General Notes to Applicants on the nature of the documents

1. Paper selection: Paper size is A4. Margins for top, bottom, header, footer are 12.5mm, and margins for left and right are, 25mm, respectively
2. Paragraph: line space Single
3. Font: Font (Times New Roman), letter space 0%, size 12point
4. The weight of the font should be in such a way that it should be legible when copied
5. The cover of the dossier should be in "hard cover" and labeled with the name of Product, dosage form, strength, and Name of the manufacturer.
6. One hard copies of the application of the registration dossier may be submitted along with CD-ROM and other relevant documents
7. The attached data and documents should be in the English Language
8. Any abbreviation should be clearly defined
9. The compilation of the document should be outlined according to their respective guideline and should be indexed or annotated.

   For example

   Contents Page
   Application form…….. 4
   Agency agreement ……..... 5
   Etc.
10. Well organized and compiled documents will facilitate the evaluation process and decrease the screening time. In contrast, badly compiled documents may lead to unnecessary wastage of time and such kinds of documents may be discarded or returned to the applicant. Therefore, documents should have unambiguous contents: title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check.

9. Differences in dosage form; strength, category, specialty, indication etc require separate application.
10. A covering letter (from the manufacturer and the local agent) and application fee should be accompanied with the application.
11. Evaluation and Notification: Application submitted for registration will be screened chronologically according to date of submission to the Authority and the evaluation results will be notified to the applicant within 30 days of its submission to the Authority.
12. Fast Track Registration: Life saving, Antimalarial, Antiretroviral, Ant tuberculosis drugs and drugs for emergent humanterian aid shall have priortity

for registration and the Authority will prepare separate SOPs for such kinds of fast track registration.

13. In case of requesting changing of contents of specifications and test methods for drugs, appropriately notified after reviewing of the screening application, comparison table between a copy of the approved items (including copy of approval certificate) or the original copy of screening result notification and the contents desired to be changed and the reason for change should be prepared and attached along with variation fee.

14. Supplement period for the requested query should be submitted within 30 days of notification to missing elements. If supplement submission is not executed within the period, urge to be supplemented within 15 days shall follow. If the supplement document is not submitted within the urge period or the contents of replenishment is inappropriate, the speculation shall be clarified and the document shall be returned and/or rejected. However, if the applicant calls for an extension, the submission period shall be determined based on the speculation.
15. The following general items should be considered when preparing Registration application: Starting materials and the quantity, dosage form and description, manufacturing methods, efficacy and effectiveness, dosage and administration, interchangeability study, matters to be especially concerned for usage, package unit, stability data, labeling requirement, manufacturing approval for In vitro diagnostics, etc., other than the above items compilation of the documents shall be prepared with provisions of respective guidelines.
16. Brand (Trade Name)-Generally the first and the last three letters of any trade name should not be identical with a registered drug in Ethiopia.

Section I Requirements for Abbreviated New Drug Application (ANDA)

1. Application form

The application form for New Drug Application, Abbreviated New drug application, Re-registration and Variation application to an existing marketing authorization is as indicated in Annex I. 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 product in Ethiopia.

2.1.1. Where a product is manufactured or supplied in the country, the responsible person (the manufacturer or his agent) has to keep product information file accessible to the authority.

2.1.2. Where the product is manufactured under contract, a written contract between the contract giver and acceptor, which clearly states the duties of each party, and an agency agreement made between the contract giver and the local agent should be submitted.

2.1.3. Where the product is manufactured at two or more places, the agreement and responsibility of each party made between the manufacturers should be submitted. In such case the agency agreement between the local agent and the manufacturer should be the site where the file kept available.

2.1.4. In case where there is a third party involved in the shipment of product but nothing to do in the manufacture of the product, the manufacturer should ensure that there is no problem associated with the product quality. Here, an agreement made between the manufacturer and local agent, manufacturer and the other party, the local agent and the third party and a certificate for good storage from the competent authority in the country of origin of the third party is required.

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 for that product in Ethiopia. In case the manufacturer needs more than one distributor this has to be mentioned in the agreement, but the maximum number of distributor is limited to three.

2.4. The agreement should state that if any fraud or unsuspected and un acceptable adverse event occurs to the consumer under normal utilization, both party will be responsible to collect the product from the community and are responsible to substantiate any event.

2.5. The agent representing the manufacturer for importation should hold a license issued by the ministry of trade and certificate of competence issued by DACA at the time of importation of the product.

3. Certificate of pharmaceutical products

3.1. Certificate of pharmaceutical products issued by the national competent authority as recommended by WHO. (Format and explanatory notes of the certificate is attached as annex II).

3.2. When the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:

(a) applies identical GMP standards to the production of all batches of pharmaceutical products manufactured within the facility.

(b) consents, in the event of identification of a quality defect, to report to the Authority.

3.3. If the exporting country has authorized the product to be placed on its own market, the WHO-type certificate, in addition to certifying the manufacturing standard at the site in question, implies that the country issuing the certificate accepts that the product is of adequate quality, safety and efficacy to remain on its own market. Therefore an officially approved product information document, such as summary of product characteristics, should normally accompany the certificate (Annex III). If this document is not available, then summary basis of approval that summarizes the technical basis on which the product has been authorized should accompany the certificate.

