



GUIDELINES FOR SUBMISSION OF POST- APPROVAL VARIATION MEDICINE APPLICATIONS

*FOOD, MEDICINE AND HEALTH CARE ADMINISTRATION AND CONTROL
AUTHORITY OF ETHIOPIA (EFMHACA)*

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ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
CE	European Conformity
CEP	European Pharmacopoeia Certificate of suitability
NDRA	National Drug Regulatory Authority
EFMHACA	Food, Medicine and Healthcare Administration and Control Authority of Ethiopia
GMP	Good Manufacturing Practice
FPP	Finished Pharmaceutical Product
ICH	International Conference on Harmonization
INN	International Non-Proprietary Name
'N'	Notification
NDA	New Drug Application
Ph Int	International Pharmacopoeia
JP	Japanese Pharmacopoeia
OOS	Out Of Specification
Ph Eur	European Pharmacopoeia
SmPC	Summary of Product Characteristics
SRA	Stringent Regulatory Authority
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
WHO	World Health Organization

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INTRODUCTION

The Food, Medicine and Health Care Administration and Control Authority (FMHACA) of Ethiopia was established to protect the public health from unsafe, inefficacious and poor quality medicines by insuring effective and efficient pre and post -marketing authorization of medicines systems in the country as described in Proclamation No. 661/2009.

An applicant and/or medicine manufacturer must notify and get approval from the Authority for any changes to an approved application in accordance with Food, Medicines and Healthcare Administration and Control Regulation (Regulation No. 299/2013) article 15, sub-article 5.

In the preceding two “Guidelines for Registration of Human Drugs”, requirements for variation applications were described as one section of the documents and the types of variations described were not exhaustive to handle the current day-to-day facing variation types received by the Authority. Therefore, this guideline includes the current international accepted trend of variations types and requirements for handling of these variations.

This is, therefore, the first edition of guideline for handling variation applications to the registered medicines by Food, Medicines and Healthcare Administration and Control Authority of Ethiopia. It is prepared for the purpose of providing applicants/manufacturers with information concerning documentation to be submitted for approval variations to the previously registered medicine by the Authority.

Once a medicine is registered by the EFMHACA for sale in Ethiopia, any changes to the original information submitted with the application or set as conditions for registration must be submitted for approval. Variations to details of a medicine may be made to alter or to improve the medicines, to introduce an additional safeguard due to new scientific knowledge or to meet market demands. The conditions of registration of a medicine are therefore considered dynamic taking into account that variation to the original registered dossier may become necessary during the lifetime of the medicine.

In order to facilitate the classification of the various types of variations, the following sections explicitly define the classification of variations:

SECTION I lists major variations. These are classified by the type of variation as such and the applicable conditions. Whenever the conditions are not kept, the variation may either become major variations or may even make a new application necessary.

SECTION II lists minor variations. The minor variations further classified as minor variation require prior approval and minor variations require notification only.

The above two classes (major and minor) of variations are classified by the type of variation as such and the applicable conditions & the required documentation. There may be a situation in which the variation to be made by the applicant/manufacture do not listed in the above two classes of variations, in such situation the applicant need to consult Authority for proper categorization the variation type and the documentation needed to be submitted to the Authority.

SECTION III lists types of variation which make a new application necessary.

SECTION IV lists stability requirements for variations to registered medicines.

SECTION V describes the consideration of SRA procedure for variation application.

The guideline also contains three annexes: Annex I, describe the application form, Annex II, list types of variation applications that require laboratory testing of samples of actual product at EFMHACA laboratory and Annex III, outline the application payments requirement.

SCOPE OF THIS GUIDELINE

This guideline is applicable only to active pharmaceutical ingredients (APIs) and excipients manufactured by chemical synthesis or semi-synthetic processes and medicines containing such APIs and excipients for finished pharmaceutical products that are registered by the Authority for sale in Ethiopia. Variations to a biological API and/or biological excipient or to biological finished pharmaceutical products are assessed as major changes.

This guideline applies to all variations whether from the applicant's initiative or requested by the Authority.

This guideline does not apply to medicines whose application is still under consideration by EFMHACA.

DEFINITION

Authority

Authority means the Ethiopian Food, Medicine and Healthcare Administration and Control Authority.

Major Variations

Major variations mean changes that could have major effects on the overall safety, efficacy and quality of the finished pharmaceutical product. They are variations to the documentation which can neither be deemed to be minor variations nor to be variations for which the submission of a new dossier would be necessary (Section I).

Minor Variation

Minor variations mean variation to the registered pharmaceutical finished product in terms of administrative data and/or changes that could have minimal or no adverse effects on the overall

safety, efficacy and the quality of finished pharmaceutical product. These variations are variations which can be found listed in Section II of this guideline.

Notification

Notifications means changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance, but must be notified to the Authority before implementation of the change. e.g Periodic Safety Update Reports.

Variation

Variation means a post approval change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished pharmaceutical product, ingredients, container and container labelling, and product information.

APPROVAL OF VARIATIONS

As the applicant submits an application in the appropriate format and with application form. EFMHACA assessors conduct pre-screening of application for completeness and confirmation of type of variation. Incomplete applications and improper categorization of variations will then be

notified to applicants at this stage. If the completeness of applications and proper categorization of variation confirmed by EFMHACA assessor at this stage, applicant will be notified to pay appropriate variation payment as indicated in annex III and then be considered as the applications officially submitted to EFMHACA.

The regulatory approval process of the variations would be:

- 1) For all major variation applications as indicated in section I of these guidelines, prior approval by EFMHACA is always necessary before the variations can be implemented.
- 2) Variations as indicated under “A. Minor variations which require prior approval” of section II of these guidelines need to be submitted to the authority and require prior approval before implementation.
- 3) Variations as indicated under “B. Minor variations require notification” of section II of these guidelines need to be notified to the Authority but can be implemented if the authority has no objection immediately after proper categorization confirmed by EFMHACA experts and official submission to the authority.

Section I & II clarifies what documentation should be submitted with regard to each type of major and minor variations.

In principle, all parts of the dossier that are affected by a variation need to be resubmitted according to the structure of Guideline for Registration of Medicines of the Authority. Moreover, any further documentation required for a particular change is identified.

Applicants should present a summary of the intended change in tabular form in which the current state/situation and the situation after the intended change are compared to outline the scope of the change in a transparent manner. A justification for the introduction of the change should always follow.

Applicants should be aware that submitting redundant or irrelevant information may hamper approval procedures. Deficient documentation can lead to non-validation or rejection of the change.

The titles of the changes are numbered and subcategories are depicted by numbers. The conditions necessary for a given change are outlined for each subcategory and listed below each change.

Certain variations are so fundamental that they alter the terms of the registered dossier and consequently cannot be considered as a “variation”. In such cases a new dossier must be submitted (Section III).

