INTRODUCTION

In order to provide appropriate health care to animals in the country, the provision of veterinary drugs of proven safety, efficacy and quality is indispensable.

One important method of ensuring the safety, efficacy and quality of these products is thorough evaluation and registration of veterinary products, which are to be imported or locally produced before they offered for use in the country.

The drug Administration and Control Authority of Ethiopia has issued this guideline for the registration of veterinary drugs with the objective of providing applicants with information concerning documentation to be submitted for registration of veterinary products.

The guideline consists of four sections, namely,

- Requirements for abbreviated registration of veterinary drugs (section I)
- Requirements for registration of new veterinary drugs (section II), and
- Requirements for re-registration of veterinary products (section III), and
- Requirements for various other forms of registration of veterinary drugs (section IV)

One of these types of applications, which necessitate special mention, is re-registration application. After a veterinary product is registered, its registration is valid for five years only. It is, therefore, mandatory for manufacturers to apply for re-registration by submitting the required documents before the due date.

Samples for various standard formats and a table have been annexed to the four sections of the guideline and applicants are advised to use these standard formats whenever they apply. Moreover, all applications to be submitted should be in the English language. When any part of the document, except the package labeling, is originally written in another language, a legalized translation in to the English language must be submitted along with the original version.

The guideline is subject to revision in the light of current development in science and technology. Therefore, comments and suggestion are welcomed and can be sent to the Drug Administration and Control Authority of Ethiopia, P.O. Box 5681, Addis Ababa, Ethiopia.

Definitions

For the purposes of this guideline, the following have the meanings hereby assigned to them.

1. **"Abbreviated Veterinary drug registration"**
   Application for the registration of new dosage forms, new route of administration, new strengths, and new claims of an already registered chemical entity and application for the registration of a product containing an already registered chemical entity.

2. **"Active Ingredient"**
   A substance with a therapeutic, diagnostic or prophylactic activity used in a pharmaceutical product.
   "Drug Substance" and "Active Substance" are synonymous to "Active Ingredient".

3. **"Bio Availability"**
   The rate and relative amount of the administered drug which reaches the general circulation intact, or

   The rate and extent to which the active drug ingredient is absorbed from a drug product and becomes available at the site(s) of action.

4. **"Bioequivalence"**
   Comparative bioavailability of two formulations of a drug. Two formulations of the same drug are considered bioequivalent if the extents and rates of absorption of drug from them are so similar that there is likely to be no clinically important difference between their effects, either therapeutic or adverse.

5. **"Branded Generics"** Are unpatented products sold under a brand name.

6. **"Change in pack size"** - means an increase or decrease in the quantity of a dosage form with no change in the nature of the immediate container or specifications.

7. **Change of origin**

7. **"Change in Formulation"**
   designates a qualitative and quantitative change in inactive ingredient(s) and in the production process of the finished drug.

8. **"Closure"** - is a part of the container.

9. **"Container"**

is that which holds the article and is or may be in direct contact with the drug.

10. **"Dosage Form"**

Formulation of an active ingredient(s) so that it can be administered to an animal in specified quantity/strength eg. tablets, capsules, injection solution, syrups, ointments, suppositories, etc. "Pharmaceutical Form" and "Finished Product" are synonymous to "Dosage Form".

11. **"Veterinary drug"**

Any substance or combination of substances that is manufactured, sold, offered for sale, or represented for use in :

a. The treatment, mitigation, prevention, or diagnosis of disease, abnormal physical state, or the symptoms therefore in animal, or
b. The restoration, correction, or modification of organic functions in man or animal.

12. **"Generic Product"**

Pharmaceutical product sold under the non-proprietary name of the active substances, often by reference to a pharmacopoeial monograph. "Generic Drug", "Standard Product" and "Non Proprietary Product" are synonymous to "Generic Product".

13. **"Immediate Container"**

is that which is in direct contact with the drug at all times.

14 **"Label"**

A display of written, printed or graphic matter upon the immediate container or the outside container or wrapper of package.

15. **"Labelling"**

All labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container.

16. **"Package Labelling"**

Labelling includes package leaf let, label on the immediate container, outer wrapper or carton.

17. "Packaging material" - Container – Closure

18. **"Proprietary Product"**

A medicinal product sold or supplied under a special name (a brand or trade name) rather than the generic name of the ingredient alone.

"Pharmaceutical Specialty", and "Branded Product" are synonymous to "Proprietary Product".

19. **"Reference Standard/Substance"**

Authentic specimens that have been verified for suitability for use as comparison standards in compendia tests and assays.

20. **"New veterinary drug"**

One which has not been previously registered or marketed in Ethiopia for veterinary purposes, including any new salts and esters of an active substance , new fixed combinations of substances previously marketed or any veterinary drug previously marketed if its indication , mode of administration, or formulation are changed.

21. **"Withdrawal time"**

The minimum time that must elapse between the cessation of treatment of a food -producing animal and either the slaughter of the animal for human consumption or the resumption of the supply from human consumption of products , such as eggs, milk derived from the animal.

22. **"Pharmacuetical product"**

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Section I Requirements for abbreviated new Veterinary drug registration

1. Application form

1.1 The application form for abbreviated veterinary drugs registration consists of 2 pages with 13 numbered items to be filled out completely by the applicant (manufacturer or agent)

1.2 The date of application should correspond to the date of submission of the application to the Drug Administration and Control Authority of Ethiopia.

2. Agency agreement

2.1 An agency agreement should be made between the manufacturer of the drug in question and the agent responsible for the import, distribution and sale of the drug in Ethiopia.

2. 2 The agreement should be signed by both parties and such is what is to be presented. The seal/stamp of both parties should also be affixed to the document.

2. 3 The agreement should specify that the representative chosen is the sole agent in Ethiopia.

2. 4 The agent representing the manufacturer should hold a license issued by the ministry of Trade.

3. Certificate of pharmaceutical products

3.1 The content of the certificate shall be as indicated in Annex IX.
3.2 The certificate must be issued by the competent authority in the country of origin
3.3 The certificate must be original and current
3.4 The certificate should be authenticated by the Ethiopian Embassy in the country of origin. Where this proves to be difficult, consultation with the Drug Administration and Control Authority of Ethiopia is necessary.

4. Chemical and pharmaceutical documentation

4.1 Chemical Data on Active Ingredient

4.1.1 Nonproprietary or generic name, molecular formula, chemical name, structure, physicochemical properties, synthesis, stability, analytical specifications and test methods, key raw materials, key intermediates, degradation profile, including analytic procedures used in the detection and determination of by products.

4.2 **Formulation Report**

4.2.1 **Data on Composition**

4.2.1.1 Complete qualitative and quantitative composition of the finished product, including quality specifications (requirements) and control methods.

4.2.1.2 Active ingredient(s) present in the form of salts or hydrates shall be described quantitatively by their total mass and by the mass of the active moiety or moieties of the molecule.

NOTE: 1. The names, grades and quantities of all the ingredients used in the course of pharmaceutical manufacture shall be stated. This includes specification of ingredients, which disappear from the formulation during that course.

2. Overage shall be indicated in quantitative terms and the reasons for them shall be given. Overages will usually not be accepted unless it is proved that they are necessary to achieve a reasonable shelf life or to compensate for production losses.