3.4. If the product is not identical to that in the issuing country, the applicants must list any differences in the application form (Annex I) (under "Certification by a responsible person in the applicant company") and to justify the differences (under "justification for any differences to the product in the country or countries issuing the submitted WHO-type certificates"). The Authority will decide whether the differences are minor and have been adequately justified, and consequently whether the WHO-type certificate is relevant.

3.5. If the product for registration is manufactured in a facility in more than one country of manufacture, for example in the following circumstances.

(a) Different phases of manufacture may be conducted in different countries. For example, a batch of tablets may be prepared in bulk in country A, and packaged and subjected to quality control testing in country B.

(b) The product may be fully manufactured in both countries A and B, and the applicant wishes to obtain approval to use both sites of manufacture.

The WHO-type certificate should normally be prepared by the country that directly exports the product to Ethiopia, i.e. country B in example (a) above. However, , the certifying authority of country B should satisfy itself - in so far as it has authority to inspect the records and relevant activities of the applicant and/or manufacturer

located in country A. Product specific manufacturing and licensing information from country A should be submitted.

In example (b), certificate should be submitted from both countries.

3.6. Whenever a product is purchased through intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the product for which the applicant is not directly responsible have been undertaken in compliance with GMP as recommended by WHO.

3.7. The certificate should officially stamped and dated and all copies of product information submitted to it in support of an application for a certificate and intended to be appended to the certificate. Every effort should be made to ensure that certificates and all annexed documentation are consonant with the version of the product license operative on the date of issue. The applicant is responsible for providing a notarized translation of the contents of the certificate in English in case when the certifying Authority issued the certificate in any other language.

3.8. The certificate should be original and current.

3.9. The certificate should be authenticated by the Ethiopian Embassy in the country of origin. Where this may proves to be difficult, consultation with DACA is necessary.

4. Chemical and pharmaceutical documentation

4.1. Quality of Raw Material(s)

Raw material means all ingredients (active and inactive) which may/may not appear in the final formulation.

4.1.1. Active Pharmaceutical Ingredient(s)

4.1.1.1. Properties of Active pharmaceutical ingredient(s)

Name of the active ingredient, Chemical structure,the isomeric nature of the active ingredient (where applicable), including stereochemical configuration (e.g. racemate, pure (*S*)-isomer, 50/50 mixture of (*Z*)- and (E)- isomers), The solubility of the active ingredient in water at 25 or 37^0c; The solubility of the active ingredient in other solvents, such as ether, ethanol, acetone, and buffers of different pH (if the active ingredient is acidic or basic), Other relevant physicochemical characteristics of the active ingredient, such as partition coefficient (usually octanol/water) and the existence of polymorphs, Copies of infrared, nuclear magnetic resonance (proton and C-13), ultra- violet and mass spectra.

4.1.1.2. Sites of Manufacture of Active Pharmaceutical Ingredient(s)

State the name and street address of each facility where manufacture (synthesis, production) occurs. Include any alternative manufacturers. Attach a certificate issued by the competent authority, example, copies of GMP certificate.

4.1.1.3. Route(s) of Synthesis of Active Pharmaceutical Ingredients(s)

Provide details of the route of synthesis for each active pharmaceutical ingredient, including reagents and reaction conditions (e.g Temperature, pressure, pH, time). Provide specifications for starting materials, reagents and intermediates in the synthesis. Identify critical steps and process controls. Comment on likely synthetic by-products, degradation products, and possible impurities and discuss the results in the certificates of analysis for each site and method of manufacture.

4.1.1.4. Specification of Active Pharmaceutical Ingredients(s)

Provide a list of tests and limits for results for the API. Include test methods in sufficient detail for them to be replicated by another laboratory. Provide the results of validation of the methods for assay of the API and of impurities. If the ingredient is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced but not duplicated in the monograph. Provide details of any specifications additional to those in the pharmacopoeia. Provide certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

4.1.1.5.**Stability testing of the Active Pharmaceutical Ingredient (s)**

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities and assay, and for other tests as necessary (e.g. particle size testing). If the API is well established, studies should be conducted according to the principles outlined in the relevant WHO Guidelines. For new active ingredient and products results should be included for physical as well as chemical tests, e.g., (where relevant) particle size and polymorphic form.

The study should be designed to show whether trends in stability occur over time. State the proposed shelf-life (or retest date) and justify it in terms of the results of stability testing and the labelled storage conditions.

4.1.2. **Specification of Excipients**

Provide a list of tests and limits for results for each excipient, including solvents, liquids to adjust pH, coatings, capsule shell, and inked imprint (on the dosage form). Include test methods in sufficient detail for them to be replicated by another laboratory. If the ingredient is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced but not duplicated in the monograph. Provide details of any specifications additional to those in the pharmacopoeia. Include microbiological limits for materials of natural origin

4.2. Finished Product

4.2.1. Formulation Development

Provide information on formulation and manufacturing process development, finished product specification and container closure system development for at least three pilot scale batches.

4.2.2. Data on Composition

4.2.2.1. Complete qualitative and quantitative composition of the finished product including all ingredients that may or may not be present in the final formulation.

The tabulated unit formula should look like as follows

Name of the ingredient(s)	Quantity/Unit	Quantity/Batch	Function	Reference/Monograph

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

NOTE: Overage should be indicated in quantitative terms and the reasons for them should be given. Overages will usually not be accepted unless it is proved that they are necessary to compensate loss during production process. Each ingredient should be listed individually.