Variations considered as major as indicated in section I and “A. Minor variations which require prior approval” of section II need to be accompanied by the application form as indicated in annex I.

SECTION I: DOSSIER REQUIREMENTS FOR MAJOR VARIATIONS TO REGISTERED PRODUCTS

This section includes the list of major variations. These variations are numbered and the conditions and the require documentation are identified as below.

- 1. Replacement or addition of a manufacturing site of primary packing process of finished pharmaceutical product.**

Conditions

1. Site has approval from EFMHACA for the packaging or manufacturing of the pharmaceutical form and the product concerned.

2. Site accordingly approved for GMP by a NDRA (to manufacture the pharmaceutical form and the product concerned).

Documentation

1. Proof that the proposed site is appropriately approved for the pharmaceutical form and the product concerned:
 - a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the NDRA; and
 - A proof that the proposed site has been approved by EFMHACA as complying with current GMP for packaging or manufacturing of pharmaceutical form and the product concern
 2. Clear identification of the “registered” and “proposed” finished pharmaceutical product manufacturers in the variation application.
 3. Comparative manufacturing (packaging) process at the two locations.
 4. Written confirmation that no variation have been made to specifications, test methods or sources of packaging materials for the two sites.
 5. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to the package the product and stating the type of activity to be performed by the packager (i.e. contract agreement).
 6. Holding time studies testing of the bulk pack during storage and transportation between the bulk production site to the primary packer (where applicable).
 7. Stability study report.
 8. For sterile product, validation scheme and/or report on primary packaging processes including validation data on the new primary packing site.
- 2. Replacement or addition of a manufacturing site of manufacturing process of finished pharmaceutical product**

Conditions

1. Site has approval from EFMHACA for the packaging or manufacturing of the pharmaceutical form and the product concerned.
2. Site accordingly approved for GMP by a NDRA (to manufacture the pharmaceutical form and the product concerned).
3. Validation protocol is available and validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production-scale batches.

Documentation

1. Proof that the proposed site is appropriately approved for the pharmaceutical form and the product concerned:
 - a copy of the current manufacturing authorization, a GMP certificate and CPP issued by the NDRA; and
 - A proof that the proposed site has been approved by EFMHACA as complying with current GMP for packaging or manufacturing of pharmaceutical form and the product concern.
2. The validation report of not less than 3 production batches including validation protocol (scheme) should to be submitted. In the case where no production has started a proposed validation protocol must be submitted.
3. Clear identification of the “registered” and “proposed” finished pharmaceutical product manufacturers in the variation application.
4. Copy of approved release and end-of-shelf-life specifications.
5. Batch analysis data of three production batches and comparative data on the last three batches from the previous site.
6. For semi-solid and liquid formulations in which the API is present in a non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
7. For solid dosage forms, a comparative dissolution test data (refer to Appendix 3-General recommendation for conducting and assessing dissolution profile of Guideline for Registration of Medicines of the authority) with demonstration of similarity of dissolution

profile, performed on the last three batches from the previous site and the first three batches from the new site should be submitted.

8. Comparative manufacturing process at the two locations.
9. Specification of API.
10. Product formula.
11. Stability study (i.e. accelerated and on-going long term stability study) report.
12. Revised draft of the packaging insert and/or labelling incorporating the proposed variations i.e. site change (if applicable).
13. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to the package the product and stating the type of activity to be performed by the packager (i.e. contract agreement).

3. Change to quality control testing of the finished pharmaceutical product: Replacement or addition of the site where batch control/testing takes place

Conditions

1. Site has approval from EFMHACA to conduct quality control testing of finished pharmaceutical product concerned.
2. The site is accordingly approved for GMP/GLP by the NDRA.
3. Transfer of the method from the old to the new site or to the new test laboratory has been successfully completed.

Documentation

1. The letter accompanies the application for approval should clearly outline the “registered” and “proposed” quality control sites.
2. Documented evidence that the site is appropriately authorized by the NDRA.
3. Documented evidence (method Validation) that the transfer of the method from the old to the new site or to the new test laboratory has been successfully completed.

4. Change and/or addition of alternative manufacturer/site of the API

Conditions

1. The new manufacturer has approved for GMP by NDA for manufacturing of API concerned.
2. The specifications (including in-process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already filled in the registered product.
3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products.

Documentation

1. A complete 3.2.S section of the dossier as per EFMHACA Guideline for Registration of Medicines.
2. A declaration from the supplier of the registered FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already filled during registration.
3. Either a transmissible spongiform encephalopathy (TSE) European Pharmacopoeia certificate of suitability for any new source of material or, where applicable, documentary evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent authority and shown to comply with the current WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. To include BSE.
4. Batch analysis data (in a comparative tabular format) for at least two (minimum pilot scale) batches of the API from those filled during registration and proposed manufacturers/sites.
5. The application should clearly outline the “registered” and “proposed” manufacturers.

5. Change of (qualitative or quantitative) excipients or inactive ingredients

Conditions

1. Change will need to comply with the finished product specifications for example release and shelf-life specifications of the drug product remain the same, excluding product description.
2. Replacement of an excipient with a comparable excipient of the same functional characteristics.
3. The dissolution profile of the proposed product is comparable to that of the current approved product.
4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed new product formula.
5. Stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches and satisfactory stability data for at least 6 months (accelerated and real time) are at the disposal of the applicant together with the assurance that these studies will be finalized. Data will be provided immediately to the authority if outside specifications or potentially outside specification at the end of the registered shelf-life (with details of proposed action).

Documentation

1. Justification for the change/choice of excipients, etc. must be given by appropriate information from pharmaceutical development (including stability aspects and antimicrobial preservation where appropriate).
2. Comparative tabulated format of the current and revised product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable).
3. For solid dosage forms, comparative dissolution profile data on at least two pilot-scale batches of the finished pharmaceutical product in the new and old composition.
4. Revised batch manufacturing formula.

5. Validation scheme and/or report of the manufacturing process as per Guideline for Registration of Medicines appropriate to the proposed change in product formula should be provided upon submission.
6. Specifications of the proposed excipient.
7. Drug product release and shelf-life specifications.
8. Batch analysis data (in a comparative tabulated format) of drug product on at least two production (or one production batch and two pilot batches) according to currently approved and proposed product formula.
9. Justification for not submitting a new bioequivalence study according to the annex IV- Requirements for Bioequivalence Study-Guideline for Registration of Medicines or other guidance of the authority.
10. Either a European Pharmacopoeia certificate of suitability for any new component of animal origin susceptible to TSE risk or, where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA of the ICH region and associated countries and shown to comply with the scope of the current WHO Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products or the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products or an equivalent guide of the ICH region and associated countries. The information should include the following:
 - name of manufacturer;
 - species and tissues from which the material is derived;
 - country of origin of the source animals;
 - its use; and
 - evidence of its previous acceptance.
11. Data to demonstrate that the new excipient does not interfere with the finished pharmaceutical product specification test method (if appropriate).

