



**NATIONAL PHARMACEUTICAL CONTROL BUREAU
MINISTRY OF HEALTH MALAYSIA**

**MALAYSIAN VARIATION GUIDELINE FOR
NATURAL (TRADITIONAL MEDICINE& HOMEOPATHY)
AND HEALTH SUPPLEMENT PRODUCTS
(ABRIDGED EVALUATION)
2016**

First Edition – July 2016

	LIST OF CONTENTS	Page
1	INTRODUCTION	4
2	SCOPE OF THIS GUIDELINE	4
3	DEFINITION	4
3.1	Major Variation (MaV)	4
3.2	Minor Variation (MiV)	4
4	PROCEDURE AND TIMELINE	5
5	CHANGES LEADING TO A NEW PRODUCT REGISTRATION	7
6	OTHERS	8
7	MAJOR VARIATION (MaV)	
MaV-1	Change and/or addition of indication/dosing regimen/patient population	9
MaV-2	Change of product labeling (subject to labeling requirements as per Drug Registration Guidance Document)	9
MaV-3	Change of the specification of drug substance(active ingredient) a)Widening of limits b)Removal of test parameter	10
MaV-4	Change of the manufacturing site of the drug product	10
MaV-5	Replacement of site for primary packaging (direct contact with drug product)	11
MaV-6	Change in the manufacturing process for drug product	11
MaV-7	Change of the specification of drug product a)Widening of limits b)Removal of test parameter	12
MaV-8	Qualitative or quantitative change of excipient	13
MaV-9	Change in colour, size and/or source of hard capsule shell	14
MaV-10	Change in primary packaging material a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of new primary packaging material	14
MaV-11	Change of overage of drug substance (active ingredient)	15
MaV-12	Change of shelf-life of the drug product	15
MaV-13	Change of storage conditions of the drug product	16
8	MINOR VARIATION PRIOR APPROVAL (MiV-PA)	
MiV-PA1	Change of drug product name	17
MiV-PA2	Change of Consumer Medication Information Leaflet (RiMUP)	17
MiV-PA3	Change and/or addition of manufacturer/ manufacturing site/ supplier of a) Drug substance (active ingredient)	17

	LIST OF CONTENTS	Page
	b) Excipients in premixed form	
MiV-PA4	Change of the specification of drug substance (active ingredient) a) Tightening of limits b) Addition/replacement of new test parameter	18
MiV-PA5	Replacement of the company or party responsible for batch release	18
MiV-PA6	Change of the specification of drug product a) Tightening of limits b) Addition/replacement of new test parameter	19
MiV-PA7	Change of the specification of drug substance (active ingredient)/drug product within compendial limits	19
MiV-PA8	Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)	19
MiV-PA9	Change of batch size of drug product	20
MiV-PA10	Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking	20
MiV-PA11	Change in the test procedure of the drug product (including replacement or addition of a test procedure)	21
MiV-PA12	Replacement of a manufacturer for secondary packaging/repacker	21
MiV-PA13	Change of pack size/fill volume/carton pack sizes and/or change of shape or dimension of container or closure	21
MiV-PA14	Change in secondary packaging or any part of the primary packaging material not in contact with the finished product formulation such as colour of flip-off caps	22
MiV-PA15	Addition or replacement of measuring device for oral liquid dosage forms and other dosage form	22
MiV-PA16	Change of dimensions and/or shape of tablets, suppositories or pessaries without change in qualitative and quantitative composition and mean mass	22
9	MINOR VARIATION NOTIFICATION (MiV-N)	
MiV-N1	Change of details of product registration holder	23
MiV-N2	Change of importer and/or store address	23
MiV-N3	Change of product owner	24
MiV-N4	Change in ownership of manufacturer	24
MiV-N5	Change of the name or address (for example: postal code, street name) of the manufacturer of drug product	25
MiV-N6	Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release	25
MiV-N7	Withdrawal/deletion of the alternative manufacturer/ manufacturing	26

	LIST OF CONTENTS	Page
	site/ supplier of drug substance (active ingredient)	
MiV-N8	Deletion of pack size for a drug product	26
10	GLOSSARY	26
11	REFERENCES	26