4.3. **Data on Packaging Materials (Container and Closures)**

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

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. Identification and test methods
5. Manufacturers full name for the material, and
6. Others

Provide only a brief description for non-functional secondary packaging components (e.g., those that do not provide additional protection). Provide additional information on functional secondary packaging components.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, if applicable, and/or safety of materials of construction.

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.

4.4. **Data on Manufacturing and Packaging Procedures**

4.4.1. Flow chart for the method of manufacture

4.4.2. State all the necessary precautions and procedures for cleaning, environmental control, sampling, testing, and equipment operations

4.4.3. Detailed description of the method of preparation mentioning the quality and quantity of the starting materials used, manufacturing formulae, critical process steps and manufacturing conditions, processing and packaging instructions.

4.4.4. For the manufacture of biological products state the source, origin and suitability of the starting materials. Where appropriate microbial cultures, microbial and cell cultures, method for extraction from biological tissues and propagation of live agents in embryos or animals should be clearly stated.

4.4.5. For the manufacture of sterile products, method and precautions to minimize risks of microbiological contamination, and of particulate and pyrogen contamination should be clearly stated.

4.4.6. Final packaging and labeling procedures.
4.4.7. Description on the precautions and in-process controls that are made in connection with different stages of manufacturing process
4.4.8. Process validation report on three production batches
4.4.9. Batch manufacturing record for representative batch of production size

4.5. Analytical Report

4.5.1. Quality specifications (release and stability) and analytical procedures for the dosage form (in two copies).

Provide a list of tests and limits for results for the finished product, including sufficient detail of test methods for them to be replicated by another laboratory. If the product is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced but not duplicated in the monograph.

Provide details of any specifications additional to those in the pharmacopoeia.
Provide both release and expiry limits for test results. Provide the results of validation of the assay method for this formulation.

For pharmacopoeial methods, provide data which demonstrate that the method is applicable to this formulation.

In principle, test items to be established shall be in accordance with the following table (See the General Note). However, additional test items may be established according to dosage forms so as to show specifically the function of a preparation and prove its availability.

Dosage Forms	Specification
Topical preparations for transdermal absorption	Release test[1], Adhesion test
Granules, Powder	Particle size distribution test, Dissolution or Disintegration test, weight variation test
Eye ointments	Heavy metal impurity[(1,2)], sterility, release test[1],leak test, particle size distribution test
Aerosols (measured dose)	Relation between spray time and spray quantity, particle size distribution test (for suspensions)
Elixirs, Fluid extracts, Sprits, Tinctures	Alcohol number
Eye Drops[5]	Sterility test, Release test[(1,9)], Insoluble particulate matter test[10] , Particle size distribution test[9]
Tablets, Capsules, Troches Pills	Dissolution or Disintegration [(1,2)], weight variation or content uniformity[(3,4)]
Suppositories	Release test[1], Softness test, melting temperature test
Injections[5]	Sterility, Foreign insoluble particulate matter test[6], Insoluble fine particle test[7], Release test[(1,9)], Actual Volume variation, Weight variation or content uniformity test[4], Endotoxin or pyrogen test[8], particle size distribution test[9]
Topical and oral preparation[11]	Particle size distribution, re-dispersibility (suspension), resuspendibility(lotions)

General Note

1. Specifications and test methods of "dissolution or disintegration" and "release test" should be mentioned irrespective of the specification and test method stated in a pharmacopoeia.
2. In principle, dissolution test should be established. However, in case when the disintegration rate control during the period of use (efficacy) is assured, disintegration test may be established.
3. For coated tablets, content uniformity test should be established, if appropriate.
4. For preparations that readily become ununiform, contain little amount of active ingredients, or contain therapeutically potent active ingredients, etc., the establishment of content uniformity test shall be reviewed in order to obtain the uniformity of unit preparation.
5. If the vehicle is not a product listed in well known pharmacopoeia, specifications and test methods of the vehicle should be established.
6. Established for water-soluble injections that need to be dissolved prior to use
7. Established fro water soluble injections (that need to be dissolved prior to uses) with a net content more than 100ml.
8. Established for intravenous injections and injection solvents (except water for injection) with pre-filled volume of larger than 10ml prior to endotoxin test
9. Established for suspensions
10. Established for aqueous eye drop solutions
11. Included in this broad category are: cream, lotions, pastes, gels, emulsions, solutions, suspensions, etc

Declaration of Pharmacopoeia

In principle reference should be made to well known pharmacopoeia (such as USP, EP, BP, Ph.Int. and other pharmacopoeia accepted by the Authority). There should be data to show the suitability of the monograph for the product. If reference is non-pharmacopoeia (i.e. In-house) the validation method for the test and the specification (for at least three production scale batches) should be submitted. Typical analytical validation characteristics which should be considered are; sensitivity and specificity, precision and accuracy, linearity, ruggedness, recovery, robustness and range.

4.6. Stability Report

General

The purpose of storage stability testing is to provide evidence on how the quality of a product varies with time under the influence of environmental factors (such as temperature, humidity and light) and on the other, on the product related factors, e.g. the chemical and physical properties of the active ingredients and the dosage forms. The evidence provided by such studies will give an indication of the effect these factors may have on product quality, safety and efficacy.

The manufacturer is required to submit information on the stability of the product derived from tests on the final dosage form in its final container and packaging. For the registration purpose in order to substantiate the claimed shelf life a real time stability data must be submitted.

