc?	□□□	

	QC Laboratories		
12.11	Suitable for the intended use?	□□□	
12.12	Laboratories of adequate size?	□□□	
12.13	Appropriate level of maintenance?	□□□	
12.14	Adequate separation from production area?	□□□	
12.15	Separate entry and exit for microbiology and other laboratory rooms?	□□□	
12.16	Controlled access of authorized personnel only?	□□□	
12.17	Special laboratory to handle biological samples?	□□□	
12.18	Isolated animal laboratory with separate air handling?	□□□	
	QC documentation		
12.19	Do procedures exist for	□□□	
	• Self-inspection	□□□	
	• Release or rejection of products or materials	□□□	
	• Recalls	□□□	
	• Complaints	□□□	
	• Stability testing	□□□	
	• Storage of reference samples	□□□	
	• Validation of analytical procedure	□□□	
12.20	Specification available for raw material, bulk product, packaging materials?	□□□	
12.21	Analytical procedures for every product?	□□□	
12.22	Sampling procedure available for raw, bulk, packaging materials?	□□□	
12.23	Supplier certificate available	□□□	
12.24	Sample retention system (+ 1year minimum)	□□□	
12.25	Calibration program for analytical instrument?	□□□	
12.26	Batch records kept for expiry +1yr or 5 year minimum?	□□□	
12.27	Procedure for traceability of original analytical record from analytical report number or batch number?	□□□	
12.28	Procedure for trend analysis for analytical results, yields and environmental monitoring data?	□□□	
	Sampling		
12.29	Written procedure for taking samples	□□□	

12.30	Do procedure define		
	• Method of sampling?	□□□	
	• Necessary equipment?	□□□	
	• Quantity of sample?	□□□	
	• Subdivision of sample?	□□□	
	• Sample container?	□□□	
	• Labelling of samples?	□□□	
	• Storage conditions?	□□□	
	• Cleaning and storage of sampling of equipment?	□□□	
	• Identification of containers to be samples?	□□□	
12.31	Are samples representative for the batch the represent (sampling plan)	□□□	
12.32	Sampled container labelled with name of content, batch number, date of sampling and batch containers sampled?	□□□	
12.33	Are samples taken by authorized?	□□□	
12.34	Reference samples retained for expiry+1 year?	□□□	
12.35	Storage of reference samples under the recommended storage condition?	□□□	
12.36	Finished product stored in the final packaging?	□□□	
12.37	Retained samples allow 2 possible complete analyses?	□□□	
12.38	Sample retention room access secured?	□□□	
	Testing		
12.39	Are the methods validated/verified?	□□□	
12.40	Analytical methods in compliance with registration?	□□□	
12.41	Are all results recorded and checked for correctness?	□□□	
12.42	Are all calculation checked?	□□□	
12.43	Do the analytical testing protocol contains:		
	• Dosage form?	□□□	
	• Batch number?	□□□	
	• Specification reference number?	□□□	
	• Method reference number?	□□□	
	• Date of analysis?	□□□	
	• Name of the analyst?	□□□	
	• Statement of release or rejection?	□□□	

	• Date and signature of person authorized for release?	□□□	
12.44	Are all IPC in production approved by QC?	□□□	
12.45	SOPs for preparation of reagents and volumetric solution?	□□□	
12.46	Logbook of standardization of volumetric solution?	□□□	
12.47	Reagents labelled with date of preparation and storage condition, expiry date	□□□	
12.48	Reference standard labelled with name and potency, date of expiry, supplier name	□□□	
12.49	Reference standard access controlled?	□□□	
13	**COMPLIANTS AND PRODUCT RECALLS**		
	Complaints	□□□	
13.1	Does written compliant procedure exist?	□□□	
13.2	Are product compliant carefully reviewed?	□□□	
13.3	Is a person designated to handle complaints and to decide on measures to be taken?	□□□	
13.4	Are product complaints thoroughly investigated?	□□□	
13.5	Procedure to inform regulatory authority on serious quality problem	□□□	
	Recalls		
13.6	Does written procedure exist?	□□□	
13.7	Is a person designated for execution and coordination of recall?	□□□	
13.8	Responsible person independent of marketing and sales?	□□□	
13.9	Are the authority informed of an imminent recall?	□□□	
13.10	Does the person responsible for recall have access to the distribution records?	□□□	
13.11	Do the distribution records contain sufficient information on customers with address, phone, batch and amount delivered medical samples?	□□□	
13.12	Are recalled products stored in secured area?	□□□	
13.13	Is the final record made including reconciliation between the delivered and recovered quantities?	□□□	
13	**SELF INSPECTION**		
13.1	Does a self-inspection procedure exist, which defines	□□□	