12. The stability studies (accelerated stability and on-going long term NLT 6months) should be given.

6. Change in the qualitative and/or quantitative composition of the immediate packaging material

Conditions

1. Release and shelf life specifications of the finished pharmaceutical product remain unchanged.
2. Relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches, and at least 6 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to authority if outside specifications or potentially outside specifications at the end of the registered shelf life (with details of proposed action).

Documentation

1. Revised drafts of the package insert and labelling incorporating the proposed variation, as applicable
2. Appropriate data on the new packaging (comparative data on permeability e.g. for oxygen, carbon dioxide and moisture).
3. Proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack).
4. Validation report and /or report of manufacturing and sterilization process for sterile products.
5. The stability studies (accelerated and On-going long term stability data for at least 6 months) should be indicated.
6. Comparison of the registered and proposed specifications, if applicable.

7. Change in the batch size of the finished pharmaceutical product (change in batch size more than 10 fold both up-scaling & down scaling for non-sterile and for all batch size change for sterile product)

Conditions

1. The change does not affect the reproducibility and/or consistency of the product.
2. The product formulation remains unchanged.
3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different sized equipment.
4. A validation protocol is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size.
5. Release and shelf-life specifications of drug product remain unchanged.
6. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot-scale or production-scale batch and at least 6 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to authority if outside specifications or potentially outside specifications at the end of the registered shelf-life (with details of proposed action).

Documentation

1. Comparative tabulated format for proposed and currently approved batch manufacturing formula.
2. Batch analysis data (in a comparative tabular format) on a minimum of one production batch manufactured to both the registered and the proposed sizes. Batch data on the next two full production batches should be available on request and should be reported immediately by the supplier of the registered product if outside specifications (with details of proposed action).
3. Copy of registered release and end-of-shelf-life specifications.

4. The report of (batch numbers ≥ 3) validation study and validation protocol (scheme) be submitted.
5. The stability studies (accelerated and on-going stability studies) data as per the respective section of Guideline for Registration of Medicines.
6. For solid dosage forms: dissolution profile data on a minimum of one representative production batch and comparative data on the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside dissolution profile similarity requirements.

8. Change in the manufacture process of finished pharmaceutical product

Conditions

1. The change does not cause a negative impact on the quality, safety and efficacy of the drug product.
2. The same currently approved manufacturing site

Documentation

1. Description of the new manufacturing process and technical justification for the change.
2. Comparative dissolution profile data between the products manufactured with the currently approved and proposed manufacturing process for oral solid dosage forms as per compendium and validated dissolution test method.
3. Validation scheme and/or report of the proposed manufacturing process as per EFMHACA Guideline for Registration of Medicines.
4. Copy of currently approved release and shelf-life specifications. Or, alternatively, copy of proposed release and shelf-life specifications that supports that the new process must lead to an identical or better product regarding all aspects of quality, safety and efficacy.
5. Comparative batch analysis data of drug product for a minimum of one production batch manufactured according to currently registered and proposed processes.
6. Stability data as per EFMHACA Guideline for Registration of Medicines.
7. Justification for not submitting a new bioequivalence study according to Guidance for Biowaiver and Guideline for Registration of medicines (where applicable).

9. Change in the colouring system or the flavouring system currently used in the finished pharmaceutical product

Conditions

1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight should be made by changing the quantity of an excipient which currently makes up a major part of the finished pharmaceutical product formulation.
3. The finished pharmaceutical product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion or addition of identification test.
4. Stability studies (long-term and accelerated) in accordance with relevant guidelines have been started with at least two pilot-scale or production scale batches and at least 6 months' satisfactory stability data are at the disposal of the applicant, together with assurance that these studies will be finalized. Data should be provided immediately to the authority if outside specifications or potentially outside specifications at the end of the registered shelf-life (with details of proposed action). In addition, where relevant, photo-stability testing should be performed.
5. Any proposed new components must comply with appropriate section of guideline for registration of medicines.
6. Any new component does not involve the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current WHO Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products or the note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products or an equivalent guide of the ICH region and associated countries

Documentation

1. A declaration that the change does not interfere with the finished product release and shelf life specifications and test methods.

2. Revised product formulation and batch manufacturing formula.
3. Qualitative and quantitative information of the current and proposed colouring/flavouring agent in comparative table.
4. Revised release and end-of-shelf-life specifications of the finished product.
5. Stability data (accelerated and on-going long term stability data) as per the EFMHACA Guideline for Registration of Medicines.
6. Sample of the new product.
7. Either a European Pharmacopoeia certificate of suitability for any new component originating from an animal susceptible to TSE risk or, where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by a DRA in the ICH region or associated countries and shown to comply with the scope of the current guideline in the countries of the ICH region or associated countries. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is a derivative;
 - country of origin of the source animals; and
 - its use.
8. Data to demonstrate that the new excipient does not interfere with the finished pharmaceutical product specification test methods, if appropriate.

10. Change in coating weight of tablets or change in weight of capsule shells

Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot-scale batches is comparable to the old one.
2. The coating is not a critical factor for the release mechanism.
3. The release and the shelf-life specifications of the finished pharmaceutical product remain unchanged except for the weight and/or size, if applicable.

4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot-scale or production-scale batches and at least 6 months' satisfactory stability data are at the disposal of the applicant with assurance that these studies will be finalized. Data will be provided immediately to the authority if outside specifications or potentially outside specifications at the end of the registered shelf-life (with details of proposed action).

Documentation

1. A declaration that the change does not interfere with the drug product release and shelf-life specification test method
2. Comparative dissolution profile data on at least two pilot-scale batches of the new formulation and two production batches of the registered formulation (no significant differences regarding comparability to appendix 3, general recommendation for conducting and assessing dissolution profile of guideline for registration of medicines.
3. Current and proposed unit and batch manufacturing formula.
4. Revised release and shelf-life specifications of the finished pharmaceutical product.
5. Justification for not submitting a new bioequivalence study according to the current guidelines on bioequivalence such as annex IV: Requirement for bioequivalence study-guideline for registration of medicine or other guidelines of the authority.
6. Stability study report with the protocol i.e. accelerated stability study with minimum of 6 months long term.

11. Change in the specification of the finished pharmaceutical product (Addition of new of test parameter & limit)

Conditions

1. Test procedures remain the same, or changes in the test procedure are minor.
2. Not applicable officially recognized compendial drug product
3. The change should not be the result of unexpected events arising during manufacture.
4. Any change should be within the range of registered limits.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Justification for change substantiated with scientific data to be provided.
2. Revised specification of the drug product.
3. Tabulated comparison of registered and proposed specifications.
4. Details of any new analytical method and validation data (please refer to guideline ICH Q2 (R1)).
5. Batch analysis data on two production batches of the finished pharmaceutical product for all tests in the new specification.
6. Certificate of analysis of the drug product for all tests with the new specification.