A tentative shelf-life of 24 months based on accelerated stability study may be accepted provided that the following conditions are satisfied:

- The active ingredient is known to be stable (not easily degradable)
- The submitted accelerated stability data covers the four climatic zone
- When six month real time stability data submitted
- Supporting data indicate that similar formulations have been assigned a shelf life of 24 months or more
- The manufacturer submitted a commitment letter to continue a real time studies and to submit such data every six months until the proposed shelf life has been covered.

4.4.1 **Test Samples-** Two different production batches for fairly stable active ingredients and three batches of products containing easily degradable active ingredients or substances on which limited stability data are available. The batches to be sampled should be representative of the manufacturing process. Detailed information on the batches should be included in the test records, namely the packaging of the drug product, the batch number, the date of manufacture, the batch size, sampling schedule, etc.

4.4.2 **Test Condition**

4.4.2.1 **Accelerated studies-** Study data for six months at a temperature of at least 15°C above the expected actual storage temperature for products intended to be stored at 25^0C(together with appropriate relative humidity condition). Higher temperature may also be recommended, eg. 3 months at 45-50 °C and 75%RH relative humidity. Where significant changes occur in the course of

accelerated studies, additional tests at intermediate conditions should be conducted, eg.30± 2°C and 60± 5% relative humidity

4.4.2.2 **Real time studies-** The experimental storage conditions should be as close to the projected actual storage conditions in the distributions system as practicable. The frequency of the test should be every 3 months in the first year, every six months in the second year and then annually until the end of shelf life**.**

4.4.3 **Analytical method and stability specification-** All product characteristics likely to be affected by storage, e.g. assay value or potency, content of product decomposition, physicochemical properties (hardness, disintegration, particulate matter etc) should be determined; for solid dosage forms or semisolid oral dosage forms, dissolution tests should be carried out. A systematic approach (test method) for the evaluation of stability information, which should include as necessary, physical, chemical, biological and microbiological test characteristics should be indicated clearly. Sterility test (initially and at the end of the study).The test method to demonstrate the efficacy of additives, such as antimicrobial agent. The test method should be stability indicating and validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity.

4.4.4 **Test Data-** All test data should be reported. A table of the following information is useful as a summary. Any table should include the following data:

4.4.4.1 Product Name
4.4.4.2 The formulation
4.4.4.3 Batch number and size (minimum of two)
4.4.4.4 Date of manufacture
4.4.4.5 Temperature and relative humidity
4.4.4.6 Type, appearance and chemical nature of the packaging materials
4.4.4.7 Test results obtained

4.4.5 **Calculation-** a statistical method for interpretation of results

4.4.6 **Conclusion/Discussion-** a general statement as to the suitability of the product and packaging should be made. 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).

4.4.7 **Appendices-** The test report should include at least one representative chromatogram from the analytical method. Chromatograms and any other relevant test data can be added as appendices to the test report

4.4.8 **Data on the degradation product(s)** Which is found under various stress conditions and 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.

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

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

4.4.11 In use stability data to determine the utilization period of multiple dose preparation

5. Bioequivalency Report (Relative Bioavailability Report)

General

Bioequivalence report is required for those oral dosage forms of drugs which are known to pose bioavailability problem. The study should be innovator or marketing leading registred with the Authority.

Assessment of equivalence will normally require an in vivo study, or justification that such a study should not be required in a particular case. An invitro test can be used if the product is in the same solid dosage form but in a different strength and is proportionally similar in its active and inactive ingredients as another product made by the same manufacturer and of known bioavailbility.

Bioequivalence studies are preferred where a drug produces meaningful concentrations in accessible biologic fluid, such as plasma. Where a drug does not produce measurable concentrations in accessible biologic fluid, comparative clinical trials or pharmacodynamic studies may be necessary.

Names and affiliations of the responsible investigator(s) and analyst(s), site of the study and period of its execution should be stated. Detailed information on clinical and analytical facilities of the institution(s) should be stated clearly. The names and batch numbers of the pharmaceutical products used in the study as well as the composition(s) of the test product(s) should be given. The Analytical validation report should be attached. The responsible investigator(s) should sign for their respective section of the report. In addition the applicant should submit a signed statement confirming the identity of the test product with the pharmaceutical product, which is submitted for registration.

Equivalence Studies are not necessary for

a) Parenteral preparations(eg. Intravenous, Intramuscular, subcutaneous, Intrathecal adminstration) as aqueous solution

b) Ophthalmic or otic products prepared as aqueous solutions and contain the same active substances in the same concentration and essentially the same exciepients in comparable concentration

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 (a) or (e) above.
g) Inhalation and nasal preparations-special invitro testing should be required to document comparable device performance
h) Other dosage forms where absorption from the site of administration is not a requirement for their efficacy.

NOTE: For elements (b), (e) and (f) above, it is incumbent up on the applicant to demonstrate that the exciepient (s) in the multi-source product are essentially the same and in comparable concentrations as those in the reference product. In the event this information about the reference product can not be provided by the applicant and the Authority does not have access to these data, invivo equivalence studies should be performed.

Equivalence Studies are a must for

a. Oral immediate release pharmaceutical products with systemic action when one or more of the following criteria apply:
b. Non-oral and Non-parenteral products designed to act by systemic absorption (such as transdermal patches, suppositories)
c. Sustained or otherwise modified release pharmaceutical products designed to act by systemic absorption
d. Fixed combination products with systemic action
e. Non solution pharmaceutical products which are for non-systemic use (oral, nasal ocular, dermal, rectal, vaginal etc) application and are intended to act with out systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence. This does not, however, exclude the potential need for drug concentration measurements in order to assess un intended partial absorption.