4.2.2 **Data on Packaging Materials (Container and Closures)**

Detailed information is required about the packaging material, which comes in to such contact with the drug. Information required is:

1.Materials of which the drug containers are made.

2.Toxicity of all added substances during manufacture.

3.Technical properties of the finished packaging materials

4.Quality requirements and test methods

5.Manufacturers full name for the material, and

6.Others.

NOTE : When accessories such as infusion sets or disposable syringes are enclosed in the package, data and documentation shall be submitted for these in the same way as for the packaging material.

4.2.3 **Data on Manufacturing and Packaging Procedures**

4.2.3.1 A Concise description of the method of preparation mentioning the quality and quantity of the raw materials used including the final packaging and labeling.

4.2.3.2 Description on the precautions and in-process controls that are made in connection with different stages in the pharmaceutical manufacturing process, that are of importance in ensuring the quality of the finished product.

4.3 **Analytical Report**

The manufacturer should submit:

4.3.1 Quality specifications (requirements) and analytical procedures for the dosage form (in two copies).

NOTE : Should the manufacturer use the quality specifications contained in well-known pharmacopoeias or compendiums, reference can be made to these.

4.4 **Stability Report**

The stability report should consist of stability data sheet and a summary.

4.4.1 The Stability data sheet must show:

4.4.1.1 The formulation

4.4.1.2 The batch number and size (minimum two)

4.4.1.3 Date of manufacture

4.4.1.4 Type and chemical nature of the packaging materials (Test should be performed in the proposed market container-closure systems).

4.4.1.5 Analytical methods that will quantitatively measure the characteristic structural and chemical properties of each active ingredient of a dosage form and distinguish them from their degradation products so that active - ingredient content can be measured.

4.4.1.6 Initial and all subsequent results of chemical, physical and/or biological testing. The data must include the result of studies at suitable test intervals. Frequent testing in the first two years is required. The following is an example of suitable test intervals: 0, 3, 6, 12, 18, 24, 30, 36, 48, and 60 months. It should be emphasized that an initial result plus one further result, as for example, three years is not considered adequate.

4.4.1.7 Data on the degradation product(s) found under various stress conditions and a description of the degradation pathway. The data submitted should contain at least the following information:

a) Chemical structure

b) Cross-reference of any available information about biological effect and significance at the concentrations likely to be encountered

c) Mechanism of formation, including order of reaction

d) Physical and chemical properties

e) Procedure for isolation and purification

f) Specifications and directions for testing for their presence at the levels or concentrations expected to be present, and

g) Indication of pharmacological action or inaction.

4.4.1.8 Stability study results on each solution recommended, where mixing of the dosage form with solutions or intravenous infusions is recommended.

4.4.1.9 Stability and compatibility test results on reconstituted solutions or suspension dry powders.

4.4.1.10 A commitment to continue stability studies on production batches.

4.4.2 The Summary should consist of:

4.4.2.1 Proposed shelf life, which should coincide with the length of study at the recommended storage conditions (e.g. If the proposed shelf life of a product is three years then the result of tests performed at the recommended storage conditions to account for three years should be supplied).

4.4.2.2 Storage recommendations based on the data generated.

4.4.3 **Test parameters for specific dosage forms.**

The tests for stability at each sampling period should be related to the formulation and to the storage condition and the study should include tests for the following characteristics:

4.4.3.1 **Tablet** : Appearance, friability, hardness, color, odor, moisture, strength and dissolution.

4.4.3.2 **Capsules** : Strength, moisture, color, appearance, shape, brittleness and dissolution.

4.4.3.3 **Emulsions** : Appearance (such as phase separation and color), odor, PH, viscosity, strength. It is recommended that a heating, cooling cycle be employed,

e.g. between 4 ^{0}C and 45 ^{0}C.

4.4.3.4 **Drenching Suspenstion**: Appearance (precipitate, cloudiness), strength, PH, color, odor, redispersibility (suspensions) and clarity (solutions).

Liquids and suspensions should be stored both upright and inverted in order to determine whether contact of the drug with the closure system affects product integrity. After storage, samples of suspensions should be prepared for assay in accordance with the recommended labeling under "Directions for Use".

4.4.3.5 **Oral Powders** :

a. The Dry Powder/Granules : Appearance, strength, color, odor and moisture.
b.**The Reconstituted Material** : Appearance, PH, dispersibility and strength throughout the recommended storage period.

4.4.3.7 **Topical and Ophthalmic Preparations** : Included in this broad category are - ointments, cream, pastes, gels, solutions, and sprays for application to the skin.

For stability studies of topical ointments, creams, and solutions the following characteristics should be examined for all sizes as appropriate to the dosage form:

Appearance (clarity, color, homogeneity), odor, PH, resuspendibility (lotions), consistency, particle size, strength and weight (plastic containers).

Evaluation of Ophthalmic Ointments, Solutions, and Suspensions should include as appropriate to the dosage form**:**

Appearance, odor, consistency, PH, resuspendibility, particle size, homogeneity (suspensions, creams, and ointments), strength and sterility.

4.4.3.8 **Small Volume Parenterals** : Strength, appearance, color,clarity (freedom from visible foreign matter), PH and sterility (at reasonable intervals)**.**

4.4.3.9 **Large Volume Parenterals (LVP'S)** : Stability tests for LVP's are similar to those appropriate for small volume parenterals. All container-closure sizes should be studied. A minimum evaluation should include the following:

Strength, appearance, color, clarity, particulate matter, PH, volume (Plastic containers), extractable (plastic containers) and sterility (at reasonable intervals).

4.4.3.10 **Drug Additive** :

A suggested protocol for any drug that is intended for use as an additive to another drug should provide for tests to be conducted at 0, 6, 8, and 24 hours intervals. These should include:

Assay of the drug and additive, PH (especially for un buffered LVP'S), color, clarity and interaction with the container.

4.4.3.11 **Intramammary Infusion:** Appearance, (clarity, color, homogeneity), PH, odour, strength sterility (at reasonable interval).

NOTE : Solid dosage forms, e.g. tablets, capsules, suppositories, powders (oral and parenteral), should be assayed for concentration per unit dose and per unit weight, when possible. This will permit more accurate assessment of product stability by explaining data fluctuations caused by variations in filling, tableting, etc.

4.4.4 **Other general test parameters** (where applicable)

4.4.4.1 **Microbiological**

-Microbial challenge test or assay of preservatives.

-Test for microbiological contamination (viable count).

- Absence of specific pathogenic organisms (eg. Pseudomonas cepacia, Aspergillus niger, Candida albicans etc.,).

- Sterility test (initially and at the end of the study)

- Microbiological assay; etc.

4.4.4.2 **Physicochemical**

- Identification

- Test for related substances; etc.

4.4.4.3 **Others**

- Abnormal toxicity.

5. Bioequivalency Report (Relative Bioavailability Report)

Bioequivalence report is required for those oral dosage forms of drugs which are known to pose bioavailavility problem. The department shall prepare a list of such kinds of problem drugs from time to time.

5.1 **Summary**

5.2 **Objective**

5.3 **Subjects**

5.3.1. Inclusion criteria.

5.3.2. Number, sex, animal species, age, weight and screening tests done prior to commencement of the study.

5.3.3. Exclusion criteria.

5.4 **Materials**

Type of formulations used in study.

