International Journal of Medicine and Pharmaceutical Research
CODEN (USA): IJCPNH | ISSN: 2321-2624
Journal Home Page: www.pharmaresearchlibrary.com/ijmpr

RESEARCH ARTICLE

# Guidelines for Submision of Post Approval Variation Medicine Applications

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**ABSTRACT**
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.

**ARTICLE INFO**

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JOURNAL QR-CODE

**ARTICLE HISTORY: Received** 05 Oct 2019, **Accepted** 30 Nov 2019, **Available Online**10 Feb 2020



**Citation:** *B. Ranganayakulu, et al.* Guidelines for Submision of Post Approval Variation Medicine Applications.*Int. J. Med. Pharm. Res., 2020, 8(1): 14-17.*

**CONTENTS**



## 1. 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 must notify and got 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. 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/manufacturer 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.

## 2. Scope of this Guidelines

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.

**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.

**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 require documentation are identified as below.

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

**Conditions:**

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:**

- 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
- Clear identification of the "registered" and "proposed" finished pharmaceutical product manufacturers in the variation application.
- Comparative manufacturing (packaging) process at the two locations.
- Written confirmation that no variation have been made to specifications, test methods or sources of packaging materials for the two sites.
- 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).
- Holding time studies testing of the bulk pack during storage and transportation between the bulk production sites to the primary packer (where applicable).
- Stability study report.
- For sterile product, validation scheme and/or report on primary packaging processes including validation data on the new primary packing site.

**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**

- Change of local agent (s)
- Change in the name of the finished pharmaceutical product (FPP)
- Addition or replacement of the company or party responsible for batch release of finished pharmaceutical product
- Replacement or addition of a manufacturing site of secondary packing process of finished pharmaceutical product
- Minor change in the manufacturing process of API
- Change in the batch size of the API
- Change in the specification of an API
- Change in test procedure for API
- Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an API
- Change in the shelf life or re-test period and storage condition of API
- 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).

**B. Minor Variations Requires Notification**

- Change in the name and/or address naming of the marketing authorization holder of the registered product
- Change in the name and/or address naming of a manufacturer of the active pharmaceutical ingredient
- Change in the name and/or address naming of a manufacturer of the finished pharmaceutical product (FPP)
- 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)
- Submission of a new or updated European Pharmacopoeia certificate of suitability for an API
- 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 Pharmacopeia
- Submission of a new or updated European Pharmacopoeia certificate of suitability for an excipient
- Submission of a new or updated TSE European Pharmacopoeia certificate of suitability for an excipient
- Correction and/or statements of the label or Periodic update prescribing information Conditions

**SECTION III: Variations that make a new application/ extension application necessary:** Variations that make a new application necessary consist of:

**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.

**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.

**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.

**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.

**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.

**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.

**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:

**Table 1:** Type of application (check the box applicable)

| |
|---|
| New Application |
| Periodic re-registration |
| Variation to existing marketing authorization (if selected complete the information below |
| Previous registration number |
| Previous registration condition |
| Brief description of the change intended |
| Reasons for variations |

**Table 2**

| |
|---|
| Proprietary name (trade name) |
| Approved generic name (s) (INN) |
| Strength (s) per dosage unit |
| Dosage form |
| Applicant |
| Manufacturer |

**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.

**ANNEX III- Payments for post approval variations**: The Post approval variation application should accompanied by the appropriate payments as per the Authority regulation to handling of payment. The current payments for different types variations divided in to two i.e. for those variations require laboratory analysis; the payment will be $200.00 while for other variations not requiring laboratory sample analysis, the payment will be $100.00.

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