The report on invivo bioequivalence studies should include but not limited to the following information and data:

5.1 **Study protocol**
5.2 **Summary of the study**
5.3 **Objective**
5.4 **Subjects**

Subjects in this context mean that individual volunteers involved in the study
5.3.1. Inclusion criteria.
5.3.2 Number (minimum 12), sex, race, age, weight and screening tests done prior to commencement of the study.
5.3.3. Exclusion criteria.

5.4. **Materials**

Product Name, formulation type and complete composition of the drug used in the study both for the test and reference product. Certificate of analysis for reference and test product and comparative dissolution (performed during formulation development) data should be submitted where applicable.

5.5. **Study Design**

Description of the test procedure including:

a) Number of treatment group
b) Treatment periods
c) Type of test
d) Doses, rout of administration
e) Administration schedule (fasting state, with or after meal), etc.
f) Sampling times and method for collection of samples
g) Storage condition (from time of collection to analysis)

5.6 **Chemical Analysis**

Method used to determine plasma (or other biologic fluid) concentrations of the drug and during and pre study validation data.

5.7 **Result**

5.7.1. All results (raw data) should be presented clearly

5.7.2. Sufficiently detailed statistical and/or any other procedures for calculating the parameters used

5.7.3. Clinical findings

5.7.4. Plasma concentrations of the drug in the formulations compared:

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.

5.7.4 Subjects

Number, sex, age and weight of volunteer(s) who have completed the study. For those who have not completed the study, the reasons there of should be stated. Also a list of repeat analysis together with the reason for doing so should be presented.

5.7.5 Representative chromatograms obtained from pre study and within study analytical validation from analysis of subjects samples should be attached.

5.8 Discussion and Conclusion

6. Labeling Requirements

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

6.1. **General requirements for package labeling**

a) All information required on the label shall be in English and must appear clearly and conspicuously so that it will be read and understood by the ordinary individual under the customary conditions of purchase and use.
b) Other information found acceptable may be added, but not at the expense of clarity and legibility or other essential information.
c) The manufacturers are required to provide legible labels. When the available space left for essential information is limited the manufacturers are encouraged to provide carton and/or package insert where all the required information can be written. It is possible to use vial labels with a pouch containing a small insert or vial labels with an overlap.
d) Each label should be affixed/mounted on a separate "8½X11" sheet of paper so that the entire label (front and back) can be read without taking apart from the paper.
e) Only original labels or computer-ready colour-printed labels are accepted for final approval
f) Photocopies of labels or submissions by fax are not accepted
g) In the case where the text of the labels is printed directly on plastic bottles through a silk screen process, photocopies of these labels will be accepted for approval
h) All claims written on the labels must be supported by relevant data.
i) 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.
j) The manufacturer should submit a letter confirming that the labeling materials submitted are identical to the ones used in the country of origin.
k) Two copies of each labeling material should be submitted concurrent with the application.
l) Two copies of promotional materials (if any) should be submitted along with application for registration. The content of promotional material should be as stated in the label claim or wording equivalent to this.

6.2. 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:

6.2.1. The name of the product; brand and generic/INN
6.2.2. Description, appearance, pharmaceutical form and route of administration
6.2.3. Qualitative and quantitative composition of active ingredient(s), preservative(s), and other ingredients that require precaution in their use
6.2.4. Clinical Pharmacology
6.2.5. Indication(s)
6.2.6. Warnings, precautions, and contraindications
6.2.7. Adverse reactions/side effects
6.2.8. Dosage and administration (directions for use.)
6.2.9. Over dosage (signs and symptoms, and treatment); where applicable
6.2.10. Potential for drug abuse and dependence: when applicable
6.2.11. Pharmaceutical precautions
6.2.12. Storage instructions
6.2.13. How supplied (package quantities)
6.2.14. Name and address of manufacture
6.2.15. The establishment (license number) of the manufacturer
6.2.16. 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. 7.2 excluding 7.2.4 should appear on the label of the immediate container.

6.3. **Label of the immediate container**

The label of the immediate container should at least include:

6.3.1. The name of the product; brand and generic/INN
6.3.2. Pharmaceutical form, and route of administration
6.3.3. Qualitative and quantitative composition of active ingredient(s),preservative(s)
6.3.4. The volume of the contents, and/or the number of doses or quantity in container
6.3.5. Directions to consult the package insert, or the carton label for complete directions for use
6.3.6. Handling and storage requirements
6.3.7. The establishment (license number) of manufacturer
6.3.8. Batch number
6.3.9. Manufacturing date
6.3.10. Expiry date (the actual dates are not required)
6.3.11. Name and address of manufacturer

Note Where the immediate container of the medicament does not, on account its small size (small containers, ampoules, and unit packaging), enable the particulars required under item No. 7..2 to be displayed, the label on the container shall at least include : 7.3.1, 7.3.3, 7.3.4, 7.3.5,and 7.3.10,

No other statement, design, device or trade name shall overshadow the generic name. The size of the letters of the generic name should not be less than the size of the letters of the trade name.

The preferred format for the date manufacture and/or expiry date is yy/mm (year/month). It is understood that the expiry date corresponds to the last day of the month. Since the expiry date is calculated from the date of the start of the potency testing, the month that is indicated must fall within the total expiry time stipulated in the outline of the production. Example: potency testing started June, 14, 2004, for a product with an expiry dating of 12 months: Expiry date will be "2005/04"

6.4. **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.