5.5 **Study Design**

Description of the test procedure including:

a. Number of treatment groups/ No. of animals in each group

b. Treatment periods

c. Type of test
d. Site of the study

e. Route of administration

f. Sampling times
g. Doses
h. Method of administration (fasting state, with or after feed), etc.
i. The responsible investigator should sign for their respective section of the report.

5.6 **Chemical Analysis**

Method used to determine plasma concentrations of the drug

5.7 **Result**

a) Mean area under the plasma concentration time curve (AUC)
b) Mean peak plasma concentrations (Cmax)
c) Mean time to reach peak plasma concentrations (Tmax)
d) Steady state plasma concentration.

5.9 **Subjects**

Number, sex, age and weight of target animals that have completed the study.
For those who have not completed the study, the reasons thereof should be stated.

5.10 **Discussion and Conclusion**

5.11 **Exemption**

The following dosage forms are exempted from bioequivalence study requirements:

a) Parenteral preparations(Except sustained/or extended release IM injection)
b) Ophthalmic or otic products
c) Topical preparations
d) Gases
e) Solutions for oral use which contain the active substance(s) in the same concentration as the innovator product and do not contain an excipient that affects gastro-intestinal transit or absorption of the active substance.
f) Powders for reconstitution as a solution and the solution meets the criteria indicated in (e) above.
g) Sprays
h) Other dosage forms where absorption from the site of administration is not a requirement for their efficacy.

NOTE : Generic products should be compared with the innovator's brand or the market leader formulation (brand) for that drug in Ethiopia. Results should be presented in tables and also graphically. In case of ectoparasiticdes (topical application) and anthelmintics (oral administration) where blood concentration studies may not be most appropriate, clinical result of clinical end-point studies should be presented

5 Sample of package labeling

Package labeling includes package leaflet, label on the immediate container, and outer wrapper or carton.

All of the labeling information required must be in English and must appear conspicuously so that it will be read and understood by the ordinary individual.

The applicant should submit a letter confirming that the labeling materials submitted are identical to the ones used in the country of origin. Four samples of each labeling material should be submitted concurrent with the application.

6.1 Package leaflet

The package leaflet should consist of factual and scientific information consistent with the application. A leaflet must bear adequate information for use and it should at least include:

6.1.1 The name of the product; brand and generic/INN

6.1.2 Description, appearance, pharmaceutical form, route of administration

6.1.3 Qualitative and quantitative composition of active ingredient(s), preservative(s), and other ingredients that require precaution in their use

6.1.4 Clinical Pharmacology

6.1.5 Indication(s)for target animal species and application goal.

6.1.6 Warnings, precautions, and contraindications

6.1.7 Adverse reactions/side effects

6.1.8 Dosage and administration (application type, application to pregnant and lactating animals and peculiarity of animal species.)

6.1.9 Over dosage (signs and symptoms, and treatment); where applicable

6.1.10 Pharmaceutical precautions (storage instructions)

6.1.11 How supplied (package quantities)

6.1.12 Must indicate ***"withdrawal period"*** of the drug to be administered to animals whose meat and other products shall be used for human consumption.

6.1.13 Name and address of manufacturer.

6.1.14 Date of preparation or last review of the leaflet

NOTE : If the product does not have an insert, then the particulars required under item No. 6.1 excluding 6.1.4 and 6.1.9, should appear on the label of the immediate container.

6.2 Label of the immediate container

The label of the immediate container should at least include:

6.2.1 The name of the product; brand and generic/INN

6.2.2 Pharmaceutical form, and route of administration

6.2.3 Qualitative and quantitative composition of active ingredient(s), preservative(s), and

6.2.4 Quantity in container

6.2.5 Technical directions for use

6.2.6 Contraindications, warnings, and precautions

6.2.7 Handling and storage requirements

6.2.8 Batch number

6.2.9 The titles for Manufactory and expiry dates (the actual dates are not required)

6.2.10 Name and address of manufacturer.

6.2.11 "***For Veterinary use only"*** should be stated

6.2.12 Must indicate the ***" withdrawal period"*** when applicable

6.2.13 Must describe the residual resistance time in case of drugs to be used for ectoparasites.

NOTE : Where the immediate container of the medicament does not, on account of its small size (small containers, ampoules, and unit packaging), enable the particulars required under item No. 6.2 to be displayed, the label on the container shall at least include : 6.2.1, 6.2.2, 6.2.3, 6.2.4, 6.2.8,6.2.10, 6.2.11 6.2.12 and 6.2.13.

6.3 Outer wrapper or carton

The outer wrapper or carton must bear all of the information required to appear on the label of the immediate container itself or else the wording on the label of the immediate container must be legible through the outer wrapper or carton.

6.4 General Note

The titles for batch number, manufacturing and expiry dates should be part of the printing (type written materials, stickers, etc. are not acceptable). If the labeling technology of the manufacturer is such that this information is to be printed on the label on production line using ink jet, laser printing, rubber stamp, etc, a written commitment to show all the required information on the label of the finished product must be submitted.

7. Sample of Actual Products and of Reference Standard Substance (Active Ingredients)

7.1 Sample of actual products and reference standard substance (active ingredients) will be requested only after document approval by the Office of the Drug Administration and Control Authority. Applicants are therefore advised not to submit samples along with registration documents.

7.2 An adequate quantity of sample will be submitted for quality control analysis (see Annex VIII) and the samples should be accompanied with the certificate of analysis.

7.3 Sample should be identical to the actual commercial product ie. it should not be sample for detailing purpose.

7.4 An adequate quantity of active ingredient(s) or standard substance(s) should be submitted if the method of analysis calls for the use of these particulars.

7.5 Sample of any other ingredient, that can be expected to be of importance in the control of the specialty, should also be submitted.

NOTE : If special requirements must be imposed on the storage of samples or standards, information about their storability should be given and details on their appropriate storage should be affixed to the containers.

Section II Requirements for the registration of New Veterinary Drugs

1. Application form

1.1 The application form for the registration of new veterinary drugs as indicated in section I No.1

1.2 The date of application should correspond to the date of submission of the application to the Drug Administration and Control Authority of Ethiopia.

2 Agency agreement

As indicated in Section I, item number 2 of the requirements for abbreviated new veterinary drug registration.

3. Certificate of pharmaceutical products

As indicated in Section I, item number 2 of the requirements for abbreviated new veterinary drug registration.

4. Chemical and pharmaceutical documents

As indicated in section I, item number 4 of he requirements for abbreviated registration of veterinary drugs.

5. Report on pre clinical studies

5.1 **Animal Pharmacology**

5.1.1 **Summary**

The manufacturer should furnish a summary of the observations and conclusions that have been made in respect of the pharmacological properties of his product. Investigations forming the bases of the summary should be cross-referenced to the works included under each section.

The summary should give the animal species, number of animals, doses, information on dosage formulation, route of administration, concise description of the methodology, results, conclusions and an overall evaluation of the pharmacodynamic and pharmacokinetics properties of the drug based on the findings in laboratory animals or in invitro systems.

5.1.2 **Pharmacodynamics**

5.1.2.1 Studies providing the primary basis for clinical trials of the drug, mechanism of action (wherever practicable), minimum effective dose (where relevant) but emphasizing adequate description of dose-effect relationships that produce pharmacological responses in each species of animal investigated.

