Variation Guidelines for Medicines

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Medicines Regulatory Division
National Medicines Regulatory Authority
Sri Lanka

1) Introduction :

The marketing authorization holder is responsible for the quality, safety, and efficacy of a medicine (i.e. a finished pharmaceutical product) that is placed on the market, throughout its life cycle. Changes may be required to the content of particulars related to the medicine that were submitted to the National Medicines Regulatory Authority (NMRA), due to various reasons such as technical and scientific advances, new findings that affects its quality, safety, efficacy, or simply changes of administrative nature. Marketing authorization holder is legally bound to inform any such changes to the NMRA.

This guideline intends to provide the marketing authorization holders with information on requirements for submission of variation applications in order to implement the intended change. Variation applications are categorized as major variations, minor variations requiring approval and, minor variations requiring notification. The guideline will be updated periodically, as required.

2) Scope :

The document will serve as a guide to establish national requirements for regulation of post-approval changes relevant to finished pharmaceutical products. In this document, such post-approval changes are categorized depending on the level of risk to the public.

3) Definitions :

Major variations (MAV)

Proposed changes that may affect directly and/or significantly the aspects of its quality, safety and efficacy of a registered medicine and they do not fall within the definition of a minor variation or a new registration. Prior to implementation of such changes, approval of the NMRA is necessary.

Minor variations requiring approval (MIV_1)

Proposed changes may have minimum impact on the quality, safety, and efficacy of a registered medicine. NMRA approval for the change is still required prior to implementation.

Minor variations requiring notification (MIV_2)

These changes are mainly of administrative nature with no significant impact on quality, safety, and efficacy of the registered medicine. Marketing authorization holder requires only notifying the change to the NMRA.

4) Definitions

API	-	Active Pharmaceutical Ingredient (drug substance)
FPP	-	Finished Pharmaceutical Product (drug product)
MAH	-	Marketing Authorization Holder
NMRA	-	National Medicines Regulatory Authority
PIL	-	Product Information Leaflet
SmPC	-	Summary of Product Characteristics

5) Procedure :

i. In terms of NMRA Act and regulations, a marketing authorization holder shall make a variation application to the Authority in the form specified in regulations for prior approval or notification of a change to the content of particulars relevant to a registered medicine.

ii. Each variation shall require a separate application. A processing fee shall be charged for each application relevant to variations requiring prior approval.

iii. Nevertheless, grouping of variations shall be allowed in certain cases, in order to facilitate smooth review and ease administrative burden. E.g. when several changes are interrelated such as variations leading to revision of product information (SPmC, PIL and labeling) or when a change affects several marketing authorizations of the same marketing authorization holder (change of name of the manufacturer)

iv. For major variations and minor variations requiring prior approval, a letter shall be issued to the marketing authorization holder conveying whether the proposed change is acceptable to NMRA.

v. Minor variations requiring only a notification shall make the variation application after the change has been implemented, but not more than 12 months of implementation. If NMRA does not issue an unfavorable opinion on a minor variation for notification within 30 days of receiving the notification, the variation deemed acceptable to NMRA.

vi. On certain instance, amendments may be also needed to the existing certificate of registration. E.g. Change of shelf life (MAV), deletion of a pack size (MIV_2)

vii. NMRA reserves the right to request for additional data in order to determine the acceptability of the variation.

viii. NMRA reserves the right to re-categorize the variation type indicated by the applicant, or to determine whether the change necessitate a new product registration altogether.

ix. Category of any variation not listed in this guideline shall be determined by the Authority

6) Timelines :

Type of variation	**Timeline for the MAH**	**Procedure**	**Timeline for NMRA**
Major variation	Prior to implementation	If the application fulfills the requirements, NMRA shall issue an approval for the proposed change	120 working days
Minor variation requiring approval	Prior to implementation	If the application fulfills the requirements, NMRA shall issue an approval for the proposed change	90 working days
Minor variation requiring notification	Within one year of implementation	To consider as approved if no response from NMRA within 30 working days	30 working days, if there is a concern

7) Changes leading to a new product registration:

Certain variations to the product, which are mostly not listed in this guideline, may lead to a 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 type such as vial to ampoule or a pre-filled syringe. NMRA would consider whether a new registration is required, case by case.

NMRA also applies separate registrations for products from different sites. Therefore, if a manufacture of a product is moved to a different site, a new application has to be submitted. If different processes in the production are carried out at multiple sites, NMRA would consider the site responsible for product release as the actual manufacturer.