7. Sample of Actual Products and/ or 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 Department of the Drug Evaluation and Registration. 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 (the quantity will be stated during the requisition of samples) and the samples should be accompanied with the certificate of analysis.

7.3. Sample should be identical to the actual commercial product i.e. 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 Drugs Application (NDA)

1. Application form as indicated in Section I, No.1
2. Agency agreement, as indicated in Section 1, No.2 (when applicable)
3. Certificate of pharmaceutical product, as indicated in section 1, No.3
4. Chemical and Pharmaceutical data, as indicated in section I,
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 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.

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 strain 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 at last three species (one non-rodent) by the appropriate 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 human 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.

5.2.7. **Dependence Liability (when applicable)**

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 superinfection.

NOTE : **Drug Combinations**

1. 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 Clinical Studies

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 individuals, 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 individuals , 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 iscussion and evaluation of the pharmacologic properties of the drug based on the findings of available completed studies, and conclusion.

6.1.2. Pharmacodynamics

Studies of single and multiple doses in volunteers, 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 investigations 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, complete quantitative and qualitative composition of the product used in the study.

6.1.5.5. **Test conditions**- Bioequivalence must be conducted in the spirit of Good Laboratory practice regulation

6.1.5.6. Study Design

Description of the test procedure including

a. Number of treatment groups
b. Treatment periods
c. Type of test
d. Doses,route of administration
e. Sampling times
f. Storage condition (from time of sampling to analysis)
g. Method of administration (fasting state, with or after meal).

6.1.5.7. **Chemical Analysis**

Method used to determine plasma (applicable biologic fluid) concentration of the drug.

6.1.5.8. **Result**

6.1.5.8.1. **Subjects**

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

6.1.5.8.2. **Plasma concentration of the drug**

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

6.1.5.8.3. Discussion and Conclusion

6.1.5.8.4. Representative chromatogram

NOTE: Results should be presented in tables and in illustrative figures

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 patient population (age, sex, complexity of the disease, etc.) number of patients, 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.

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

Studies in special groups (e.g in children, the elderly, etc): studies to assess drug dependence liability, etc.

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 human-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, No.7

8. Samples of actual product and active ingredient (reference standard Substance,) as indicated in section I,No.8

Section III-RE-REGISTRATION APPLICATIONS

A new product registration certificate is valid for five years. Therefore an applicant is required to apply for re-registration within 120 days before the due date and the application for re-registration should consist of:

1. An application form as indicated in Annex I
2. Re-registration fee
3. Certificate of pharmaceutical products, as indicated in section I, No.3.
4. A confirmatory letter that the method of manufacture and preparation is not changed.
5. Finished product specification
6. 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
7. Samples of actual product with certificate of analysis and method of analysis, as indicated in section I, No.4,3 and 7

Section IV REQUAIRMENT FOR VARIATION APPLICATIONS

I. **Major Variation-** This is a variation where certain requirements and justification is required as indicated below.

1. Application for Change of Origin

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

1.1. An application form as indicated in Annex II
1.2. Certificate of pharmaceutical products, as indicated in section I item No.3.
1.3. Accelerated stability study data demonstrating compatibility with the previously approved drug product, plus standard commitment to continue the real time stability study. The results of the on-going stability study should be submitted every 6 month until the final shelf-life is determined.
1.4. Sample of packaging labelling as indicated in item No.7, section I
1.5. Sample of actual product as indicated in item No.8, section I
1.6. A statement confirming that 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.

2. Application of additional pack size and change of pack Size

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

2.1. Application form for change of pack size as indicated in Annex II
2.2. The requirements indicated in section I,No.7

3. Application for change in Container-Closure

Applications for change in container-closure like a change from plastic bottle to glass bottle should consist of:

3.1. Application form for change in container closure as indicated in Annex II
3.2. A statement from the manufacturer stating the reasons (s) for the change
3.3. Accelerated stability data demonstrating compatibility with the previously approved drug product, plus standard commitment to

continue the stability study under normal recommended storage conditions.

3.4. 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.

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

3.6. Sample of actual product based on case by case

4. Application for Change in Inactive Ingredient(s)

Change in formulation means a qualitative and quantitative change in inactive ingredient(s) Application for change in inactive ingredients should include:

4.1. An application form for change in inactive ingredients as indicated in Annex II

4.2. Certificate of pharmaceutical product as indicated in section I, No.3

4.3. Data on composition as indicated in section I,No.4.2

4.4. Quality specification and analytical procedure as indicated in section I, No.4.3.

4.5. 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. If the change doesn't affect the shelf life of the product, justification for these should have to be indicated.

4.6. A statement and justification confirming that the product safety, efficacy and quality are not affected. If this is so, safety and efficacy data and clinical review should be submitted.

4.7. Sample of actual product as indicated in section I,No.8

5. Application for Extension in shelf-life

5.1. An application form as indicated in Annex II

5.2. A requirement indicated under item number 4 if there is a change in inactive ingredients

5.3. A real time stability data as indicated in section I No 4.4

5.4. Sample of actual product as indicated in section I,No.8

6. Change in the Production Process

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

6.1. An application form for change in production process as indicated in Annex II

6.2. Data on manufacturing and packaging procedure as indicated in Section I and all requirements indicated in section II, No. 4.3

6.3. Batch record

6.4. Finished product specification

6.5. Method of analysis

6.6. Sample of actual products as indicated in section I No.8

7. 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:

7.1. An application for change in quality control process and/or specifications (Annex II)
7.2. The new quality specifications and control methods with adequate information on accuracy, precision, and suitability of the methodology (see section I).
7.3. Sample of actual product as indicated in section I, No. 7.

