ETHIOPIAN FOOD AND DRUG AUTHORITY

Medicine Registration and Marketing Authorization Led Executive office

Guideline for Registration of Antiseptics and Disinfectants

Document No.:	EFDA/GDL/030	Version No:	002
Date of approval:	19/01/2024	Date of First issue:	19/01/2024

Document History

Version No.	Reason for Amendment	Effective Date
001	New	01/03/2021
002	To align the format as per the SOP for document management and Control	19/01/2024

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Contents

1 Background

The Ethiopian Food and Drug Authority (EFDA) is mandated by the proclamation No. 1112/2019 to register and undertake related regulatory assessment of antiseptics & disinfectants. Article 19 (1)of the proclamation decrees that "the rigor of regulatory assessment of medicines and medical devices shall be commensurate with the products type, nature and potential risk to human health" Article number 28(2) of the same proclamation explicitly describes that "the registration and related regulatory assessment of antiseptics and disinfectants shall be commensurate with the products potential risk to human health". Therefore, the evaluation process to ensure safety, quality and effectiveness of antiseptics and disinfectants, categorized as low pharmaceuticals, falls in the jurisdiction that permits abbreviated assessment of applications for granting marketing authorization.

The intention of this guideline is to outline minimum requirements for submitting applications and provides direction for applicants how to apply for getting marketing authorization for theseproducts. It describes information that applicants should submit to speed up the registration of antiseptics and disinfectants.

All users of this guideline are kindly requested to forward their valuable comments and suggestions to the Food and Drug Control Authority of Ethiopia, via P.O.Box 5681, Tel. 251-11 552 41 22, or email: regulatory@fmhaca.gov.et, Addis Ababa, Ethiopia.

2 Definition

For the purpose of this guideline the following definitions are applicable.

Antiseptics means products that are placed in contact with external parts of the human body or mucosal membranes of the oral and basal cavity to kill microorganism or eliminate microorganisms and/or inactivate viruses on living tissues (intact or broken skin and mucous membranes), or to inhibit or prevent the growth of microorganism, with the primary intent to limit or prevent infection and protect human health. These include products such as hygienic hand rub or sanitizers, wound disinfectants or pre-surgical skin disinfectants as well as antiseptics applied to burns and to open wounds to prevent sepsis by removing or excluding microbes from these areas.

Disinfectant means therapeutic products used to kill or eliminate microorganisms and/or inactivate viruses on inanimate objects and surfaces (medical devices, instruments, equipment, walls, floors) and includes; bactericides, fungicides, virucides, mycobactericides, tuberculocides, sporicides, sterilants, or combinations of these.

Bactericide means an antimicrobial agent capable of destroying bacteria, but not necessarily bacterial spores or mycobacteria

Fungicide means an antimicrobial agent capable of destroying fungi, including their spores.

Virucide means an antimicrobial agent having the capacity to destroy or inactivate viruses.

Mycobactericide means an antimicrobial agent capable of destroying mycobacteria.

Tuberculocide means an antimicrobial agent destructive to the tubercle bacillus

Sporicide means an antimicrobial agent capable of destroying bacterial spores

Sterilant means a chemical that is applied to inanimate objects (medical devise) to kill all microorganisms as well as spores

NB: Certain products may be used both as an antiseptic and as a disinfectant.

3 Scope

This guideline is applicable to assessment and market authorization of:

- antiseptics products intended for human use on external parts of human body or mucosal members for general disinfection purposes; and
- disinfectants intended for use in professional and personal settings to limit or prevent infection.

4 Objective

The main objective of this guideline is to set minimum requirements for submitting Marketing Authorization (MA) applications, assessment for registration and market authorization of antiseptics and disinfectants intended for human use to limit or prevent infections.

5 Requirements for registration

Manufacturers & importers must make sure that their products are not harmful or unsafe, and that they conform to this guideline and national or international applicable quality standards set for antiseptics and disinfectants before supplying such products for use in the country. Applicants for MA of antiseptics and disinfectants need to full fill the following general requirements.

ADMINISTERATIVE DOCUMENTS

Application letter

Applicant shall submit a dated and signed letter for submission of the application by mentioning the product proposed for registration.

Application form

Complete application form on eRIS system using https://www.eris.efda.gov.et/login. The application form is also provided in Annex I. The completed application form shall be signed and dated.