MALAYSIAN VARIATION GUIDELINE FOR NATURAL (TRADITIONAL MEDICINE & HOMEOPATHY) AND HEALTH SUPPLEMENT PRODUCTS

1. INTRODUCTION

Throughout the registration validity period of a natural (traditional medicine & homeopathy) and health supplement product, the product registration holder is responsible for the product that is placed in the market and to make any amendments to the registration dossier based on any technical and scientific progress regarding the product. This is required to enable the natural and health supplement products to be manufactured and evaluated by generally accepted scientific methods. Such amendments have to be approved by National Pharmaceutical Control Bureau (NPCB).

This guideline is intended to provide supportive information on the requirements for submission of a variation application to implement a change to a natural and health supplement product of abridged category. It is not applicable for natural and health supplement product of full evaluation category and reference shall be made to Malaysian Variation Guideline for Pharmaceutical Product instead. Variation applications are categorized into Major Variation, Minor Variation (Prior Approval) and Minor Variation (Notification). The guideline covers variation on both drug product (finished product) and drug substance (active ingredient). Updating of this guideline will be done on a periodic basis as required.

2. SCOPE OF THIS GUIDELINE

This Malaysian Variation Guideline concerns the variation applications submitted by the product registration holder for natural and health supplement products for human use only.

3. DEFINITION

3.1 Major variation (MaV)

Variation to a registered natural and health supplement finished product that may affect significantly and/or directly the aspects of quality, safety and efficacy/claimed benefit and it does not fall within the definition of minor variation and new registration.

3.2 Minor Variation (MiV-N & MiV-PA)

Variation to a registered natural and health supplement finished product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy/claimed benefit, quality, and safety.

4. PROCEDURE AND TIMELINE

4.1 Minor Variation – Notification (MiV-N)

Type of variation	Minor variation (Notification) MiV-N
Procedure	Notification “Do & Tell” If the notification fulfils the requirements (conditions and supporting documents) as per described under MiV-N, product registration holder must notify NPCB. NPCB shall acknowledge receipt of a notification.
Timeline for NPCB to acknowledge the variation notification	Within 7 working days following receipt of a notification.

- 4.1.1 A MiV-N application may be rejected in specific circumstances with the consequence that the product registration holder must cease to apply the already implemented variation.
- 4.1.2 Product registration holder must ensure validity of the manufacturer’s license prior to implementation of MiV-N.

4.2 Minor Variation –Prior Approval and Major Variation

Type of variation	Minor variation Prior approval MiV-PA	Major variation MaV
Procedure	Prior approval If the application fulfils the requirements (conditions and supporting documents) as per described under MiV-PA, NPCB shall issue an approval for the proposed change.	Prior approval If the application fulfils the requirements (conditions and supporting documents) as per described under MaV, NPCB shall issue an approval for the proposed change.
Timeline for NPCB to evaluate the variation application	Within 30 working days following receipt of an application.	Within 45 working days following receipt of an application.
Approval or correspondence	Approval or first correspondence shall be issued to product registration holder within 30 working days, provided all conditions and supporting documents are fulfilled. Subsequent correspondences which fulfill the requirements will be granted approval within 20 working days. After second correspondence, application may be rejected if still does not fulfil requirements.	Approval or first correspondence shall be issued to product registration holder within 45 working days, provided all conditions and supporting documents are fulfilled. Subsequent correspondences which fulfill the requirements will be granted approval within 30 working days. After second correspondence, application may be rejected if still does not fulfil requirements.
Timeline for product registration holder to reply	Within 20 working days failing which application will be rejected.	Within 30 working days failing which application will be rejected.
Implementation of the variation	Within 6 months after the product registration holder has been informed of the approved variations.	