5.1.2.2 Studies providing information on secondary pharmacologic actions of the drug which though they may not be relevant to its therapeutic properties are nevertheless relevant to assessment of its clinical use and risks.

5.1.3 **Pharmacokinetics**

Studies concerning absorption, distribution, metabolism, (or detoxification), enzyme induction, enzyme inhibition, excretion and microfloral effect(inhibition/induction) .

5.1.4 **Other Studies**

Studies which add to our understanding of the pharmacologic activities of the drug, which in turn contribute to the safe and effective use of the drug.

5.2 **Toxicological Data**

5.2.1 **Summary**

Summary of toxicological studies preferably should be presented in tables which indicate species, number, sex, age, weight and of animals, information on dosage formulation, route(s) of administration, treatment regimen duration of treatment, parameters evaluated, significant observations and conclusions.

The dates of studies and name(s) of the laboratories conducting the studies should be mentioned.

Under the following headings detailed description and analysis based on the available completed toxicological studies should be provided.

5.2.2 **Acute Toxicity**

Acute toxicity studies in three species (one non-rodent) by the clinical and parenteral routes with two week observation periods. Species, route of administration, dose levels and number of animals per dose level should be given together with the weight, sex and age, of animals feed and LD_{50} should provide sign(s) of toxicity, times of death, and any pertinent information should be reported.

5.2.3 **Long Term Toxicity**

Subacute and chronic toxicity studies in at least two species of healthy mature animals, one rodent and one non-rodent, by the proposed clinical route of administration. Species, route of administration, dose levels, treatment periodicity, duration, strain, numbers and age of animals per dose level should be provided. Sex, initial and intermediate and final weights of animals, and method and frequency of administration of the new drug should be documented. Where the drug is given in diet, daily intake should be stated in mg/kg.

All parameters* studied, including laboratory investigations and pathological examinations, should be listed. All other significant aspects of study design and methodology should be included.

The report should be by species and by route of administration.

5.2.4 **Reproduction and Teratology**

Reproductive and teratologic studies should be reported by species and by route of administration. For each study, dose levels employed, period of drug administration in relation to stage of pregnancy, parameters of pregnancy studied and methods of examination of the young should be specified. The report of results should include a description of effects of the new drug upon fertility, the mother, upon pregnancy and upon the fetus and post-natal development. The relationship of doses used in the reproductive and teratologic studies to known toxic doses for the same species and to proposed doses in targeted animal species should be discussed.

Parameters to be Studied

a. Effects on Parturition

Dams : Mortality, body weights, symptomatology and behavior, labor and delivery, length of pregnancy, lactation, straining of uterus.

Progeny : Number, viability, suckling ability, external abnormalities at birth.

b. Fertility and General Reproductive Performance

Males : Mortality, symptomatology, body weights, fertility.

Females : Mortality, body weights, pregnancy rate, length of gestation number of viable fetuses, and number of corpora lutea.

Progeny : Birth weights, litter sizes, still births, viability, external visceral and stained skeletal examinations.

c. Teratology Studies (Embryotoxicity-teratogenicity)

Dams - Mortality, body weights, symptomatology, number and efficiency of implantations, viable pregnancy rate, number of corpora lutea.

Progeny : Number, viability, weights, gross external, visceral and stained skeletal examinations.

d. Perinatal and Postnatal Studies

Dams - Mortality, body weights, symptomatology, pregnancy rate, parturition, length of gestation, lactation.

Progeny : Number of newborns, sex, viability, weight at 1,4,12, and 21 days of age, postnatal development, gross external and visceral examinations.

5.2.5 **Carcinogenicity**

Life span carcinogenicity studies in mice and rats (both male and female; administration period - mice 18 months, rats 2 years).

5.2.6 **Mutagenicity**

Mutagenic studies on in-vitro and in-vivo chromosome aberrations and gene mutations.

5.2.8 **Other Studies**

This section includes any studies not included in the other sections described above. These might concern tissue irritation, skin sensitization, specific toxic effects, a comparison of properties of different formulations or any of the other types of toxicity studies etc.

5.3 **Microbiology (for anti-microbial agents only)**

5.3.1 **Summary**

Summaries of all pertinent microbiologic studies, including methods used, together with a discussion and evaluation of the results. Cumulative MIC tables are highly desirable.

Under each of the following headings, detailed description and analysis based on the available completed microbiologic studies should be provided.

5.3.2 **In Vitro Studies**

-Antimicrobial Spectrum

-Minimal Inhibitory Concentrations (MIC values) : estimates determined on relevant clinical isolates and standard laboratory strains.

-Experimental evidence to support bactericidal and/or bacteriostatic action.

-Assessment of resistance studies designed to measure incidence of resistance of organisms at various drug concentrations.

-Minimal Bactericidal Concentration (MBC)

-Effect of inoculum size on the determination of MIC and MBC

-Protein binding studies

-Resistance development studies

-Regression studies to establish the size of inhibition zone as basis to determine the sensitivity of a pathogen to the specific antibiotic.

-Studies on cross-resistance and other interactions with other antimicrobial agents.

5.3.3 **Sensitivity Disc Interpretation and Validation Studies**

-include in vitro MIC/ zone diameter correlations and clinical basis for the chosen breakpoints.

5.3.4 **In Vivo Studies**

-Protection Tests. Experiments using experimentally infected animal designed to evaluate potential for therapeutic effectiveness.

-Development of Resistance in vivo. Studies designed to show any change in the characteristics of the infecting organism induced by the drug.

-Change in the body flora: Studies involving microbiologic culture techniques of body tissues and fluids designed to evaluate the drug's effect on the natural body flora and with special emphasis on overgrowth and super infection.

NOTE : 1. **Drug Combinations**

Where combination products are considered, data should be provided on the pharmacological and toxicological profile of the combination as well as the individual components unless explanation is given to justify an omission.

2. Other Works (pre-clinical studies) when have not been included in one of the above headings can be listed down so that the actual study may be requested, if necessary.

6. Report on drug trials on target animals

6.1 Clinical Pharmacology

6.1.1 Summary

The summary should concisely set out the target animal pharmacological properties of the drug. It should at least provide information on the following points:

Pharmacodynamics : Intended drug effect, methodology, number of target animals, age groups, healthy and sick, optimal dose, effect on circulation, respiration, the central nervous system and other vital systems, blood, liver and kidney function, other tolerance studies.

Pharmacokinetics : Methods of determination, number of target animals, age groups, healthy and sick, single-dose and repeated administration, absorption, plasma concentrations, half-life periods, protein binding, metabolism and excretion. It should also give results, an overall discussion and evaluation of the pharmacologic properties of the drug based on the findings of available completed studies, and conclusion.

The trial must also include determination of ***"withdrawal time"*** for drugs to be administered to target animals whose meat or other products shall be used for human consumption.

61.2 Pharmacodynamics

Studies of single and multiple doses in targeted animals, dose-range studies, studies on the effect of drugs on various organic functions, mechanism of action, studies on the relationship of between dose of drug and response in patient, drug interaction studies, etc.