12. Change in test procedure of the finished pharmaceutical product

Conditions

1. Finished product specifications are not adversely affected unless the specifications are tightened.
2. Appropriate (re-)validation studies have been performed in accordance with the relevant guidelines.
3. The results of method validation show the new test procedure to be at least equivalent to the former procedure.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Justification for the proposed change.
2. Comparative tabulated format of the currently approved and proposed release and shelf-life specification of the finished pharmaceutical product.

3. Description of the analytical methodology, a summary of validation data and revised specifications for impurities (if applicable).
4. Comparative validation results showing that the registered test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).

13. Change or addition of imprints, bossing or other markings on tablets or printing on capsules, including replacement, or addition of inks used for product marking

Conditions

1. Finished pharmaceutical product release and end-of-shelf-life specifications have not been changed (except those for physical appearance).
2. Any ink must comply with the relevant section on excipients of the Guideline for registration medicines.
3. Score/break line is not meant for cosmetic purpose.

Documentation

1. Detailed drawing or written description of the current and proposed new appearance.
2. Details and specifications of the proposed inks (where applicable).
3. Certificate of analysis of the ink/printing materials (pharmaceutical grade and of food grade) (where applicable).
4. Release and shelf life specifications of the finished product with the new product description.
5. On score/ break line, Justification for the change (i.e. change in dosing regimen)
6. Data on test for content uniformity of the subdivided parts of the tablets a release should be submitted.
7. Certificate of analysis of two production/pilot scale batches, if the change is score/break line.
8. Submit a sample of the product.

14. Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean Mass

Conditions

1. The dissolution profile of the reformulated product is comparable to the old one.
2. Release and end-of-shelf-life specifications of the product have not been changed (except for dimensions).

Documentation

1. Detailed drawing or written description of the current and proposed appearance.
2. Comparative dissolution data on at least one pilot-scale/production batch of the current and proposed dimensions (with no significant differences regarding comparability according to the appendix 3-General recommendation for conducting and assessing dissolution profile-the guideline for registration of medicines.
3. Justification for not submitting a new bioequivalence study according to the current guidelines on bioequivalence such as annex Iv: Requirement for bioequivalence study-the guideline for registration of medicines and other guideline of the authority.
4. Samples of the finished pharmaceutical product.
5. Where applicable, data on breakability test of tablets at release must be given together with a commitment to submit data on breakability at the end of the shelf-life.
6. Release and shelf life specifications of the finished product.

15. Change in the fill weight/fill volume and/or change of shape or dimension of container or closure for non-sterile product

Documentation

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. Justification for the new pack-size, showing that the new size is consistent with the dosage regimen and duration of use as registered in the SmPC.

3. Written commitment that stability studies will be conducted in accordance with the guideline for registration of medicines for products where stability parameters could be affected. Data are to be reported immediately if outside specifications (with details of proposed action).

16. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid of drug product.

Condition

1. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert.
2. The packaging material remains the same.
3. Release and shelf-life specifications of the drug product are not affected, except pack size/fill volume specification.

Documentations

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert.
3. Validation data of the manufacturing process, sterilization and container closure system (where applicable).
4. Stability data as per section IV of this guideline and report if any results fall outside shelf-life specifications (with proposed action).

17. Extension of the shelf-life of the finished pharmaceutical product (As packaged for sale, after first opening, after dilution or reconstitution) and change in the storage condition

Conditions

1. Stability studies have been done according to the registered protocol. The studies must show that the agreed relevant specifications are still met.
2. The shelf-life does not exceed 5 years.

Documentation

1. Revised draft of the package insert and labelling incorporating the proposed variations.
2. Justification letter for the change of shelf-life of the drug product(where applicable)
3. A copy of the registered end-of-shelf-life finished pharmaceutical product specification and, where applicable, specifications after dilution/reconstitution or first opening.
4. Results of appropriate real-time studies covering the duration of the proposed shelf-life as per section IV: Stability requirements for variations and changes to registered finished pharmaceutical product of this guideline in the registered packing material and/or after first opening or reconstitution, as appropriate; where applicable, the results of appropriate microbiological testing should be included.

18. Change and/or additional indications/dosing regimen/patient population/inclusion of clinical information extending the usage of the product)

Conditions

1. Product labelling refers to package insert (PI). Patient Information Leaflet (PIL) outer carton and immediate labels
2. As subsequent change due to revision of summary of product Characteristics (SmPC) or equivalent document
3. Potential benefits of the product, when used to treat the identified disease or condition, outweigh the known and potential risks of the product.

Documentation

1. Currently approved product labelling.
2. Proposed product labelling, a clean and annotated version highlighting the change made
3. Approved PI/SmPC/PIL from an approved reference regulatory authority or the country of origin containing the proposed changes(where applicable)
4. Justification for the change proposed.

5. Data on safety and effectiveness for recommended indication under the recommended conditions of use such as dosage and dosage, status and age of patients eg pregnancy paediatric, liver or kidney insufficiency or other co-morbidities.
6. Clinical expert reports and/or clinical trial reports where applicable
7. Clinical document as per module 5 of the guideline for registration of medicines.

SECTION II: DOSSIER REQUIREMENTS FOR MINOR VARIATIONS TO REGISTERED PRODUCTS

This section clarifies what documentation should be submitted with regard to each type of minor change. The titles of the changes are numbered and subcategories are depicted by letters and

numbers. The conditions necessary for a given change are outlined for each subcategory and listed below each change

A. MINOR VARIATIONS WHICH REQUIRE PRIOR APPROVAL

1. Change of local agent (s)

Conditions

1. Must hold a valid medicines import license.
2. The importer has no pending disciplinary case with the EFMHACA.

Documentations

1. Agency agreement made between the local agent and the manufacturer/Marketing Authorisation Holder as described in the guideline for registration of medicines
2. A copy of import license

2. Change in the name of the finished pharmaceutical product (FPP)

Conditions

1. There is no change to the product (formulation, release & shelf-life specifications, manufacturing source & process) except for the product name change.
2. No confusion with the International Non-proprietary Name (INN).
3. The first and the last three letters of trade name is not identical with a registered finished pharmaceutical product in Ethiopia

Documentation

1. Update CPP from the national drug regulatory authority (DRA) in which the new name is approved.
2. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the drug product name change.
3. Revised draft of package insert and labelling incorporating the proposed variation.

3. Addition or replacement of the company or party responsible for batch release of finished pharmaceutical product

Conditions

1. Only applicable for batch release.
2. The manufacturer of the finished pharmaceutical product remains the same.
3. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed.