4.3 Additional notes to product registration holder prior to submission

- 4.3.1 NPCB reserves the right to re-categorize the application type, where deemed appropriate. Re-categorization may require the product registration holder to withdraw the original application and resubmit a new application according to the category.
- 4.3.2 Variation application is appropriate to be submitted along with a declaration letter undersigned by the product registration holder that declares
- There is to be no other changes except for the proposed variation;
 - The change will not adversely affect the quality, efficacy/claimed benefit and safety of the product;
 - The required supporting documents as specified for the variation have been submitted;
 - The proposed change has been checked in reference with the currently approved data in the system;
 - The information written in other languages such as Chinese/Tamil/ Arab carry the same meaning as the data approved/ proposed in English/ Malay.
 - All information provided is accurate, valid and current.
- 4.3.3 Submission of revised draft of package insert and labeling is subject to current regulatory requirements as per latest Drug Registration Guidance Document (DRGD), Directives and Circulars from the Authority.
- 4.3.4 NPCB reserves the right to request for additional information, when deemed necessary or reject the application if the submission is incomplete.

5. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

The following changes require new product registration.

- 5.1 Changes to the active ingredient.
- Change of an active ingredient to a different active ingredient.
 - Inclusion of an additional active ingredient to the product.
 - Removal of an active ingredient from the product.
 - Change in the strength of one or more of the active ingredients including change in the percentage of standardized extract and assay of the principal active constituent/s
 - Increase in overage (exception for vitamins and minerals as per pharmacopoeia).
- 5.2 Changes to the dosage form.
- 5.3 Changes in the route of administration.
- 5.4 Addition of a new manufacturer to a registered product.
- 5.5 For natural products, change from a currently approved contract manufacturer or own plant (local or overseas) to another contract manufacturer (local or overseas) not under crisis situation.
- 5.6 For health supplement products, change from a currently approved contract manufacturer or own plant (local or overseas) to another overseas contract manufacturer not under crisis situation.
- 5.7 Changes from general claims to functional claims or general claims/ functional claims to disease risk reduction for health supplement.

6. OTHERS

6.1 Abbreviations:

C	=	Conditions to be fulfilled
D	=	Documents to be submitted
HS	=	Health Supplement Products
MaV	=	Major Variation
MiV-N	=	Minor Variation (Notification)
MiV-PA	=	Minor Variation (Prior Approval)
TM	=	Traditional Medicine Products

6.2 Definitions:

Drug product	=	Refers to finished product
Drug substance	=	Refers to active ingredient

7. MAJOR VARIATION

Major Variation (MaV)	
MaV-1	Change and/or addition of indication/ dosing regimen/patient population
C	1. Product labeling refers to Package Insert (PI), unit carton label, inner label and/or blister strips. 2. Not applicable to health supplement for change or addition of product indication.
D	1. Proposed revised indication/dosing regimen/patient population. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justifications for the changes proposed. 4. Established references or relevant documents to support the changes 5. Letter of endorsement from the recognized associations of traditional practitioners on the proposed change of indication and dosing regimen in children (where applicable).
MaV-2	Change of product labeling (subject to labeling requirements as per Drug Registration Guidance Document) Includes: a) Change of the layout/artwork without altering meaning. b) Addition/deletion/replacement of pictures, diagrams, bar code, logos (Halal, organic) and/or texts that do not imply an unapproved indication. c) Addition/strengthening of warnings, precautions, contraindications and/or adverse events/effects to the approved product labeling. d) Changes to comply with any current Directive, Circular or Drug Registration Guidance Document. e) Change of distributor's details.
C	1. Product labeling refers to Package Insert (PI), unit carton label, inner label and/or blister strips. 2. Use of additional word/phrase/graphic/logo on product labeling must comply with the current Drug Registration Guidance Document.
D	1. Proposed data at relevant sections of the system. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Established references or relevant documents to support the changes such as valid Halal certificate recognized by JabatanKemajuan Islam Malaysia (JAKIM) or organic certificate (where applicable).