8. Application for change in label claim

An application for change of the label claim is any change on the label of the package insert, immediate container label and outer carton so as to modify the previous approved information. Each modified label claim should be accompanied by logical and scientific justification.

8.1. Application form for change of label claim (Annex II)
8.2. Safety and efficacy data and clinical review information to substantiate the label claim
8.3. Sample of new package label and labeling requirement as indicated in section I No.7
8.4. Certificate of pharmaceutical product accompanied by summary of product characteristics

II. **Minor Variations-** These are variations, which can be accepted only by notification as long as specimen of the modified labels are submitted to the Drug Evaluation and Registration Department. The allowed minor changes with notification include the following:

i. Change in the logo of the company
ii. Change in the design or layout of the package with out change in the content
iii. Change in the color design of the package. However, the change should not affect the legibility of the label
iv. Correction and/or statements of the label without any modification to the content of the message

Annex I

APPLICATION FORM FOR REGISTRATION

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

A. Type of application (check the box applicable)

☐ New marketing authorization for a pharmaceutical product

☐ Periodic review of an existing marketing authorization [state previous registration number if selected]

☐ Variation to an existing marketing authorization [if selected complete the information below]

Previous registration number_____

Previous registration condition_____

Brief description the change intended to be made
_____

Reasons for variations _____

B. Details of the product

Proprietary name (trade name) _____

Approved generic name(s) (use the INN, if any)_____

Strength(s) per dosage unit _____

Dosage form _____

Route of administration _____

Shelf Life (months) _____

Visual Description of product _____

Visual Description of packaging material_____

Proposed restriction on sale or distribution_____

☐Scheduled narcotic
☐Restricted prescription-only distribution (specify, for example, hospitals only)
☐Prescription only
☐Pharmacy only
☐Over-the-counter (OTC)

Therapeutic classification _____

_____

Therapeutic indication (main indication) and dosage

_____

_____

_____

Complete qualitative and quantitative composition (Indicate per unit dosage form like tablet, per 5ml etc)

Active Constituents	Strength/
_____	_____
_____	_____
_____	_____
_____	_____

In-Active Constituents	Strength/
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Regulatory situation in other country

[Provide a list of the countries in which this product has been granted a marketing authorization, the restrictions on sale or distribution, withdrawn from the market etc..)

_____

_____

_____

C. Details of the Applicant

Name _____

Business address _____

Postal address _____

Telephone number _____ Fax number _____

e-mail: _____

Contact person in the applicant company

Name: _____

Position in company: ._____

Postal address _____

Telephone number _____Fax number _____

E-mail address: _____

Information on the manufacturer of active pharmaceutical(s) ingredient(s)

(State the name and street address of each facility)

Name of the manufacturer(s) _____

Street address _____

Postal address_____

Telephone/Fax number_____

e-mail _____

Information on the manufacturer of finished product

(State the name and street address of each facility. State all the manufacturer if more than one manufacturers are involved in the manufacture of the finished product)

Name of the manufacturer(s) _____

Street address _____

License number of the manufacturer in the country of origin _____

Postal address_____

Telephone/Fax number_____

e-mail _____

Local Agent (Representative) in Ethiopia

Name _____

Postal address _____

Physical location _____

Tel.No _____

Fax No _____

e-mail _____

Supporting documents attached

INDEX TO THE INFORMATION REQUIRED AND DATA SET	Page
Agency agreement	
Certificate of pharmaceutical product	
Properties of Active pharmaceutical(s) ingredients	
Specification on excipients	
Formulation Data	
Data on Manufacturing and packaging procedure for finished product	
Container closure system	
Analytical Data	
Stability Data	
Summary of pharmacology, toxicology and efficacy of the product	
Bioequivalence data	
Container labeling	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I the undersigned certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)_____

Approved generic name(s) (use the INN, if any) _____

Strength(s) per dosage unit _____

Dosage form _____

Applicant company _____

is correct and true, and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO guideline on “Good manufacturing practices for pharmaceutical products” Guideline, is applied in full in all premises involved in the manufacture of this product.

2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.

3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.

4. Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications *before it is released for manufacturing purposes.*

5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.

6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.

7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications *before it is released for manufacturing purposes.*

8. Each batch of the finished product is either tested, or certified, against the full specifications in the accompanying documentation and complies fully with the release specifications *before it is released for sale.*

9. The person releasing the product for sale is an authorized person as defined by the WHO guideline “Good manufacturing practices: Authorized person - the role, functions and training”.

10. The procedures for control of the finished product have been validated for this formulation. The assay method has been validated for accuracy, precision, specificity and linearity.

11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.

12. The market authorization holder has a standard operating procedure for handling batch recalls of its products.

13. All the documentation referred to in this certificate is available for review during a GMP inspection.

14. Any clinical trials were conducted according to WHO’s “Guidelines for good clinical practice (GCP) for trials on pharmaceutical products” .