Documentation

1. Revised drafts of the package insert and labelling incorporating the proposed variation, where applicable.
2. Proof of the proposed site is appropriately authorized by the Authority to be responsible for batch release such as a Valid GMP certificate.
3. Official letter from FPP manufacturer/marketing authorization holder to be responsible for batch release, where applicable.
4. **Replacement or addition of a manufacturing site of secondary packing process of finished pharmaceutical product**

Conditions

1. Site has approved from EFMHACA for the packaging for pharmaceutical form and the product concerned.
2. Site accordingly approved for GMP by a NDRA (to manufacture the pharmaceutical form and the product concerned).

Documentation

1. Proof that the proposed site is appropriately approved for the pharmaceutical form and the product concerned:
 - a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the NDRA; and
 - Proof that the proposed site has been approved by EFMHACA as complying with current GMP for packaging or manufacturing of pharmaceutical form and the product concern.

2. Clear identification of the “registered” and “proposed” finished pharmaceutical product manufacturers in the variation application.
3. Comparative manufacturing (packaging) process at the two locations....
4. Official letter from product license holder authorizing the new manufacturer or packager to perform secondary packaging.
5. **Minor change in the manufacturing process of API**

Conditions

1. No change in qualitative and quantitative impurity profile or in physicochemical properties.
2. The route of synthesis remains the same, i.e. intermediates remain the same.

Documentation

1. Drug Master file (DMF), or relevant updated drug substance section or equivalent document.
2. Batch analysis data (in comparative tabular format) from at least two batches (minimum pilot scale) manufactured according to the registered and the proposed process.
3. Copy of registered specifications of the API.
4. A letter of declaration stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or there is no increase in the levels of impurities, which require further safety studies.
5. Certificates of analysis for two batches of API

6. Change in the batch size of the API

Conditions

1. No changes to the manufacturing methods other than those necessitated by scale-up, e.g. use of different sized equipment.
2. Specifications of drug substance remain unchanged.
3. The change does not affect the reproducibility of the process.

4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Documentation

1. Amend the 3.2.S section of the dossier as per of the module 3 of the Guideline for Registration of Medicines.
2. The certificate of analysis of the API manufactured with on the proposed batch size.
3. Evidence indicating the reproducibility is not affected by the change in the batch size.
4. Batch analysis data (in a comparative tabular format) on a minimum of one production batch manufactured to both the registered and the proposed size. Batch data on the next two full production batches should be available on request and reported immediately to the authority if out of specifications (OOS) with details of proposed action.
5. Copy of registered specifications of the API.

7. Change in the specification of an API

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration or a major change procedure after registration).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of registered limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as indicated in the Guideline for Registration of Medicines.
2. Justification for the change
3. Comparative table of registered and proposed specifications.

4. Batch analysis data (in a comparative tabular format) on a minimum of two production batches of the API for all tests in the new specification manufactured to both the registered and the proposed specifications. (Batch data on the next two full production batches should be available on request or reported if outside specification (OOS) with proposed action).
5. Where appropriate, comparative dissolution profile data for the finished pharmaceutical product on at least one batch containing the API complying with the registered and the proposed specification.
6. Justification for not submitting a new bioequivalence study according to the current guideline for registration of medicines.
7. Stability data as indicated in section IV of this guideline.

8. Change in test procedure for API

Conditions

1. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
2. The results of method validation show the new test procedure to be at least equivalent to the former procedure.
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Description of the analytical methodology, a summary of validation data and revised specifications of API.
2. Details of any new analytical method and validation data for addition of new test parameter and limit.
3. Comparative validation results showing that the registered test and the proposed one are equivalent (please refer to guideline ICH Q2 (R1)).

9. Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an API

Conditions

None

Documentation

1. Copy of the current (updated) European Pharmacopoeia TSE certificate of suitability.
2. Replacement of the relevant pages of the dossier according to the structure listed in the Annex 1: application form-Guideline for Registration of Medicines.
3. A document providing information on any materials falling within the scope of the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products including those which are used in the manufacture of the API. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is a derivative;
 - country of origin of the source animals; and
 - its use.

10. Change in the shelf life or re-test period and storage condition of API

Conditions

1. Stability studies have been done according to the guideline for registration of medicines. The studies must show that the agreed relevant specifications are still met.
2. The change should not be the result of unexpected events arising during manufacture.

Documentation

1. Copy of approved specifications of the API.
2. Stability studies data should be presented. These must contain results of appropriate real-time stability studies conducted in accordance with the relevant stability guidelines on at least two pilot or production-scale batches of the API in the packaging material filled

during registration and covering the duration of the requested shelf-life or re-test period or requested storage conditions.

11. Change in specification of an excipient (specification limits are tightened or addition of new test parameter and limit)

Conditions

1. The change should not be the result of unexpected events arising during manufacture.
2. Any change should be within the range of registration limits.
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as listed in the Annex 1: application form-Guideline for Registration of Medicines.
2. Comparative table of registered and proposed specifications.
3. Batch analysis data on two production batches for all tests in the new specification.
4. Where appropriate, comparative dissolution profile data for the finished pharmaceutical product on at least one pilot-scale batch containing the excipient complying with the registered and proposed specification.

12. Change in test procedure for an excipient

Conditions

1. There have been no changes of the total impurity limits and no new unqualified impurities are detected.
2. Appropriate (re-)validation studies have been performed in accordance with relevant guidelines.
3. Results of method validation show the new test procedure to be at least equivalent to the former procedure.

4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Description of the analytical methodology with a comparative tabulation of the changes and a summary of validation data.
2. Comparative validation results showing that the current test and the proposed one are equivalent (please refer to guideline ICH Q2 (R1)).

13. Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material

Conditions

1. Excipient and finished pharmaceutical product release and end-of-shelf-life specifications remain the same.

Documentation

1. Declaration from the manufacturer of the material that it is purely of vegetable or synthetic origin.
2. Study of equivalence of the materials and the impact on production of the pharmaceutical product.

14. Change in the specifications of the immediate packaging of the finished pharmaceutical product

Conditions

1. The change is not a consequence of any commitments from previous assessments to review specification limits (e.g. made during the assessment procedure prior to registration of the product or a major change procedure after registration).
2. The change should not be the result of unexpected events arising during manufacture.
3. Any change should be within the range of registered limits.
4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Specifications of immediate packing materials of the finished product.
2. Comparative table of registered and proposed specifications.
3. Details of any new analytical method and validation data (please refer to the guideline ICH Q2(R1)).
4. Batch analysis data on two batches for all tests in the new specification.

15. Change to a test procedure on the immediate packaging of the finished pharmaceutical product

Conditions

1. Appropriate (re-)validation studies were performed in accordance with relevant guidelines.
2. Results of method validation show the new test procedure to be at least equivalent to the former procedure.
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Description of the analytical methodology and a summary of validation data.
2. Comparative validation results showing that the registered test and the proposed one are at least equivalent (please refer to guideline ICH Q2 (R1)).