MaV-3	Change of the specification of drug substance (active ingredient) Widening of limits Removal of test parameter
C	- The change should not be the result of unexpected events occurring during the manufacturing process or because of stability concerns unless otherwise justified. - Specifications of drug product remain unchanged. Refer MaV-7 or MiV-PA6 if there is a change in specifications of drug product. - For tightening of limits and/or addition of new test parameter, refer to MiV-PA4. - For change of limits within the compendial specification, refer to MiV-PA7.
D	- Description of any new analytical method (where applicable). - Technical justification for the change. - Certificate of analysis of the drug substance for one commercial batch for all tests in the new specification. - For compendial specifications, a copy of the relevant monograph from the compendium. - Tabulation of the current and revised specifications of the drug substance with changes highlighted.
MaV-4	Change of the manufacturing site of the drug product
C	- Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. - For replacement of the company or party responsible for batch release, please refer to MiV-PA5. - If there are changes to the manufacturing process, MaV-6 is also applicable.
D	Change of manufacturing site applications are categorised into 5 types with each requiring different set of documentations. Product registration holders are advised to refer to Appendix 13: Supporting Documents Required For Change Of Manufacturing Site Application Of Drug Registration Guidance Document for more details. Change of manufacturing site type IV is applicable for special category products such as sterile products for parenteral route hence it is not applicable for natural and health supplement products of the abridged category.

MaV-5	Replacement of site for primary packaging (direct contact with drug product)
C	1. No other changes except for replacement of the site of primary packaging (direct contact with drug product).
D	1. Proposed name and address of the primary packaging site. 2. Technical justification for the change. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Proof that the proposed site is authorized for the packaging activity of the dosage form concerned, i.e. a valid GMP Certificate. 5. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 6. Letter of commitment to undertake the proposed change under real time stability study. 7. Description of the activity (including assembling process) of primary packaging.
MaV-6	Change in the manufacturing process for drug product
C	1. The change does not cause a negative impact on the quality, safety and efficacy/claimed benefit of the drug product. 2. The manufacturing process is carried out in the same currently approved manufacturing site. If there is a change in manufacturing site, MaV-4 is also applicable.
D	1. Proposed detailed manufacturing process and flowchart. 2. Justification for the change. 3. Certificate of analysis of drug product for a minimum of one pilot batch manufactured according to proposed process and letter of undertaking to submit batch data on one full production batch when requested. 4. Stability data (at least 6 months of accelerated stability data and 6 months of real time stability data, with a letter of commitment to complete the stability study) of minimum one batch of the drug product of at least pilot scale manufactured according to the proposed process and report if any results fall outside shelf-life specifications (with proposed action).

MaV-7	Change of the specification of drug product a) Widening of limits b) Removal of test parameter
C	1. The change should not be the result of unexpected events occurring during the manufacturing process or because of stability concerns unless otherwise justified. 2. Test procedures remain the same/ changes in the test procedure are minor. 3. For tightening of limits and/or addition of new test parameter, refer to MiV-PA6. 4. For change of limits within the compendial specification, refer MiV-PA7.
D	1. Description of any new analytical method (where applicable). 2. Revised specification of drug product. 3. Technical justification for the change. 4. Tabulation of the current and revised release and shelf-life (where applicable) specifications of the drug product with changes highlighted. 5. Certificate of analysis of the drug product for all tests in the new specification for at least one pilot scale batch and letter of undertaking to submit batch data on one full production batch when requested. 6. Copy of the relevant monograph from the compendium (where applicable). 7. For (a) only, stability data (at least 6 months of accelerated stability data and 6 months of real time stability data, with a letter of commitment to complete the stability study) of one batch of the drug product of at least pilot scale manufactured according to the proposed specification of drug product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-8	Qualitative or quantitative change of excipient
C	1. Replacement of an excipient with a comparable excipient of the same functional characteristics. 2. Quantitative change of the excipient should comply with the limits allowed as stipulated in the Drug Registration Guidance Document, compendium or recognized reference. 3. If the excipient is a colouring/flavouring agent, the agent must not have been rejected for pharmaceutical use. 4. Not applicable for change of hard capsule shell (Refer MaV-9). 5. Weight of finished product of solid dosage forms to remain within the specifications as per uniformity of weight specifications. 6. Final concentration of liquid dosage forms to remain unchanged.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the change. 3. Comparative tabulated format of the current and revised product formulation. 4. Revised batch manufacturing formula (where applicable). 5. Specifications of the proposed excipient (where applicable). 6. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued by a competent authority of the issuing country or a letter of declaration from the supplier (where applicable). 7. Revised drug product release and shelf-life specifications (where applicable). 8. Certificate of analysis of drug product for at least one pilot batch according to proposed product formula and letter of undertaking to submit batch data on one full production batch when requested. 9. Stability data (at least 6 months of accelerated stability data and 6 months of real time stability data, with a letter of commitment to complete the stability study) of minimum one batch of the drug product of at least pilot scale manufactured according to the proposed formula and report if any results fall outside shelf-life specifications (with proposed action). 10. Revised manufacturing process (where applicable).