Agency agreement

1. An agency agreement should be submitted in line with the requirements indicated under the Module 1 (Administrative and product information section) of the **Medicine registration guideline, 4th Edition,** 2020.
2. The agreement should state that if any fraud or unsuspected and unacceptable adverse event occurs to the user under normal utilization, all the party's (local agents, manufacturer, and/or license holder) mentioned in the agreement will be responsible for the product recall and for substantiating any related consequences and liable for legal action as per article 38 (1&4) of proclamation No 1112/2019 or other relevant laws of the country

Certificate of good manufacturing Practices

A Copy of valid Good Manufacturing Practice (GMP) of the antiseptic or disinfectant manufacturer granted by the responsible National Regulatory Authority in the exporting country should be provided. Generally, inspection of the manufacturing site by EFDA is not a pre-request for submission of application for registration of these products. However, the authority may inspect the manufacturer facility prior to issuance of MA if the Authority believes it is deemed necessary.

Marketing Authorization status

The applicant should submit a valid manufacturing license of manufacturing site of the product and marketing authorization to demonstrate that the product is registered or licensed in the country of origin. List of countries in which the product under consideration has already been marketed along with the approval paperwork for granted marketing authorization should also be attached when applicable. The information submitted should be true and have confirmations for composition, strength, specifications, packaging, and product information sameness with the product on the market in the listed countries.

Product information

Product information including list of all ingredients, the primary use or purpose of the product, effect of ingredients on the body, how the product is applied, precautionary measures and labeling should be provided. All product information label statements are required to be in English and Amharic. The information provided should not vary significantly from the claims made for the same product in any other jurisdiction. Any information appearing in the product information should be based on scientific justification. Both immediate and outer labels should be only original labels or computer-ready colour-printed labels and in the case where the text of the labels is printed directly on primary packaging through a silk screen process, photocopies of these labels will be accepted for approval. The titles for batch number, manufacturing, and expiry dates should be part of the printing (typewritten 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 during production, a written commitment to show all the required information on the label of the finished product must be submitted. The contents of the label should at least contain:

1) The name of the product– brand and/or generic
2) Nature or use of the product
3) Net quantity of contents of the product in the package
4) If the distributor is not the manufacturer or packer, the label should bear "manufactured for ……" or "Distributed by…" wordings
5) Conspicuous ingredients declaration
6) Appropriate label warnings
7) Batch number
8) Manufacturing date
9) Expiry date
10) Name and address of the firm manufacturing or packer of the product
11) The product label should be presented in English language and Amharic printed in a clear and legible manner. It should contain adequate and truthful information to enable users to make informed decisions and use the product correctly.

Receipt for payment of service fees

Each application should be accompanied by copy of receipt of service fee paid for registration as per the applicable service fee regulation in force at the time of application. For details, the applicants are advised to contact the Authority for the amount and modalities of payment.

TECHNICAL DOCUMENTS

In addition to the administrative documents, the application should contain the required technical information, including data that support the safety, quality & performance of the antiseptic or disinfectant product. For registration of these products, the applicants are not required to submit full product dossier in Common Technical Document (CTD) format. But, applicants should submit relevant technical documents containing the following information online:-

Description of active ingredients and their functions

Applicant should provide the name, structure formula, physico-chemical property of the active ingredient(s).

The signed and dated specifications and method of analysis of the active ingredient (s) should also be included in this section.

Data on Quantitative and Qualitative composition of the finished product

All list of ingredients which will present in the final product including the qualitative composition with their amounts on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications) should be provided in tabular form.

The tables should be used to summarize the composition of the final product and express the quantity of each component on a per unit basis (e.g., mg per ml, mg) and percentage basis, including a statement of the total weight or measure of the dosage unit.

6.2.3 Method of manufacture of finished product

The method of manufacture should show

- Flow chart for the method of manufacture
- Concise description of the method of manufacture of the final product including the quality and quantity of the raw materials used including the final packaging and labelling procedure.

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

Data on specification and method of analysis of the finished product

The specification for the finished product should be provided. The specification shall describe all the relevant control parameters for the final product and their acceptance limit.

The final product should at least indicate description (appearance), identification, average weight, assay and antimicrobial efficacy test.

The method of analysis of finished product should be provided. It should include test methods for all parameters indicated in the specification of the finished product. The test method should at sufficiently detail to be used for quality laboratory analysis.