16. Change in any part of the (primary) packaging material not in contact with the finished pharmaceutical product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (i.e. different plastic used))

Conditions

1. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished pharmaceutical product.

Documentation

1. Amendment of the relevant section(s) of the dossier as per the guideline for Registration of Medicines including revised product levelling as appropriate.

17. Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); spacer devices for metered dose inhalers are excluded

Conditions

1. No deletion of packaging component or device.
2. The qualitative and quantitative compositions of the packaging components or device remain the same.
3. The specifications and quality control method are at least equivalent.
4. The sterilization method and conditions remain the same, if applicable.

Documentation

1. The names and addresses of current and the proposed sites of suppliers in tabulated form with the roles and responsibilities of each site.
2. Data to demonstrate accuracy, precision and compatibility of the device or certification to this effect.
3. Tabulated comparison of registered and proposed specifications, if applicable.

18. Change to in-process tests or limits applied during the manufacture of the finished product (including tightening and addition of new in-process)

Conditions

1. The change is not a consequence of any commitment from previous assessments (e.g. made during the assessment procedure prior to registration of the product or a major change procedure after registration).
2. The change should not be the result of unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of registered limits.

4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. A revised in-process specification together with justification.
2. Tabulated comparison of registered and proposed specifications.
3. Details of any new analytical method and validation data (please refer to guideline ICH Q2(R1)).
4. Batch analysis data on two production batches of the finished product for all tests in the new specification.
5. Justification for addition of new tests and limits.

19. Change in the batch size of the finished pharmaceutical product (Up to 10-fold compared to the registered batch size and down scaling)

Conditions

1. The change does not affect the reproducibility and/or consistency of the product.
2. The change relates only to non-sterile solid,/semi solid dosage forms and to non-sterile liquid forms.
3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different sized equipment.
4. A validation protocol is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size.
5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

Documentation

1. Comparative tabulated format of proposed and the current batch manufacturing formula.

2. Process validation study report of at least three (≥ 3) of proposed batches should be indicated or validation protocol (scheme) be submitted.
3. Batch analysis data (in a comparative table) of drug production a minimum of one production batch according to currently approved and proposed batch sizes and a letter of undertaking to submit batch data on the next full production batch.

20. Minor change in the manufacture of the finished pharmaceutical product

Conditions

1. The overall manufacturing principle remains the same.
2. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
3. In case of a change in the sterilization process, the change is to a standard pharmacopoeial cycle only.
4. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot-scale or production-scale batch and at least 6 months' stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to authority if outside specifications or potentially outside specifications at the end of the registered shelf-life (with details of proposed action).

Documentation

1. Replacement of the relevant pages of the dossier according to the structure as indicated in the Guideline for Registration of Medicines.
2. *For semisolid and liquid products in which the API is present in non-dissolved form:* appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology, and comparative size distribution data obtained by an appropriate method.
3. *For solid dosage forms:* dissolution profile data on one representative production batch and comparative data on the last three batches from the previous process. Batch data on the next two full production batches should be available on request and should be reported

immediately by the supplier of the registered product if outside specifications (with details of proposed action).

4. Justification for not submitting a new bioequivalence study according to the annex IV- Requirements for Bioequivalence Study-Guideline for Registration of Medicine or other guidance of the authority.
5. In case of a change to the sterilization process, validation data should be provided.
6. Copy of registered release and end-of-shelf-life specifications.
7. Batch analysis data (in a comparative tabular format) on a minimum of one batch each, manufactured according to the registered and the proposed process. Batch data on the next two full production batches should be made available upon request and reported immediately by the supplier of the registered product if outside specifications (with details of proposed action).
8. Stability study report with the protocol i.e. accelerated stability study with minimum of 6 months long term.

21. Change in pack size of the FPP i.e. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack including outer carton pack sizes for FPP

Conditions

1. The new pack size should be consistent with the posology and treatment duration as registered in the SmPC.
2. The primary packaging material remains the same.

Documentation

1. Revised draft of packing insert and labelling incorporating the proposed variation (where applicable).
2. Justification for the new pack-size, showing that the new size is consistent with the dosage regimen and duration of use as registered in the SmPC.
3. Written commitment that stability studies will be conducted in accordance with the guideline for registration of medicines for products where stability parameters could be

affected. Data are to be reported immediately if outside specifications (with details of proposed action), where applicable.

4. In case of outer carton pack size change, letter of declaration stating that no other changes except for the change of outer carton pack sizes for FPP.

22. Addition, replacement or deletion of a measuring or administration device that is not an integrated part of the primary packaging (spacer devices for metered-dose inhalers are excluded)

Conditions

1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the registered posology, and results of such studies should be available.
2. The new device is compatible with the FPP.
3. The FPP can still be accurately delivered.

Documentation

1. Revised draft of the packing insert and labelling incorporating the proposed variations (where applicable).
2. Description of the device including detailed drawing and composition of the device material and supplier where appropriate.
3. Reference to CE marking for device, where applicable, or data to demonstrate accuracy, precision and compatibility of the device.
4. Samples of the new device.
5. In case of deletion, Justification for deletion of the device should be provided.

23. Reduction of the shelf-life of the finished pharmaceutical product (As packaged for sale, after first opening, after dilution or reconstitution) and change in the storage condition

Conditions

1. Stability studies have been done according to the registered protocol. The studies must show that the agreed relevant specifications are still met.

Documentation

1. Revised draft of the package insert and labelling incorporating the proposed variations.
2. Justification letter for the change of shelf-life of the drug product(where applicable)
3. A copy of the registered end-of-shelf-life finished pharmaceutical product specification and, where applicable, specifications after dilution/reconstitution or first opening.
4. Results of appropriate real-time studies covering the duration of the proposed shelf-life as per section IV: Stability requirements for variations and changes to registered finished pharmaceutical product of this guideline in the registered packing material and/or after first opening or reconstitution, as appropriate; where applicable, the results of appropriate microbiological testing should be included.

24. Other minor variations such as (Change logo of applicant/manufacturer, Change in the design or layout of packaging, Change in the colour of design of the package, Correction and/or statements of the label or Periodic update prescribing information)

Conditions

1. There is no change in the content of finished pharmaceutical product.
2. The change in colour design of the package is not affect the legibility of the label.
3. There is no change in the indication and safety of the product.

Documentations

1. The summary of the change made in comparison with the previous approved package labelling.
2. Reason for making such changes.
3. Actual sample and/or colour print out of the new and the present package labelling.