6.1.3 **Pharmacokinetics**

Studies on the absorption, distribution plasma concentration, protein binding, half-life, biotransformation, kinetics, elimination of the drug and also report on metabolic studies. Physicochemical properties which may act on absorption and distribution should be stated. The methods of assay or determination should be specified. The pharmacokinetics investgations should make separate provision for one-time or

single-dose administration and, when this is possible, for repeated administration (maintenance dose). To ascertain any first-pass effect, the plasma concentration in relation to different dosage levels should be examined. It will be useful to have information about those plasma concentrations at which pharmacological and therapeutic effects are obtained and, where applicable, about the concentrations at which adverse reactions appear.

6.1.4 **Combinations**

Reports on combined preparations, in addition to details on their individual components, should also give information on the pharmacological properties of the particular combination that is being considered.

.

6.1.5 **Bioavailability Report**

This requirement concerns only dosage forms where systemic absorption is a requirement for their efficacy.

Report on bioavailability should include the following information and data:

6.1.5.1 **Summary**

6.1.5.2 **Objective**

6.1.5.3 **Subjects**

6.1.5.3.1 Inclusion criteria.

6.1.5.3.2 Number, sex, name, age, weight and screening tests done prior to commencement of the study.

6.1.5.3.3 Exclusion criteria.

6.1.5.4 **Materials**

Type of formulation used in the study.

6.1.5.5 **Study Design**

Description of the test procedure including

(a) Number of treatment groups

(b) Treatment periods

(c) Type of test
(d) Site of the study
(e) Route of administration

(f) Sampling times

(g) Doses

(h) Method of administration (fasting state, with or after feed).

(i) The responsible investigator should sign for their respective section of the report.

6.1.5.6 **Chemical Analysis**

Method used to determine plasma concentration of the drug.

6.1.5.7 **Result**

a) Mean area under the plasma concentration time curve (AUC)
b) Mean peak plasma concentrations (Cmax)
c) Mean time to reach peak plasma concentrations (Tmax)
d) Steady state plasma concentration.

6.1.5.8 **Subjects**

Number, sex, age and weight of targeted animals that have completed the study.
For those who have not completed the study, the reasons there of should be stated.

6.1.5.9 **Discussion and Conclusion**

NOTE : Results should be presented in tables and in illustrative figures. In case of ectoparasiticdes (topical application) and anthelmintics (oral administration) where blood concentration studies may not be most appropriate, clinical result of clinical end-point studies should be presented.

6.2 **Clinical Trials**

6.2.1 **Summary**

The summary should concisely set out the clinical properties of the drug. Special emphasis should be put on that documentation which lends support to the cited indications. It should provide information on targeted animal population (age, sex, complexity of the disease, etc.) number of targeted animal, dosage formulation, doses, methods, etc; and also give an overall discussion and evaluation of the safety, efficacy, dosages, adverse reactions (untoward side effects) and contraindications of

the drug based on the findings of available completed clinical trials, and conclusion providing a discussion of the benefits and risks of the drug under the conditions of use recommended.

The conclusion should at least consider the following points: comparison of the expected clinical benefits with possible adverse effects, and assessment and comparison of the benefit/risk ratio of the drug in relation to related drugs or others used as standards in controlled clinical trials, etc.

Clinical trials* should be grouped under the following headings.

6.2.2 **Pivotal Trials**

Studies providing the basic evidence to determine the efficacy, properties and conditions of use of the drug conducted by qualified investigators at the recommended doses with the proposed formulation and for indications which are being claimed.

6.2.3 **Non-Pivotal Trials**

Other studies which add useful information on the efficacy and safety of the drug.

6.2.4 **Special Clinical trials**

The clinical trail conducted for the determination of ***"withdrawal period"*** of drugs to be administered to target animals whose meat and other products shall be used for human consumption should be indicated.

6.2.5 **Combinations**

In respect of combined preparations clinical trials should be presented which show that the combination as such is medically useful and confers advantages over and above any of its components when taken separately in an effective dose.

All ingredients which are not constituents or which have another exclusively pharmaceutical function should be medically justified in the combination.

NOTE : Summaries should be cross-referenced to the animal-pharmacological and clinical studies grouped under the different headings.

The human pharmacological and clinical material appended should be limited to major works for each indication. The other works can be listed down so that the actual study may be requested, if necessary.

7. Samples of package labeling

As indicated in section I, item number 6 of the requirements for abbreviated registration of veterinary drugs

8. Samples of actual actual products and active ingredients (reference standard Substances)

As indicated in section I, item number 7 of the requirements for abbreviated registration of veterinary drugs.

Section III Requirements for the re-registration of veterinary drugs

Application for re-registration of veterinary products should consist of :

1. An application form for re-registration (Annex II)
2. Certificate of veterinary products, as indicated in section I of this guideline.
3. Samples of packaging materials or a statement from the manufacturer confirming that the type of packaging materials and the labels are identical to the one submitted during the time of previous registration of the product with the Drug Administration and Control Authority of Ethiopia.
4. Samples of actual product and active ingredient(s), as indicated in section I, number 7 of this guideline.

Section IV Requirements for various other types of applications

1. Application for Change of Pack Size or additional pack size

Applications for changes in pack size with no change in materials or specifications should consist of :

1.1 Application form for change of pack size (Annex III)

1.2 The requirements indicated in section I, No.6 of this guideline.

2. Application for Change in Container - Closure

Applications for change in container-closure should consist of:

2.1 Application form for change in container closure (Annex IV)

2.2 Accelerated stability data demonstrating compatibility with the previously approved drug product, plus standard commitment to continue the stability study under normal recommended storage conditions.

For significant changes of products known to be relatively unstable, six month's data at the normal recommended storage temperature as well as the data from accelerated conditions.

The results of the on-going stability study should be submitted every 6 month until the final shelf-life is determined.

2.3 Sample of package labeling as indicated in section I, item No. 6 of this guideline.

3. Application for Change in Formulation

Change in formulation means a qualitative and quantitative change in inactive ingredient(s) and in the production process of the finished drug.

3.1 **Change in Inactive Ingredient(s)**

Application for change in inactive ingredients should include:

3.1.1 An application form for change in formulation (Annex V)

3.1.2 All requirements as indicated in section I No. 3, 4.2. 4.3 (if there is change) 6,7;if there is any change in analytical procedure and/or specifications.

3.1.3 If there is a change which is known to affect the stability of the product, accelerated stability data and commitment to continue the stability study under normal recommended storage conditions should be submitted. The results of the on-going stability study should also be submitted every 6 month until the final shelf-life is determined.

3.2 **Change in the Production Process**

An application for making major change in the earlier, reported production process of a finished product shall include:

3.2.1 An application form for change in formulation (Annex IV)

3.2.2 All requirements as indicated in Section I, numbers 4.2.3, 4.3 (where relevant), and section IV, No. 3.1.3

4. **Application for change in the quality control process and/or specifications**

An application form for making a change in the quality control method (both in-process and finished product Q.C) and specifications leading to a change in the limits or to major changes in the control methods shall include:

4.1 An application for change in quality control process and/or specifications (Annex VI)

4.2 The new quality specifications and control methods with adequate information on accuracy, precision, and suitability of the methodology.

4.3 Sample of actual product as indicated in section I, No. 7 of this guideline.

5. **Application for change of origin**

Change of origin includes change of country of origin or change of manufacturing site.