	frequency and program?		
13.2	Are self-inspections carried out to check compliance with GMP rules	□□□	
13.3	Is the self-inspection conducted in an independent and detailed way?	□□□	
13.4	Are the self-inspection recorded and appropriate corrective action taken?	□□□	
14	**CONTRACT MANUFACTURING AND ANALYSIS**		
14.1	Written contract between contract giver and contract acceptor available?	□□□	
14.2	Are responsibilities and duties clearly defined?	□□□	
14.3	All arrangements in accordance with marketing authorization of the concerned product	□□□	
	The contract giver		
14.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	□□□	
14.5	Acceptor informed of safety aspects?	□□□	
14.6	Conformance of products quality supplied by the acceptor ensured?	□□□	
14.7	Products released by a qualified person on the acceptor's side?	□□□	
	The contract acceptor		
14.8	Does the acceptor have adequate premises, equipment, knowledge, experience, competency and manufacturing authorization?	□□□	
14.9	Does the acceptor ensure that all products or materials delivered to him are suitable?	□□□	
14.10	There must be no work passed to a third party without the permission of the giver?	□□□	
14.11	If the third party involved it must have the necessary manufacturing and analytical information.	□□□	
15	**Any other observation and comments**		
16	**Declaration by the applicant**		
	I the undersigned certify that all the information in the accompanying documentation concerning the		

	inspection checklist of: Name of the company_____duly authorized to represent (Applicant company name) _____ is correct and true, and reflects the total information available. I further confirm that the information referred to in the check list is available for verification. I also agree that I am obliged to comply with the requirements of the Authority related to GMP any time point in future. Name _____ Signature _____ Position in company _____ Date: _____	
17	**Recommendation of the inspector:**	
18	**Name and Signature of inspector**	
		Name: _____ Signature: _____ Date_____
		Name: _____ Signature: _____ Date_____
		Name: _____ Signature: _____ Date_____
19	**Certification by owner/designated person**	
	I (Full Name of owner/designated person) _____ Certify that my proposed site/premises/plan has been reviewed/ inspected by above named inspector(s) and I agree with the information provided in the checklist and report. Signature_____ Date _____	

የኢትዮጵያ የምግብ፣ የመድኃኒትና የጤና ክብካቤ አስተዳደርና ቁጥጥር ባለሥልጣን

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

Annex IV Format for Manufacturing Certificate of Competence

Manufacturing Certificate of Competence

Ethiopian Food, Medicine and Health care Control and Administration Authority

This is to certify that the premises certificate of competence number _____ is issued to M/S _____ of (Postal Address) _____ which is located in (particular area name) No _____Situated between _____Street, in _____Village/Town/Kifleketema/Sub-City, have permit to manufacture _____
_____
_____
_____

Subject to the following conditions:

1. The premises and the manner in which the manufacturing is to be conducted must conform to requirements of Ethiopian Food, Medicine and Health care Control and Administration and/or any other guidance at all times.

2. Any change in the ownership, name and location of certified premises shall be subject to approval by the Authority.

3. This certificate of competence is not transferable to other premises or to any other person

4. This certificate of competence shall be displayed conspicuously in the registered premises.

5. This certificate of competence is permitted only to manufacture the products listed in the attachment

_____

_____

Date and Signature

የኢትዮጵያ የምግብ፣ የመድኃኒትና የጤና ክብካቤ አስተዳደርና ቁጥጥር ባለሥልጣን

Ethiopian Food, Medicine and Healthcare Administration and Control Authority

Annex V: Format for GMP certificate

GMP certificate number_____

This is to certify that the premises operated with certificate of competence _____ is authorizedon _____for Good Manufacturing Practice of the products listed in the attachment. The certificate is valid for two years from the date of its issuance.

This certificate is hereby granted to MS of _____of (Postal Address) _____ to the premises located in (Block/street number) _____Situated between_____ _____Street,in_____Village/Township/Kifleketema/Sub-City, for the manufacture of _____ _____

This certificate shall have and continue to have effect for two years from and including the day when it is issued.

Subject to the following conditions:-

1. The GMP certificate is issued to operate under the presence of competent staffs indicated in the over leaf
2. The GMP certificate is issued to the premises only to manufacture the product listed in the attachment.