The certificate of analysis of for two batches finished product which performed with the indicated method should also be submitted.

Container closure system of finished product

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

Stability Report

The real time report should be provided. The report should include the proposed shelf-life of the final product and storage conditions. The real time stability report data sheet should indicate:

a) The name of finished product

b) The batch number (minimum two) and batch type

c) Date of manufacture

d) Expiry date or any statement which may explain for example "use within two years from the date of manufacture"

e) Type and chemical nature of the packaging materials

f) Analytical methods that will qualitatively and quantitatively measure the characteristic physical, chemical and biological properties of active or functional ingredients of the finished product and distinguish them from their degradation

products so that active ingredient content can be measured. If such a method is mentioned elsewhere in the dossier it is enough just to mention the page number.

g) Initial and all subsequent results of chemical, physical and/or biological testing. The frequency of testing must be every three months for the first year, every six months for the second year and every year for year thereafter.

h) Summary of the study and storage recommendations based on the data generated

Specific Requirements for Antiseptics

1. Efficacy

Data supporting the effectiveness of the antimicrobial claim, microbiological tests performed and test results should include at a minimum:

a. Identification of the standard method used to verify the product efficacy
b. Proof of the effectiveness of the neutralizer utilized in the tests for both the reference standard and the test product
c. Supporting data for log reduction, persistence and /or time to kill claims as applicable
d. The relationship of each test to specific area of application
e. The time differential used in the test and whether the time stated is enough to meet the required criteria of specific activity
f. Initial number of the test organisms, and validation of microbiological tests
g. Information on the batch number, expiry date, and date of manufacture for each batch tested
j. Proof of glove compatibility for surgical scrub products
k. The minimum inhibitory concentration (MIC) for the product, when available
l. Conclusion, describing whether the product meets the specific criteria relative to the reference method(s) employed

2. Safety

a) Antiseptics preparations should contain well-established active ingredients documented to be safe and effective antiseptic in internationally recognized, evidence-based scientific references, such as Martindale, Pharmaceutical Pharmacopoeias etc.

b) Topical antiseptics shall not contain prohibited ingredients listed in the banned chemicals list by World Health organization (WHO) and/or stringent regulatory authorities (SRAs).

c) Active ingredients in topical antiseptics may include chemicals listed in annex of this guideline

d) Published or unpublished safety data testing local tolerance, such as: irritation and sensitization and preferably conducted in human species; photo-allergenicity; photo-carcinogenicity, etc. must be submitted

e) Toxicity data duct should be submitted when evidence is not available to show that topically applied medicinal ingredients are not absorbed systemically to a significant degree.

f) For antiseptics with long history of use and well established safety, the applicants are not required to submit test data. However, for new antiseptic preparations, safety tests should be performed in accordance with relevant internationally accepted test methods

3. Quality

The quality related data should at minimum contain:

a) Full disclosure of the chemical formula of the product in the form of a quantitative listing of all ingredients used in its manufacture
b) the percentage of the chemical formulation components which should add up to 100% in the final product formulation.
c) Active substance should be identified by its non-proprietary name, chemical name and CAS number (if available).
d) Up to date information on the antimicrobial resistance
e) Analytical method and validation report
f) Evidence that active ingredients are registered in a reference country as an antiseptic in the same concentration and with the same claim
g) Applicants are encouraged to submit review of available data of active ingredient(s) and additional supporting data to support the quality of the finished antiseptic product.
h) Accelerated stability testing at conditions (40±2 ºC / 75±5 % RH) and real time study at conditions (30±2 ºC / 65±5 % RH) are required

4. General principles for claims in topical antiseptics

   a) The product must not make any claim or reference to a specific infection, disease or disorder, including its related conditions or any effectiveness against a specific or broad-spectrum of microorganism

   b) Any claim made for topical antiseptics must not be false or misleading in any way by ambiguity, exaggeration, omission or otherwise imply about the product's contents, quality, safety or that the product has properties and benefits beyond that of a general disinfection purpose.

   c) All claims made should be substantiated by internationally recognized, evidence-based scientific references. Examples of acceptable claims for topical antiseptics may include the following:

      1) antiseptic hand rub
      2) hygienic hand sanitizer
      3) kill germs
      4) antimicrobial
      5) wound cleansing
      6) wound disinfection

d) The description of antiseptics should contain:

   1) Upper and lower limits & nominal concentration of each ingredient in the finished product (over its shelf life)
   2) Chemical name of each active ingredient
   3) Purpose or function of each ingredient
   4) Microbicidal mode of action of the final product

Specific Requirements for disinfectants

1. Efficacy requirements

The applicant should submit a valid study conducted to demonstrate efficacy by using internationally recognized methodologies. Document(s) which indicates the right concentration of the product that provide the required cidal actions, such as bactericidal, virucidal, etc supported by data

2. Quality requirements

The applicant should provide brief discussion on how the formulation was developed, rationale for the presence & concentration of each ingredient. The applicant is also expected to disclose the chemical formulation of the product in the form of quantitative listing of all ingredients and the grades of ingredients used in its manufacture as well as percentage of each chemical in the final product which shall add up to 100%. Each ingredient should be identified by its trade name, supplier, and proper chemical name and CAS number (if applicable). The applicant shall submit technical documents; such as:

a) Documents which indicates that the products meet requirements of revenant ISO or ES standards

b) QC test reports and reference for published methods or cited submissions

c) A proof for active ingredients registration in a reference country as a disinfectant product in the same concentration and with the same claim.

d) Physical & chemical properties, microbiology, toxicology, residue and intended use comparison data for new disinfectant

e) the applicant is advised to submit all relevant supporting data, depending on the product type and claim, to support the quality of the finished product.

f) Actual test reports from ISO 17025 accredited laboratory, test protocols, observations, statistical analysis, conclusions and comments on the test results. The test reports shall not be older than one year at the time of submitting application.

g) Accelerated stability testing at conditions (40±2 ºC / 75±5 % RH) and real time study at conditions (30±2 ºC / 65±5 % RH) are required for three batches

3. Safety requirements

Information regarding, acute oral toxicity, inhalation toxicity and skin irritation, mutagenecity and carcinogenicity should be provided for all grades of disinfectants and other toxicity studies (cytotoxicity, neurotoxicity etc) may be required to be provided based on the intended use of the disinfectant.

6 Application and Assessment procedure

APPLICATION PROCEDURE

As this types of applications need the shortest review process, generally shortest MA issue target times apply to such types of applications.

The authority may make requests for further information from the applicant if there are issues arising at any stage of the evaluation process

THE OVERALL REVIEW PROCESS

Verifying eligibility of the product under consideration

Applications for registering antiseptics and disinfectants should be validated to determine whether the product is eligible for approval by low risk pathway, completeness of application and whether it meets the requirements for an effective application.

Before starting the assessment, the application needs to be verified against the list of products recognized by the authority as antiseptics and disinfectants, as indicated in Annex 2 of this guideline.

Return to the applicant

The applicant will be advised to shift the application path way or provide additional supporting data if the application is found ineligible for this approval pathway or found to be incomplete to initiate review process. However, submitting fabricated data will end up in rejecting the application or all subsequent applications from the same manufacturer based on the severity of consequences of the fabricated data.

Review of documents

Administrative Documents

The countries in which the antiseptic or disinfectant product under consideration has already been marketed should be listed and the approval paperwork for granted marketing authorization should be provided. Validity period and the authenticity of submitted documents should be verified from certificate numbers and provided websites of issuing authorities especially for marketing authorization and GMP certificates issued from country of origin or from the country at which the licensing holder of the product located.

Technical section of dossier Assessment

The evaluation should mainly focus on the administrative documents as per the requirements indicated in this guideline but special emphasis shall be given to the basic technical information provided regarding safety, efficacy & quality data. These should be evaluated by taking product specific characteristics and intended purpose in to considerations. These include specifications, antimicrobial effectiveness tests, analytical methods, stability studies, and analytical test reports.

Additional Data request

The Authority may during assessment of application require the applicant to submit additional samples, documents, and information and the applicant should give clarification as the case may be.

Granting Marketing authorization

Granting the marketing authorization will be based on the outcome of the abbreviated review process. The Authority after being satisfied that the product complies with requirements prescribed in these guidelines it will grant the marketing authorization and notify the applicant online via eRIS system that the product has been granted market authorization.

7 Post approval

The registration of a product shall be valid for five (5) years unless suspended, cancelled or revoked by the Authority or withdrawn by a registrant. However, these products need to be surveyed on regular basis as a part of the post approval vigilance scheme so as to minimize the unpredicted risks that could be associated with their safety as well as antimicrobial effectiveness as quality defects might contribute to AMR.