Applications for change of origin should consist of :

5.1 An application form for change of origin (Annex VII)

5.2 Certificate of veterinary products, as indicated in section I, No. 3 of this guideline.

5.3 Accelerated data demonstrating compatibility with the previously approved drug product, plus standard commitment to continue the stability study.

5.4 Sample of package labeling as indicated in section I, item No. 6 of this guideline

5.5 Samples of actual product and / or reference standard/active as indicated in section I, No. 7 of this guide line.

5.6. A statement confirming that the product formula, manufacturing process, quality control standards are not changed. If this is not so, the new data on each of these components should be submitted as indicated in their respective item numbers of section I.

Annex I

APPLICATION FORM FOR NEW VETERINARY DRUGS REGISTRATION

Drug Administration and Control Authority of Ethiopia
P.O.Box 5681
Addis Ababa, Ethiopia

TO BE FILLED IN BY APPLICANT

1. Date of Application _____

2. Name of the Preparation _____

3. Pharmaceutical Form (dosage form) _____

4. Strength _____

5. Pack size (presentation) _____

6. Type and nature of container and closure_____

7. Registration number of product in the country of origin _____

8. Shelf-Life or Expiry Date of the Product from the Date of Manufacture
_____

9. Name and Address of Manufacturer _____
_____
_____

10. License number of the manufacturer in the country of origin
_____

11. Name and address of the agent in Ethiopia _____
_____
_____

12. Complete Composition of the Product (Use Nonproprietary or Generic Name)

A.	Active Constituents	Strength
	_____	_____
	_____	_____
	_____	_____

_____	_____
_____	_____
_____	_____
_____	_____

B. In-Active Constituents Strength

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

11. Pharmacological category _____

12. Therapeutic Use (Main Indications)

_____
_____
_____
_____

13. Supporting Documents or Materials Attached

_____
_____
_____
_____
_____

Name, Official Designation and Professional Status of the applicant

_____
_____

Signature _____

14. Regulatory status in other countries (indicate also the date)

14.1 Countries where:

a) Marketed with out approval
b) Approved and marketed
c) Under trial, with phase
d) Withdrawn, if any with reasons

14.2 Restrictions on use, if any, in countries where marketing is approved

15. Proposed legal sales category _____

Annex II

APPLICATION FORM FOR RE-REGISTRATION

Drug Administration and Control Authority of Ethiopia
P.O.Box 5681
Addis Ababa, Ethiopia

TO BE FILLED IN BY APPLICANT

1. Date of application _____
2. Name of the product to be re-registered _____
3. Pharmaceutical form _____
4. Strength _____
5. Presentation (pack size) _____
6. Type and nature of container-closure _____
7. Name and address of the manufacturer _____
8. Name and address of the Agent in Ethiopia _____
   _____
9. Previous registration No. in Ethiopia _____
10. Supporting document (materials) attached: _____

Name, official designation and professional status of the applicant
_____

Signature _____

Date: _____

Annex III

APPLICATION FORM FOR CHANGE OF PACK SIZE OR ADDITIONAL PACK SIZE

Drug Administration and Control Authority of Ethiopia
P.O.Box 5681
Addis Ababa, Ethiopia

TO BE FILLED IN BY APPLICANT

1. Date of Application _____
2. Name of the Preparation _____
3. Pharmaceutical form _____
4. Strength _____
5. Previous pack size (presentation) _____
6 New Pack size (presentation) _____
7. Type and nature of container and closure _____
8. Previous registration No. in Ethiopia _____
9. Does the change also involve change in container - closure ?
   Yes ☐ No ☐

10. If yes to No. 9 above, please describe the type and nature of both the old and new container - closures. _____
    _____
11. Name and address of the manufacturer _____
    _____
    _____
12. Name and Address of the Agent in Ehtiopia_____
    _____
13. Supporting documents attached_____
    _____

Name and official designation and Professional status of the applicant

_____

Signature _____

Annex IV

APPLICATION FORM FOR CHANGE IN CONTAINER - CLOSURE

Drug Administration and Control Authority of Ethiopia
P.O.Box 5681
Addis Ababa, Ethiopia

TO BE FILLED IN BY APPLICANT

1. Date of application _____
2. Name of the preparation _____
3. Pharmaceutical form _____
4. Strength _____
5. Pack size (presentation) _____
6. Previous registration No. in Ethiopia _____
7. Type and nature of the new container - closure _____
   _____

8. Does the change also involve pack size ?
   Yes ☐ No ☐

9. If yes to No. 8 above, please describe the new pack size
   _____
10. Name and address of the manufacturer _____
    _____
    _____
11. Name and Address of the Agent in Ethiopia _____
    _____
12. Supporting documents _____
    _____

Name and official designation and professional status of the applicant

_____

Signature _____
Date _____

Annex V

APPLICATION FORM FOR CHANGE OF FORMULATION

Drug Administration and Control Authority of Ethiopia
P.O.Box 5681
Addis Ababa, Ethiopia

TO BE FILLED IN BY APPLICANT

1. Date of Application _____
2. Name of the Preparation _____
3. Pharmaceutical form _____
4. Strength _____
5. Pack size (presentation) _____
6. Type and nature of container and closure _____
7. Previous registration No. in Ethiopia _____
8. Does the change involve:
   a) change in inactive ingredients ? Yes ☐ No ☐
   b) change in the manufacturing process? Yes ☐ No ☐
   c) change in both of the above? Yes ☐ No ☐
9. If yes to No. 8(a) or 8(b) above, please list the ingredients in the spaces provided below:

Previous inactive ingredients

Name	Quantity/unit
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	

The New inactive ingredients

Name	Quantity/unit
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	

14. Name and address of the manufacturer _____
_____

11. Supporting documents attached_____
_____

Name, official designation and professional status of applicant _____

Signature _____

Annex VI

APPLICATION FORM FOR CHANGE IN THE QUALITY CONTROL PROCESS AND OR SPECIFICATIONS

Drug Control and Administration Authority of Ethiopia
P.O.Box 5681
Addis Ababa, Ethiopia

TO BE FILLED IN BY APPLICANT

1. Date of Application _____
2. Name of the preparation_____
3. Pharmaceutical form_____
4. Strength_____
5. Pack size (presentation)_____
6. Type and nature of container and closure _____
7. Registration No. in Ethiopia_____
8. Name and address of the Manufacturer_____
9. Name and address of the agent in Ethiopia_____
10. Brief description of the change intended to be made.
11. Reasons for changing the quality control process or specifications
    _____
    _____
12. Supporting documents attached:_____
    _____
    _____

    Name, official designation and professional status of the applicant
    _____
    _____

    Signature _____

    Date _____

Annex VII

APPLICATION FORM FOR CHANGE OF ORIGIN

Drug Administration and Control Authority of Ethiopia
P.O.Box 5681
Addis Ababa, Ethiopia

TO BE FILLED IN BY APPLICANT

1. Date of Application _____
2. Name of the Preparation _____
3. Pharmaceutical form _____
4. Strength _____
5. Pack size (presentation) _____
6. Previous registration No. in Ethiopia _____
7. Previous origin (country) _____
8. Planned new origin (country) _____
9. Reason for changing the origin: _____

   _____
   _____

10. Name and address of the manufacturer _____
11. Name and address of the agent in Ethiopia _____
12. Supporting documents attached _____