8) Classification of Variations

(i). 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 labeling (which includes the PIL and the patient information leaflet) as subsequent changes due to revision of the SmPC.
3. Change and/or addition of alternative manufacturer/site of API [where European Pharmacopoeial Certificate of Suitability (CEP) is not available].
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 drug product)
6. Change of the specification of API and/or FPP
7. Change of batch size of a sterile drug product
8. Change of batch size of non-sterile drug product when change is more than 10 fold to the current batch size.
9. Major change in the manufacturing process for the drug product
10. Qualitative or quantitative change of excipients in critical dosage forms such as modified release, sterile injections
11. Quantitative change in the coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form
12. Change in primary packaging material for sterile product
13. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product.
14. Inclusion or replacement of the solvent/diluent for the drug product
15. Extension of shelf-life of the drug product.
16. Change of storage conditions of the drug product (Lowering from the current approved storage condition)

(ii). Minor Variations requiring prior approval

1. Change of drug product name without changes to the product.
2. Change of product labeling in accordance to Sri Lanka specific labeling requirements.
3. Addition or replacement of the company or party responsible for batch release (FPP manufacturer remains the same)
4. Change and/or addition of alternative manufacturer/site of API [where European Pharmacopoeial Certificate of Suitability (CEP) is available].
5. Change of batch size of the API [where European Pharmacopoeial Certificate of Suitability (CEP) is not available].
6. Change of in-process controls applied during the manufacture of the API [including tightening and addition of new in-process tests and where European Pharmacopoeial Certificate of Suitability (CEP) is not available].
7. Change of manufacturing process of the API [where European Pharmacopoeial Certificate of Suitability (CEP) is not available].
8. Change of specification of the API
9. Change of the analytical procedure of non-compendial API
10. Change of shelf-life or retest period for API
11. Change of storage conditions for API
12. Revision of European Pharmacopoeial Certificate of Suitability (CEP) of API
13. Change of batch size of non-sterile FPP (change is up to 10 fold to the current batch size)
14. Reduction or removal of overage
15. Qualitative or quantitative change of excipient in non-critical dosage forms
16. Quantitative change in in coating weight of tablets or weight and/or size of capsule shell for immediate release oral dosage form
17. Change (addition, deletion or replacement) of the colouring/flavouring agent of the product
18. Deletion of the solvent/diluent for the drug product
19. Change of in-process controls applied during the manufacture of the drug product (including tightening and/or addition of new in-process test)
20. Minor changes of the manufacturing process for non-sterile product
21. Change of specifications of an excipient
22. Change of test procedure for an excipient, including replacement of an approved test procedure by a new test procedure

23. Change in the source of empty hard capsules
24. Change of release and shelf-life specifications of the drug product
25. Change of imprints, embossing or other markings on the tablets or printing on capsules including addition or change of inks used for product marking
26. Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass.
27. Change in the analytical procedure of the drug product (including replacement or addition of a test procedure)
28. Change in primary packaging material for non-sterile product (E.g.: qualitative and quantitative composition and/or type of container and/or inclusion of primary packaging material)
29. Addition or replacement of a manufacturer for secondary packaging
30. Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product
31. Change of outer carton pack sizes for a drug product.
32. 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)
33. Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms
34. Reduction of shelf-life of the drug product
35. Change of storage conditions of the drug product (Increasing from the current approved storage condition)

(iii). Minor variations requiring notification

1. Change in name and/or address of the marketing authorization holder
2. Change of the product owner
3. Change in ownership of the manufacturer
4. Change of the name or address (E.g.: postal code, street name) of the manufacturer of the FPP
5. Change of the name or address (E.g.: postal code, street name) of the company or manufacturer responsible for batch release
6. Change of the name and/or address (E.g.: postal code, street name) of a manufacturer of an API
7. Withdrawal/deletion of the alternative manufacturer(s) for API and /or FPP and/or packager
8. Renewal of European Pharmacopoeial Certificate of Suitability (CEP) of API

9. Change of release and shelf life specifications of the FPP and/or API and/or excipient, following updates in the compendium
10. Deletion of a pack size for a product

9. References:

i. ASEAN variation guideline for pharmaceutical products, Final Draft 7.2, 2013

ii. WHO general guidance on variations to multisource pharmaceutical products, Annex 10, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fiftieth report.