VARIATION

For post approval variations, the applicants are advised to refer to and provide all relevant sections of documents in line with the requirements of **guideline for submission of post approval variation medicine application** as applicable. Whenever a product has been withdrawn from the market and/or its marketing authorization has been rejected, deferred, or withdrawn from market for any reason (deficiencies in GMP or product quality defect) in other countries, the local agent or the manufacturer should notify EFDA as per the article 67(17) of proclamation 1112/2019.

RE- REGISTRATION

Applications for re-registration of these category of products shall follow requirements specified in Appendix 4 (Requirements for Re-registration) of the Authority`s guideline for registration of medicines,4th Edition, 2020**.** The re-registration of antiseptic and disinfectant products should be mainly based on the outcomes of post market safety and effectiveness related complaints from user of these products.

Annex 1: Application Form

Application Form
Food and Drug Authority of Ethiopia
P.O. Box 5681, Addis Ababa, Ethiopia

A. Type of application (check the box applicable)

New Application		☐
Periodic re-registration		☐
Variation to existing marketing authorization		☐
For variation, please provide information on:	• Previous registration number	
	• Previous registration condition	
	• Brief description of change intended	
	• Reasons for variations	

B. Details on the product

Brand name (if any)			
Approved generic name (s)			
Standard claimed (Pharmacopeia or ISO standards)			
Net content			
Formulation (powder, liquid, gel, spray etc)			
Strength(s) (percentage, mg, etc per ml or gram or per unit pack)			
Means of application (spray, hand rub, fumigation etc)			
Shelf life (months)			
Storage condition			
Visual description			
Description of container closure			
Packaging and pack size			
List the qualitative and quantitative composition of ingredients per unit pack (please add/delete as many rows and columns as needed).	Composition	amount	purpose
Active ingredients registration in another countries (Provide a list of countries in which this product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)			

C. Details on the applicant

Applicant`s Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, Packer or distributor if different from the above mentioned	<<Insert the required information as indicated above>>>

D. Details on active ingredient(s)

Active ingredient	Name of manufacturer	Street and postal address	Telephone /Fax number	E-mail	Retest period/Shelf life

E. Details on local agent (representative) in Ethiopia

Name of local agent	
Address of the company (Sub-city and postal address…etc)	
Telephone/Fax number	
E-mail	
Details of contact person in the company	

F. Details on administrative & technical documents submitted with the application

Section of dossier	**Annex, page number, etc.**
Administrative section	

Technical Documents	Quantitative and Qualitative composition of the formulation Introduction of active ingredients and their functions	
	Method of Manufacture	
	Certificate of Analysis(CoA)	
	Product specification and test Methods	
	Toxicity data	
	Antimicrobial efficacy test	

Annex 2: List of ingredients for Antiseptics and Disinfectants

The most commonly used antiseptic and/or disinfectant groups; alcohols, quaternary ammonium compounds, chlorhexidine and other digu anides, antibacterial dyes, chlorine and hypochlorite, inorganic iodine compounds, metals, peroxides and permanganates, halogenated phenol derivatives and quinolone derivatives preparations with the appropriate strength & formulations containing active ingredients listed below are products eligible for approval under the antiseptics and disinfectants category.

1. Benzalkonium chloride
2. Benzethonium chloride
3. Benzoyl peroxide
4. Brilliant green
5. Cetalkonium chloride
6. Cetrimide
7. Cetylpyridinium chloride
8. Chlorhexidine
9. Chlorhexidine acetate
10. Chlorhexidine gluconate
11. Chlorhexidine gluconate chlorhexidine)
12. Chlorocresol
13. Chlorophene
14. Chloroxylenol (parachlorometaxylenol)
15. Chlorquinaldol
16. Crystal violet
17. Dequalinium chloride
18. Diiodohydroxyquinoline
19. Dofanium chloride
20. Domiphen bromide
21. Ethanol
22. Gentian violet
23. Hexachlorophene

24. Hydrogen peroxide
25. Hydroxyquinoline sulphate
26. Iodine / Povidone iodine
27. Isopropanol
28. Methylbenzethonium chloride
29. n-propanol
30. Potassium hydroxyquinoline sulphate
31. Potassium permanganate solution
32. Proflavine hemisulphate
33. Triclosan
34. Triphenylmethane