B. MINOR VARIATIONS REQUIRES NOTIFICATION

1. Change in the name and/or address naming of the marketing authorization holder of the registered product

Conditions

1. The marketing authorization holder of the registered product shall remain the same legal entity.

Documentation

1. Revised draft of the packaging insert and labels incorporating the proposed variation, where applicable
2. A formal document from a relevant official body (e.g. the national drug regulatory authority (NDRA)) in which the new name and/or address is mentioned.

2. Change in the name and/or address naming of a manufacturer of the active pharmaceutical ingredient

Conditions

1. The manufacturing site shall remain the same.

Documentation

1. Updated information of the manufacturer of the drug substance.
2. A formal document from a relevant official body (e.g. NDRA) in which the new name and/or address is mentioned.

3. Change in the name and/or address naming of a manufacturer of the finished pharmaceutical product (FPP)

Conditions

1. The manufacturing site shall remain the same.

Documentation

1. Revised draft of the packaging insert and labels incorporating the proposed variation.

2. Copy of the modified manufacturing authorization, GMP certificate, CPP or a formal document from a relevant official body (e.g. NDRA) in which the new name and/or address is mentioned.
1. Official letter from marketing authorization holder authorizing the manufacturer with the new name /address name to manufacture the finished pharmaceutical product.

4. Deletion of any manufacturing site (including for an API, intermediate or finished pharmaceutical product, packaging site, manufacturer responsible for batch release, site where batch control takes place)

Conditions

1. Reason for deletion was provided.
2. Alternative manufacturer is registered.

Documentation

1. The letter that accompanies the application for approval should clearly name the manufacturer to be deleted.
2. Reason for withdrawal/deletion.

5. Submission of a new or updated European Pharmacopoeia certificate of suitability for an API

Conditions

1. The finished pharmaceutical product release and end-of-shelf-life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for impurities and product-specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The API will be tested immediately prior to use if no retest period is included in the European Pharmacopoeia certificate of suitability or if data to support a retest period is not provided.
4. The manufacturing process of the API does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

Documentation

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2. Amend the relevant section of the dossier according to 3.2.S section of the module 3 of EFMHACA guideline for Registration of Medicines.
3. The variation application should clearly outline the “registered” and “proposed” manufacturers.

6. Change to comply with an officially recognized pharmacopoeia (BP, Ph Int, JP, Ph Eur, USP)-Change in the specification of API & Excipients to comply with Pharmacopoeia

Conditions

1. The change is made exclusively to comply with a officially recognized pharmacopoeia.
2. Unchanged specifications (additional to the pharmacopoeia) for product specific properties (e.g. particle size profiles, polymorphic form), if applicable.

Documentation

1. Revised specifications of API or excipients
2. Comparative table of registered and proposed specifications.
3. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.
4. Analysis of the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities.
5. Where appropriate, batch analysis data (in a comparative tabular format) on two production batches of the finished pharmaceutical product containing the substance complying with the registered and proposed specification and additionally, where appropriate, comparative dissolution profile data for the finished pharmaceutical product obtained on at least one pilot batch.

7. Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient

Conditions

1. The finished pharmaceutical product release and end-of-shelf-life specifications remain the same.
2. Unchanged additional (to European Pharmacopoeia) specifications for product-specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The manufacturing process of the excipient does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

Documentation

1. Copy of the current (updated) European Pharmacopoeia certificate of suitability.
2. Specification and method of analysis of the excipient under consideration.
3. Where applicable, a document providing information on any materials falling within the scope of the WHO Guideline on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products or the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products or an equivalent guideline of the ICH region and associated countries including those which are used in the manufacture of the excipient. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is derived;
 - country of origin of the source animals; and
 - its use.

8. Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an excipient

Conditions

None.

Documentation

1. Copy of the current (updated) TSE European Pharmacopoeia certificate of suitability.

2. Specification and method of analysis of the excipient under consideration.
3. A document providing information on any materials falling within the scope of the Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products including those which are used in the manufacture of the excipient. The following information should be included for each such material:
 - name of manufacturer;
 - species and tissues from which the material is derived;
 - country of origin of the source animals; and
 - its use.

9. Correction and/or statements of the label or Periodic update prescribing information

Conditions

1. The correction and statements of the label do not have any modification to the content of the message.
2. There is no change in the indication and safety of the product.

Documentations

1. The summary of the change made in comparison with the previous approved package labelling.
2. Reason for making such changes.
3. The new prescribing information.

SECTION III: VARIATIONS THAT MAKE A NEW APPLICATION/ EXTENSION APPLICATION NECESSARY

Variations that make a new application necessary consist of:

1. **Changes to the API**
 - a. Change of the API to a different API.

- b. Inclusion of an additional API to a multi-component product.
 - c. Removal of one API from a multi-component product.
 - d. Change in the dose of one or more APIs.
2. **Changes to the pharmaceutical form/dosage form**
- a. Change from an immediate-release product to a slow- or delayed release dosage form and vice versa.
 - b. Change from a liquid to a powder for reconstitution, or vice versa.
3. **Changes in the route of administration**

SECTION IV: STABILITY REQUIREMENTS FOR VARIATIONS AND CHANGES TO REGISTERED FINISHED PHARMACEUTICAL PRODUCTS (FPPS)

It is the purpose of this section to outline the stability data which have to be generated in case of variations.

The scope and design of stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs. The available information that must be taken into account includes:

For APIs:

- a. the stability profile including the results of stress testing.
- b. the supportive data
- c. the primary data on accelerated and long-term testing.

For FPPs:

- a. the supportive data
- b. the primary data on accelerated and long-term testing.

In all cases of variations and changes, the registered medicine license authorization holder and /or manufacturer has to investigate whether or not the intended change will have an impact on the quality characteristics of the APIs and/or FPPs and consequently on their stability.

When stability data are required, the choice of test conditions defined in this Section refers to the Guideline for Registration of Medicines of the Authority.

In all cases of variations which require generation of stability data on the FPP, the stability studies required, including commitment batches, should always be continued up to the end of the shelf-life and the authority should be informed immediately if any problems with the stability occur during storage, e.g. if outside specifications or potentially outside specifications.

Major Variations

For major variations as listed in section I of this guideline, which require generation of stability data on the FPP, the minimum set of data to be submitted with the variation application is defined

in Section I. The results of these studies covering the requested time period as defined in Section I, using accelerated and long-term testing conditions, should be compared to the results of studies performed on the unchanged API/ FPP to ensure that the change does not have any negative impact on the stability profile, i.e. that the specification limits of the API/FPP are still met at the end of the proposed re-test period/shelf-life.

To support the stability requirement indicated in the respective section of the variations, the following may guide as an example of major variations.

- a. change in composition of the FPP;
- b. change of immediate packaging of the FPP.

Change in composition of the finished pharmaceutical product

- A. *For conventional dosage forms* (e.g. conventional release solid dosage forms, solutions) *and when the API is known to be stable*, comparative stability data from a study of 6 months duration, under long-term and accelerated testing conditions on two pilot-scale batches are required.
- B. *For critical dosage forms* (e.g. prolonged release form) *or when the API is known to be unstable*, comparative stability data, from a study of 6 months duration, under long-term and accelerated stability testing conditions on three pilot-scale batches are required.

Change to immediate packaging of the finished pharmaceutical product

In the case of less protective packaging or when a risk of interaction occurs, mainly for semisolid or liquid dosage forms, comparative stability data are required from a study of 6 months duration, using accelerated and long-term testing conditions, on three pilot-scale batches of the finished pharmaceutical product.

Minor Variations

In the case of minor variations, as listed in section II of this guideline, which require generation of stability data on the FPP, the minimum set of data to be submitted with the variation application is defined in Section II. The results of these studies covering the requested time period as defined in Section II, using accelerated and long-term testing conditions, should be compared to the results of studies performed on the unchanged API/ FPP to ensure that the change does not have any

negative impact on the stability profile, i.e. that the specification limits of the API/FPP are still met at the end of the proposed re-test period/shelf-life. The comparison data may come from earlier studies and need not necessarily be collected in combination with the study on the unchanged product.

Commitment batches

Major variations

For all major variations that require the generation of stability data on the FPP, at least the first production-scale batch manufactured according to the registered variation should undergo long-term stability testing using the same stability testing protocol as described above unless the respective data on stability testing have already been submitted as part of the variation application. Stability studies need to be continued to cover the entire shelf-life. The results of these stability studies should be made available on request and the Authority should be informed immediately if any problems occur during the stability studies

Minor variations

For all minor variations that require the generation of stability data on the FPP, adequate follow-up studies on commitment batches need to be performed.

SECTION V: CONSIDERATION OF SRA PROCEDURE FOR VARIATION APPLICATION

An applicant claiming to have a certificate and/or acceptance letter of approval for variation application (under consideration) by Stringent Regulatory Authority (SRA) as defined in Guideline for Registration of Medicines of the Authority, 2014, need to fulfill conditions and submit all documentations as per the respective sections of variation indicated in this guideline. However, the applicant may not require submit samples for laboratory analysis at EFMHACA facility.

Applicant requesting to follow this procedure requires:

- To provide evidence of approval of such variation(s) by the regulatory authority in the SRA regions.
- To provide a certificate of analysis by GMP approved laboratories and/or independent ISO accredited laboratories.

ANNEX I-APPLICATION FORM

APPLICATION FORM FOR REGISTRATION

Food, Medicine and Health Care Administration and Control Authority of Ethiopia

P.O.Box 5681, Addis Ababa, Ethiopia

A. Type of application (check the box applicable)

New Application	<input type="checkbox"/>
Periodic re-registration	<input type="checkbox"/>
Variation to existing marketing authorization (if selected complete the information below	<input type="checkbox"/>
<ul style="list-style-type: none">• Previous registration number	
<ul style="list-style-type: none">• Previous registration condition	
<ul style="list-style-type: none">• Brief description of the change intended	
<ul style="list-style-type: none">• Reasons for variations	

B. Details of the product

Proprietary name (trade name)	
Approved generic name (s) (use INN if any)	
Standard claimed (BP, Ph.In, EP, USP, IH etc)	
Strength (s) per dosage unit	
Dosage form	
Route of administration	
Shelf Life (months)	
Storage condition	
Visual Description	
Description of container closure	

Packaging and pack size			
Therapeutic category of the product			
Use category	Scheduled Narcotic <input type="checkbox"/>		
	Prescription only <input type="checkbox"/>		
	Hospital use only <input type="checkbox"/>		
	Pharmacy <input type="checkbox"/>		
	Over the counter (OTC) <input type="checkbox"/>		
Complete qualitative and quantitative composition (indicate per unit dosage form like per tablet, per 5ml etc)** ** Add/delete as much rows and columns as required	Composition	Strength	Function
Complete qualitative and quantitative composition (indicate per batch in Kg, L etc)	Composition	Strength	Function

Statement of similarity and difference of clinical, bio batch, stability, validation and commercial batch sizes			
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	
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 if different from above	<<Insert the required information as indicated above>>>

D. Details of active pharmaceutical(s) ingredient(s) Manufacturer

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

E. Details of Local Agent (Representative) in Ethiopia

Name of the local agent	
Sub city and postal address	
Telephone/Fax number	
E-mail	
Contact person in a company and address	

F. Details of dossiers submitted with the application

Section of the dossier	Annex, page number etc
Module 1	
Module 2	
Module 3	
Module 4	
Module 5	

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) (INN)	
Strength (s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

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 pharmaceutical 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 Pharmaceuticals product have been validated for this formulation.
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 including BE study 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 II-TYPES OF POST APPROVAL VARIATIONS REQUIRING SAMPLES FOR LABORATORY ANALYSIS

Those variations listed below and other variation considered as major variation by the authority require samples of actual product for the analysis at FMHACA laboratory and hence, the applicant should refer Annex V: Sample of actual product of Guideline for Registration of Medicines for the quantities of samples, types and quantities of reference substances and the accompanied documents.

1. Replacement or addition of manufacturing site of primary packing process for finished pharmaceutical product.
2. Replacement or addition of manufacturing site for manufacturing process of finished pharmaceutical product.
3. Change in manufacturer of API(s): sample of finished product manufactured using the API(s) sourced from the new API manufacturer, if deemed necessary.
4. Change in composition of the finished product including replacement excipients, colouring system, flavouring system, change in coating weight of the tablet.
5. Change in the primary container closure having the direct contact with the product including qualitative and/or quantitative composition of immediate packing materials, change in shape and dimension of container closure.
6. Change in batch size of the finished product of more than 10 fold up scaling.
7. Change in the manufacture procedure of the finished pharmaceutical Product.
8. Change in the dimension of the tablets, capsule, suppository, pessaries.
9. Change in fill weight and/or fill volume of multi-dose product.
10. Extension of shelf life of the finished pharmaceutical product.

ANNEX III-PAYMENTS FOR POST APPROVAL VARIATIONS

The Post approval variation application should be accompanied by the appropriate payments as per the Authority regulation to handling of payment. The current payments for different types of variations are divided into two i.e. for those variations that require laboratory analysis, the payment will be \$200.00 while for other variations not requiring laboratory sample analysis, the payment will be \$100.00.

REFERENCE

ASEAN Variation Guidelines for pharmaceutical Products 2013(Final draft 7.2) Available at: [http://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines on Drug Registration/ASEAN Variation Guideline for Pharmaceutical Products 7.2 cleandraft.pdf](http://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/ASEAN_Variation_Guideline_for_Pharmaceutical_Products_7.2_cleandraft.pdf)

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