Signature_____

Name _____

Position in company (print or type) _____

Date: _____

ANNEX III

Exporting(Certifying) country_____
Importing (requesting) country_____
No of Certificate _____

Certificate of a Pharmaceutical product[1]

Proprietary name (applicable) and dosage form:
Active ingredient(s)[2] and amount(s) per unit dose:[3]

1. Is this product licensed to be placed on the market for use in the exporting country?[4] If yes, complete box A, If no, complete box B.
2. Is this product actually on the market? If not explain the reason.

A
Product license holder
status of license holder[5] a ☐ b ☐ c ☐ d ☐

Number of product licence[6] and date of issue:
Is an approved technical summary appended"[7]
If the attached product information
yes ☐ No ☐
complete and consonant with the license?
Yes ☐ No ☐ Not approved ☐
Applicant for certificate if different
from the license holder[8]

B
Applicant for certificate

Status of applicant[5] a☐ b ☐ c ☐ d ☐
Why is authorization lacking?
Not required ☐ Not requested ☐ Under consideration ☐

refused ☐

Remarks[9]

2.Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced
yes ☐ no ☐ If no proceed to question, 3

Periodicity of routine inspections (years):

Has the manufacture of this type of dosage form been inspected?
yes ☐ no ☐
Do the facilities and operations conform to GMP as recommended by the World Health Organizatin?[10]
yes ☐ no ☐

3. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party?[11]
Yes ☐ No ☐ if no explain

Name of authorized person
Signature:

Address of certifying Authority:

Telephone/fax numbers

General instruction and explanatory notes overleaf

General Instruction

Please refer to the guidelines for further information on how to complete this for and on the implementation of the Scheme.
Forms should be completed using a typewriter to ensure legibility.
A cross should be placed in squares as appropriate to indicate which options apply.
Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

[1]This certificate which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
[2]Use, whenever possible International Nonproprietary Names (INNs) or national nonproprietary names.
[3]A qualitative listing of other ingredients contained in the dosage form should be appended.
[4]When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is entered on the product license.
[5]Specify whether the person responsible for placing the product on the market:

(a) manufactures the active ingredients and the finished dosage form
(b) manufactures the finished dosage form
(c) packages and/or labels a finished dosage from manufactured by an independent company; or
(d) is involved in none of the above

[6]Indicate, when applicable, if the licence is provisional, pending technical review.
[7]This refers to the document, prepared by certain national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
[8]In this circumstance, permission for issuance of the certificate is required from the product licence holder.
[9]please indicate the reason the applicant has provided for not requesting registration:

(a) the product has been developed exclusively for the treatment of conditions-particularly tropical diseases-not endemic in the country of export,
(b) the product has been reformulated with a view to improving its stability under tropical conditions
(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import
(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient,
(e) any other reason, please specify.

[10]The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those adopted by the Twenty-eighth World Health Assembly in its resolution WHA28,65(see WHO Official Records, No.226, 1975,Part1,Annex 12). Proposals for the amendment of these requirements are included in the Thirty-second report of the WHO Expert Committee on Specification for pharmaceutical preparations. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series No.822, 1992, Annex1)

[11]This section is to be completed when the product-license holder or applicant conforms to status (c) or (d) as described in note 5 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and to indicate the extent and nature of any controls exercised over each of these parties.

Annex IV

Structure of the Summary of Product Characteristics (SPC)

(with proposed sentence patterns and illustrative examples)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

{(Invented) name of product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<This pharmaceutical product is for diagnostic use only. >

4.2 Posology and method of administration

Adults (for example)
Children and adolescents (4 to 17 years of age) (for example)
General administration recommendations (for example)
Special dosing considerations in adults (for example)

4.3 Contraindications

<Hypersensitivity to the API(s) or to any of the excipients <or {residues }>.

4.4 Special warnings and special precautions for use

Drug interactions (for example)
Acute haemolytic anaemia (for example)
Hyperglycaemia (for example)
Patients with coexisting conditions (for example)
Other

4.5 Interaction with other FPPs and other forms of interaction

Rifabutin (for example)
Ketoconazole (for example)
Other

4.6 Pregnancy and lactation

Use during pregnancy (for example)
Use during lactation (for example)

4.7 Effects on ability to drive and use machines

< {Invented name} has <no or negligible influence> <minor or moderate influence> <major influence> on the ability to drive and use machines.> [describe effects where applicable]

4.8 Undesirable effects

Laboratory test findings (for example)

Post-marketing experience (for example)

4.9 Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group}
ATC code: {code}
Mechanism of action
Microbiology (when applicable)
Drug resistance (when applicable)
Cross resistance (when applicable)

5.2 Pharmacokinetic properties

Absorption
Distribution
Biotransformation
Elimination
Characteristics in patients

5.3 Preclinical safety data

<Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.>
<Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

<Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.>

Mutagenicity
Carcinogenicity
Developmental Toxicity

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content (for example)
Capsule shell (for example)
Printing ink (for example)

6.2 Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this pharmaceutical product must not be mixed with other pharmaceutical products.>

<This pharmaceutical product must not be mixed with other

pharmaceutical products except those mentioned in 6.6.>

6.3 Shelf life

6.4 Special precautions for storage

<Do not store above <25°C> 30°C»
<Store at 2°C - 8°C (in a refrigerator» <Store in a freezer>
<Do not <refrigerate> <or> <freeze»
<Keep the container in the outer carton>
<No special precautions for storage>
<in order to protect from <light> <moisture»

6.5 Nature and contents of container

6.6 Instructions for use and handling <and disposal>

7. MARKETING AUTHORISATION HOLDER

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT