



LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

P. O. Box 1994

Monrovia, Liberia

Cell: +231 – 777140555/888140555

Email: info@lmhra.gov.lr Website: www.lmhra.gov.lr



REGULATIONS ON VARIATION OF MEDICAL PRODUCTS

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DECLARATION

This Regulation, made in fulfilment of the Liberia Medicines and Health Products Regulatory Authority Act of 2010, confers upon the Authority the responsibility of regulating medicines and health products within the Republic of Liberia. The Board of Directors by consensus, hereby promulgates this regulation designed for Medical Devices this **20th** day of **April**, 2023.

ACRONYMS

API	Active Pharmaceutical Ingredient (drug substance)
CEP	European Pharmacopoeia Certificate of Suitability
FPP	Finished Pharmaceutical Product (drug product)
MAH	Marketing Authorization Holder
PIL	Product Information Leaflet
SmPC	Summary of Product Characteristics

CHAPTER I INTRODUCTION

Section 1. Title

This Regulation shall be cited as the Regulation on Variation of Medicines and Health Products.

Section 2: Application and Scope

This regulation shall apply to the variation of all Medicines and Health Products that are manufactured, imported, distributed, stored, sold, and used in Liberia.

Section 3: Purpose

The purpose of this regulation is to provide a legal framework for the effective and efficient handling of Medicines and Health Products variation.

Section 4. Definitions

In this Regulation, unless the context otherwise requires, the following words and phrases shall have the meanings as ascribed to them in this section.

“Act” means the Liberia Medicines and Health Products Regulatory Authority Act of 2010.

“Authority” means the Liberia Medicines and Health Products Regulatory Authority.

“Applicant” means a person or entity who applies product variation to the Authority and is responsible for all the product information.

“Drug” means any substance or preparation used or intended to be used for internal or external application to the human or animal body in either the treatment, prevention, or diagnosis of disease for improving physiological functions, or for agricultural or industrial purposes.

CHAPTER II GUIDANCE FOR IMPLEMENTATION OF VARIATION

Section 1 Types of Variation

Minor Variations Requiring Approval (MIV-1)

Proposed changes may have minimal impact on the quality, safety, and efficacy of registered Medicines and Health Products. The Authority's approval for the change is still required before implementation.

Minor Variations Requiring Notification (MIV-2)

These are mainly changes of administrative nature with no significant impact on the quality, safety, and efficacy of registered Medicines and Health Products. The Marketing Authorization holder shall only be required to notify the changes of the Authority.

Section 1.1 Conditions for Minor Variations requiring approval.

1. Change of Medicines and Health Products' names without changes to the product;
2. Change of product labelling by the Authority specific labelling requirements;
3. The addition or replacement of the company or party responsible for the batch release of the Finished Pharmaceutical Product (FPP) manufacturer remains the same;
4. Change and/or addition of alternative manufacturer/site of Active Pharmaceutical Ingredient (API);
5. Change of batch size of the API;
6. Change (addition, deletion, or replacement) of the colouring and artificial flavouring agent of the product;
7. Change in the source of empty hard capsules;
8. Change of imprints, embossing, or other markings on the tablets or printing on capsules including addition or change of inks used for product marking;
9. Change of dimensions and/or shape of tablets, capsules, suppositories, or pessaries without change in qualitative or quantitative composition and the mean mass;
10. Addition or replacement of a manufacturer for secondary packaging;
11. Change of pack size/fill volume and/or change of shape or dimension of container or closure for the non-sterile product;
12. Change of outer carton pack sizes for a drug product;
13. Change in any part of the primary packaging material, not in contact with the finished product formulation (E.g. colour of the flip-off cap, colour code rings on ampoules, change of needle shield, i.e. different plastic used);
14. Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms;

15. Change of corporate office (E.g. postal code, street name) of the company or manufacturer.

Section 1.2 Conditions for Minor Variations Requiring Notification

Change in name and/or address of the marketing authorization holder

Section 1.3 Major Variations (MAV)

Proposed changes that may affect directly and/or significantly the aspects of the quality, safety, and efficacy of registered medicines and Health products and that they do not fall within the definition of a minor variation or a new registration. Before implementation of such changes, approval of the Authority is required.

Section 1.4 Conditions for Major Variations

1. Change and/or addition of an indication/ dosing regimen/patient population/inclusion of clinical information extending the usage of the product;
2. Change of content of product labelling (which includes the patient information leaflet (PIL) as subsequent changes due to revision of the Summary of Product Characteristics (SmPC);
3. Change and/or addition of alternative manufacturer/site of API;
4. Addition or replacement of an alternative manufacturing site of the FPP which is not responsible for batch release;
5. Addition or replacement of the alternative site for the primary packaging (direct contact with the medicines and Health products)
6. Change of the specification of API and/or FPP;
7. A major change in the manufacturing process for medicines and Health products ;
8. Qualitative or quantitative change of excipients in critical dosage forms such as modified release, sterile injections;
9. Quantitative change in the coating weight of tablets or weight and/or size of capsule shell for modified release of the oral dosage form;
10. Change in primary packaging material for a sterile product;
11. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid medicines and Health products ;
12. Inclusion or replacement of the solvent/diluent for the medicines and Health products ;
13. Extension of shelf-life of the medicines and Health products ;
14. Change of in-process controls applied during the manufacture of the API;
15. Change of manufacturing process of the API;
16. Change of specification of the API;
17. Change of the analytical procedure of non-compendia API;
18. Change of shelf-life or retest period for API;
19. Change of storage conditions for API;
20. Revision of European Pharmacopoeia Certificate of Suitability (CEP) of API;
21. Reduction or removal of overage;

22. Qualitative or quantitative change of excipient in non-critical dosage forms;
23. Quantitative change in a coating weight of tablets or weight and/or size of capsule shell for the immediate release of the oral dosage form;
24. Deletion of the solvent/diluent for the Medicines and Health Products.
25. Change of in-process controls applied during the manufacture of the Medicines and Health Products (including tightening and/or addition of new in-process test);
26. Minor changes in the manufacturing process for the non-sterile product;
27. Change of specifications of an excipient;
28. Change of test procedure for an excipient, including replacement of an approved test procedure by a new test procedure;
29. Change of release and shelf-life specifications of the Medicines and Health Products;
30. Change in the analytical procedure of the medicinal product (including replacement or addition of a test procedure);
31. Change in primary packaging material for the non-sterile product (E.g. qualitative and quantitative composition and/or type of container and/or inclusion of primary packaging material);
32. Reduction of shelf-life of Medicines and Health Products;
33. Change in ownership of the manufacturer;
34. Change of the name or address (E.g. postal code, street name) of the manufacturer of the FPP;
35. Change of the name or address (E.g. postal code, street name) of the company or manufacturer responsible for the batch release;
36. Change of the name and/or address (E.g. postal code, street name) of a manufacturer of an API;
37. Withdrawal/deletion of the alternative manufacturer(s) for API and /or FPP and/or packager;
38. Renewal of European Pharmacopoeia Certificate of Suitability (CEP) of API;
39. Change of release and shelf-life specifications of the FPP and/or API and/or excipient, following updates in the compendium;
40. Deletion of a pack size for a product.

Section 2 Procedure for Variation Application

- a. In terms of the Authority's Product Registration Guidelines and Regulations, a marketing authorization holder shall make a variation application to the Authority in the form specified in these regulations for prior approval or notification of a change to the content of particulars relevant to a registered medicine and Health product.
- b. Each variation shall require a separate application. A non-refundable variation fee shall be charged for each application relevant to variations requiring prior approval.
- c. Nevertheless, a grouping of variations shall be allowed in certain cases to facilitate smooth review and ease the administrative burden. E.g. when several changes are

- interrelated such as variations leading to a revision of product information (SmPC, PIL, and labelling) or when a change affects several marketing authorizations of the same marketing authorization holder (change of name of the manufacturer);
- d. For major and minor variations requiring prior approval, a letter shall be issued by the Authority to the marketing authorization holder conveying whether the proposed change is acceptable or not;
 - e. Minor variations requiring only a notification shall make the variation application before the change has been implemented. The Authority shall approve minor variations.
 - f. Variations that affect the medicines and Health products amendments shall be required to the existing certificate of registration. E.g. Change of shelf life (MAV), deletion of a pack size (MIV-2);
 - g. The Authority reserves the right to request additional data to determine the acceptability of the variation;
 - h. The Authority reserves the right to re-categorize the variation type indicated by the applicant, or to determine whether the change necessitates a new product registration altogether;
 - i. The category of any variation not listed in this regulation shall be determined by the Authority;

Section 3. Timelines for Variation Application (FOR GUIDELINES)

Type of variation	Timeline for the MAH	Procedure	Timeline for the Authority approval
Major variation	Before implementation	If the application fulfils the requirements, the Authority shall issue an approval for the proposed change	40 working days
Minor variation requiring approval	Before implementation	If the application fulfils the requirements, the Authority shall issue an approval for the proposed change	20 working days
Minor variation requiring notification	Within four (4) months of implementation	To consider as approved if no response from the Authority within 10 working days	10 working days, if there is a concern

Section 4. Changes Leading to New Product Registration

Certain variations to a product, which are mostly not listed in this regulation, may lead to new product registration and it may be necessary to submit a new application for marketing authorization of the varied product. E.g. Change of API, change of dosage form, change of release profile such as normal release to sustained release, change of coating of tablets such as sugar-coated to film-coated, and change of primary packaging types such as vial to ampoule or a pre-filled syringe. The Authority shall consider whether a new registration is required, case by case.

The Authority shall apply separate registrations for products from different sites. Therefore, if the manufacture of a product is moved to a different site, a new application must be submitted. If different processes in production are carried out at multiple sites, the Authority shall consider the site responsible for the finished product release as the actual manufacturer.

CHAPTER III: THE FEES FOR VARIATION (TO BE MOVED TO GL)

The fees for a variation on medicinal products shall differ based on the types of variation.

1. The applicant shall pay the amount of One Hundred and Fifty United States Dollars **(US\$150.00)** for major variation;
2. The applicant shall pay the amount of One Hundred United States Dollars **(US\$100.00)** for minor variations requiring Approval;
3. No fee shall be required for minor variations requiring notification.

CHAPTER IV: OFFENCES AND PENALTIES

In keeping with Part VIII, Sections 1, 2 & 3 of the Authority Act of 2010, the following measures shall apply:

Failure to obtain approval for Minor variations from the Authority shall lead to the imposition of a fine or administrative penalty of not less than \$2,000.00 (Two Thousand United States Dollars).

Failure to obtain approval for Major variations from the Authority shall lead to the imposition of a fine or administrative penalty of not less than \$4,000.00 (Four Thousand United States Dollars).

This Regulation shall take effect immediately upon the approval of the Board of Directors.

A Regulation on Variation for Medicinal Products is Hereby Promulgated and Submitted for Approval to the Board of Directors on This 20th Day of April A. D. 2023 by the Managing Director of the Authority.



Dr. Keturah C. Smith-Chineh
Managing Director / LMHRA

A Regulation on Variation for Medicinal Products is Hereby Approved by the Board of Directors.

Approved This 20th Day of April A. D. 2023

Pharm. Luke Bawa
Chairman / Board of Directors/LMHRA