    _____
    _____
    _____
    _____

Name, official designation and professional status of applicant _____

Signature: _____

Annex VIII

SIZE OF SAMPLES TO BE SUBMITTED

FOR QUALITY CONTROL LABORATORY ANALYSIS

Ser.No.	Dosage form	Sample size
1	Tablets, Bolus	
2	Oral Suspensions (Drenching) of 1lt. Oral Suspension (Drenching) of 5 lt.	
3	Dry Powder / Granuels	
4	Injectable Solutions of 100ml , Injectable Solutions of 50 ml.	
5	Lyophilised vials	
6	I.V Solutions (Infusions).	
7	Ointment (Topical and Opthalmic)	
8	Emulsion of 1lt. Emulsion of 5 lt. Emulsion of 10 lt.	
9	Intra-mammary Infusion	

G U I D E L I N E S

ON THE REQUIREMENTS

FOR THE REGISTRATION OF

PHARMACEUTICAL MANUFACTURERS

P A R T II

CONTENTS

Page

INTRODUCTION

Experience in the past has shown that there is wide variation in technological competence of pharmaceutical manufacturers. This difference has been evidenced by variations in the quality of products supplied to the country.

The situation has thus created a necessity to develop a system for the evaluation and registration of pharmaceutical manufacturers.

Consequently, the Drug Administration and Control Authority of Ethiopia has prepared a guideline for the registration of pharmaceutical manufacturers with the purpose of ensuring the safety, quality and efficacy of pharmaceutical products that are imported into the country.

The guideline consists of two sections:

Section I Dealing with legalized documents; and
Section II Dealing with Company Profile.

All manufacturers intending to export their pharmaceutical products (both raw material as well as finished products) to Ethiopia are, therefore, required to be registered with the Drug Administration and Control Authority of Ethiopia.

DEFINITION

For the purpose of this guideline, the following have the meanings hereby assigned to them:

1. Pharmaceutical Product - refers to drugs and medical supplies

2. Medical Supply - refers to surgical dressing, clinical equipment, ligatures and sutures.

SECTION I: LEGALIZED DOCUMENTS

This section deals with certificates and legalized documents (s) to be submitted by the applicant.

1. **Cerificate of Pharmaceutical Products**

1.1. The certificate to be submitted for the registration of manufacturers of Veterinary Drug products (both raw materials and finished products) should be the **WHO** type certificate of pharmaceutical products issued by the National Competent Authority communicated in the " WHO Certificate Scheme on the quality of pharmaceutical products moving in the International Commerce" (Sample of the certificate is annexed to the Guideline on the requirement of the registration of Veterinary Drugs).

1.2. The Certificate of Good Manufacturing Practice (GMP) and Product Certificate (which could be combined in one certificate) to be submitted for the registration of manufacturers of medical supplies must be indicated in the " Guideline on the Requirement for the Registration of Medical Device) .

1.3. All certificates should be authenticated by the Ethiopian Embassy in the country of origin.

1.4. The certificates should be original and current.

2. **Agency Agreement**

2.1 An agency agreement should be made between the manufacturer and the and responsible t act on behalf of the manufacturer.

2.2 The agreement should specify that the representative is the sole agent in Ethiopia.

2.3 The agreement should be signed by both parties.

2.4 The agent representing the manufacturer should hold a license issued by the Ministry of Trade.

SECTION II: COMPANY PROFILE

This section deals with documents to be supplied by the manufacturer.

1. Back ground information

The manufacturer should submit background information about the company indicating the following major points.

1.1. Year of establishment
1.2. Development since establishement
1.3. Capital
1.4. Organogram
1.5. Total working force
1.6. Ownership
1.7. Subsidiaries (if any)

2. Production unit

A. The manufacturer should submit information on the production unit indicating the following.

A.2.1 Production layout
A.2.2 Major production equipment
A.2.3 Qualification and experience of production personnel
A.2.4 The source of production technology
A.2.5 Major suppliers of raw materials and packing materials

B. The information on production unit should also indicate whether the company has the following:

B.2.1 GMP procedure
B.2.2 Master file and batch production record system
B.2.3 Product specifications
B.2.4 Standard operation manual
B.2.5 Special procedures for production of penicillin's (if it formulates penicillin's)
B.2.6 List of pharmaceuticals produced by the manufacturer (specify those which are the manufacturer's innovation).
B.2.7 Other relevant information.

3. Quality Control Unit

The manufacturer should state:

A. Whether it performs the following:

A.3.1 Raw and packaging materials Q.C.
A.3.2 In-process Q.C.
A.3.3 Finished product Q.C.

B. The types of Q.C. tests performed (where they are applicable)

B.3.1. Physicochemical tests
B.3.2. Sterility test
B.3.3. Pyrogen test
B.3.4. Acute toxicity test
B.3.5. Biological assay
B.3.6. Microbiological assay etc.

C. Whether it has Good laboratory Practice(GLP) Procedure.

D. The major Q.C. Instruments available (where they are applicable)

D.3.1. IR spectrophotometer
D.3.2. UV visible spectrophotometer
D.3.3. Gas chromatography
D.3.4. Refractometer
D.3.5. PH-meter (with electrodes)
D.3.6. Melting point apparatus,
D.3.7. Disintegration test
D.3.8. Dissolution test apparatus
D.3.9. Karl-Fisher titrator
D.3.10. HPLC, etc.

E. Qualification and experience of Q.C. personnel

4. **Supply system**

The manufacturer should give information on its supply system indicating whether it has at least the following (where they are applicable).

4.1. Cold storage facilities
4.2. Separate stores for raw materials, packaging materials, labels etc.
4.3. Separate room for weighing raw materials
4.4. Quarantine for raw materials, finished products, etc.
4.5. Procedure for supplies control

5. **Research and Development Unit (R and D)**

The manufacturer should give detailed information on at least the following major points.

5.1. The year R and D was initiated

5.2. Qualification of the personnel engaged in R and D activities.

5.3. Major research areas and achievements attained.

5.4. Affiliation with other institutes (if there is any)

6. **Product Registration and Marketing Experience of the manufacturer**

The manufacturer should submit full information on its marketing experience and registration status of its products indicating:

6.1. List of countries to which it exports most of its products.

6.2. List of countries in which its products are registered

6.3. List of countries where its product(s) has have been withdrawn from the market. (if so, give reasons for withdrawal).

ANNEX I

APPLICATION FORM FOR THE REGISTRATION OF PHARMACEUTICAL MANUFACTURERS

TO: _____

_____

1. Date of application: _____
2. Name and address of the Manufacturer:

   _____

   _____
3. License number of the manufacturer in the country of origin

   _____
4. The type of products manufactured by the factory:

   Medical supplies ☐ Drug raw material ☐

   Finished drug products ☐
5. Documents attached:

   Certificate of Good Manufacturing Practice

   Product Certificate

   Agency agreement

   Company profile

   Consent form

   Others (Please specify below)

_____

_____

_____

_____

Name and official/designation of the applicant (person(s) representing the manufacturer).

_____

_____

Signature _____

Date _____

ANNEX 2

CONSENT FORM

We, ……..assure you that the legalized documents, the company profile, and other documents that we have submitted are true and correct.

We agree to inform the Drug Administration and Control Authority of Ethiopia, about any change or modification made on the information given in the documents submitted.

We also agree to allow officials from the Drug Administration and Control Authority of Ethiopia, to visit and have first-hand information about the factory at any time.

We recognize and accept the right of the Drug Administration and Control Authority of Ethiopia, to suspend or to revoke the registration certificate that is already issued to us if any fraud or anything contradictory to our registration documents is discovered.

Signed by:

Person authorized to
Sign on behalf of the manufacturer

Dated:

(manufacturer's full
name and address)

G U I D E L I N E S

ON THE REQUIREMENTS

FOR THE REGISTRATION OF

MANUFACTURERS OF MEDICAL DEVICES

PART III

CONTENT

PAGE

INTRODUCTION

The objective of this guideline is to provide manufacturers of medical devices with information concerning documentation to be submitted by them in order to be registered with the Drug Administration & Control Authority of Ethiopia as manufacturers of medical devices.

The guideline consists of two sections: Section I dealing with official documents and section II dealing with information associated with the profile of the applying company.

All manufacturers intending to import their medical devices into Ethiopia are required to apply to Drug Administration and Control Authority of Ethiopia for prior registration and product listing. Application forms are obtainable from the Authority.

Definitions

1. **''Diagnostics''** are biochemicals which are used to test organ function, determine blood volume, and hemopoietic function or reveal anatomic evidence of disease or other conditions by outlining various body structures and cavities. It includes all biochemicals, such as reagents, antibiotic sensitivity discs and tst kits for diagnosis of disease and other conditions (e.g. pregnancy).

2. **''Invitro diagnostics''** refer to diagnostics which are used outside the body or which do not achieve any of their principal intended purposes by chemical action in or on the body or by being metabolized.

3. **''Invio diagnostics''** refer to diagnostics which are administered or applied to human beings and achieve their principal intended purposes by chemical action in or on the body or by being metabolized. Diagnostics which work by such chemical or metabolic action are regulated as ''drugs''.

4. **''Medical device''** includes medical equipment and invitro diagnostics.

5. **''Medical Equipment''** are health care instruments which do not achieve any of their principal intended purposes by chemical action in or on the body or by being metabolized. Instruments or articles which work by such chemical or metabolic action are regulated as drugs.

   The term ''Medical equipment'' includes a great number of instruments and appliances such as Scissors, forceps, Surgical blade and handles, Burdezo, emasculator, hoof-trimmer, drenching gun, bull-holder, thermometers, B.P apparatuses, syringes and needles, catheters, gloves, tubes of all kinds, cardiac devices, kidney dialysis machines, microscopes, X-ray machine and electronic devices to name a few.

6. **''New diagnostic''** is one which has not been previously marketed in Ethiopia through the regular and legal supply system before the issuance of this guideline.

SECTION I LEGALIZED DOCUMENTS

This section deals with certificates and legalized document(s) to be submitted for registration.

1. **Certificate of compliance with manufacturing standards**

1.1. The applicant should submit:

1.1.1. A photocopy of valid manufacturing License issued by the National competent authority;

1.1.2. A valid quality system certificate issued by a recognized certifying authority (e.g. ISO, DIN, TUV, BSI,etc.) if available.

1.1.3. A confirmatory letter issued by the National competent Authority which indicates the names of the products and explains whether the products are freely sold in country of origin, If not, the reasons, therefore should be clearly stated.

1.2. The documents indicated in 1.1.1. to 1.1.3 above should be authenticated by the Ethiopian Embassy in the country of origin.

2. Agency Agreement

2.1. An agency agreement should be made between the manufacturer and the agent responsible to act on behalf of the manufacturer.
2.2. The agreement should specify that the representative is the sole agent in Ethiopia.
2.3. The agreement should be signed by both parties.
2.4. The agent representing the manufacturer should hold a license issued by the Ministry of Trade.

SECTION II COMPANY PROFILE

This section deals with documents to be supplied by the manufacturer.

1. **Back ground information**

The manufacturer should submit background information about the company indicating the following major points.

1.1. Year of establishment,
1.2. Development since establishment,
1.3. Capital,
1.4. Organogram (organizational chart of the company)
1.5. Total working force,
1.6. Ownership,
1.7. Subsidiaries (if any)

2. Production Unit

The manufacturer should describe, in words or in schematic presentation, the production system and in process standard control mechanism.

3. Quality Control Unit

The manufacturer should describe the quality control procedure on raw materials, and finished products.

4 Research and Development Unit (R and D), if there is any

The manufacturer should give detailed information on at least the following major points.

4.1. The year R and D was initiated

4.2. Qualification of the personnel engaged in R and D activities.

4.3. Major research and achievements attained.

4.4. Affiliation with other institutions (if there is any)

5. Product Registration and Marketing Experience of the Industry (Manufacturer)

The manufacturer should submit full information on its marketing experience and registration status of its products indicating:

5.1. List of countries to which it exports most of its products.
5.2. List of countries in which its products or the company itself is registered
5.3. List of countries where its product(s) has/have been withdrawn from the market. (if so, give reasons fir withdrawal).

6. Samples of package labeling (for manufacturers of diagnostics only)

6.1. Package labeling includes package leaflet, label on the immediate container, and outer wrapper or carton.

6.2. Four samples of one or more of the above package labeling materials or a catalogue which illustrates them and display the required information conspicuously should be submitted.

6.3. The label on the container must:

a) state the name and chemical formula,
b) show hazard symbols and safety recommendations
c) Percentage content of the main substance (s)
d) expiry date (where it is applicable) and batch number.

6.4. The accompanying package insert or catalogue or manual for test kits must, in addition to the information indicated in (1) C above, state:

a) use or application
b) test principle
c) testing procedure
d) reagents/test kit
e) specimen
f) calculations
g) interpretation of results
h) reference values (normal values or negative and positive reactions)
i) interference
j) specificity
k) accuracy, reliability and reproducibility of the test
l) storage instructions
m) instruction for the disposal of the diagnostic (i.e how to convert the diagnostic to ecologically acceptable or harmless compound)
n) Presentation (how supplied); and

o) other precautions or information.

Annex I

APPLICATION FORM FOR THE REGISTRATION
Of manufacturers of medical devices

FORM MMD/R

TO: _____
_____

1. Date of application: _____
2. Name and address of the manufacturer:
_____
_____
3. License number of the manufacturer in the country of origin
_____

4. Documents attached:
Certificate of compliance with manufacturing standards.

Agency agreement ☐

Company profile ☐

Consent form ☐

Others (please specify below)

_____
_____
_____
_____

Name and official/designation of the applicant (person(s) representing the manufacturer).

_____
_____

Signature _____
Date _____

ANNEX 11

CONSENT FORM

We, ……assure you that the legalized documents, the company profile, and other documents that we have submitted are true and correct.

We agree to inform the Drug Administration and Control Authority, of Ethiopia, about any change or modification made on the information given in the documents submitted.

We also agree to allow officials from the Drug Administration and Control Authority ,of Ethiopia, to visit and have first-hand information about the industry at any time

We recognize and accept the right of the Drug Administration and Control Authority of Ethiopia, to suspend or to revoke the registration certificate that is already issued to us if any fraud or anything contradictory to our registration documents is discovered.

Signed by:

Person authorized to
Sign on behalf of the manufacturer

Date:

(Manufacturer's full name and address)