MaV-9	Change in colour, size and/or source of hard capsule shell
C	1. The drug product release and end-of-shelf-life specifications of the drug product remain unchanged except for colour and/or source. 2. MaV-8 is applicable if change of excipient/ soft gel is involved. 3. From TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa. 4. No change in the formulation and manufacturing process of drug product. 5. Not allowed for changes from hard capsule to soft gel, or vice versa.
D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. Justification for the change. 3. A letter of declaration from the manufacturer or the product registration holder stating that the material is purely of vegetable, animal or synthetic origin (where applicable). 4. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert or a letter of declaration from the supplier (where applicable). 5. Certificate of Analysis of the empty hard capsule of the proposed new source. 6. Revised release specifications of the drug product. 7. Certificate of analysis for at least one pilot scale batch of the drug product and letter of undertaking to submit batch data on one full production batch when requested. 8. Stability data (at least 6 months of accelerated stability data and 6 months of real time stability data, with a letter of commitment to complete the stability study) of minimum one batch of the drug product of at least pilot scale manufactured according to the proposed capsule and report if any results fall outside shelf-life specifications (with proposed action).
MaV-10	Change in primary packaging material a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of new primary packaging material
C	1. The change includes the same packaging type (for example from Alu/PVC blister to Alu/Alu blister, from transparent glass bottle to amber glass bottle). 2. Release and shelf-life specifications of drug product remain unchanged.
D	1. Proposed revised packing particulars. 2. Revised drafts of the package insert incorporating the proposed variation (where applicable). 3. Proposed specifications of the primary packaging material (where applicable). 4. Stability data (at least 6 months of accelerated stability data and 6 months of real time stability data, with a letter of commitment to complete the stability study) of minimum one batch of the drug product of at least pilot scale packed with all the proposed primary packaging and report if any results fall outside shelf-life specifications (with proposed action). 5. Revised manufacturing process (where applicable). 6. Justification for the change.

MaV-11	Change of overage of drug substance (active ingredient)
C	1. Only for vitamins and minerals of health supplement products. 2. Proposed increase in overage should be within the acceptable limits of compendium. 3. Weight of finished product of solid dosage forms to remain within the specifications as per uniformity of weight specifications. 4. Release and shelf-life specifications of drug product remain unchanged.
D	1. Justification for the change. 2. Comparative tabulated format of currently approved and proposed batch manufacturing formula. 3. Revised batch manufacturing formula. 4. Certificate of analysis for at least one pilot batch of the finished product and letter of undertaking to submit batch data on one full production batch when requested. 5. Stability data (at least 6 months of accelerated stability data and 6 months of real time stability data, with a letter of commitment to complete the stability study) of minimum one batch of the drug product of at least pilot scale manufactured with the proposed overage and report if any results fall outside shelf-life specifications (with proposed action).
MaV-12	Change of shelf-life of the drug product
C	1. It is applicable to either reduction or extension of shelf life. 2. The stability studies must show conformance to the currently approved shelf-life specifications. 3. Stability studies should have been conducted for drug product in the authorized packaging material as a package for sale and after first opening (where applicable).
D	1. Proposed shelf life. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification for the change. 4. A letter of commitment from product registration holder to inform users of the relevant change (for cases of reduction of shelf life). 5. Results of appropriate real time stability studies (full real time stability data) under Zone IVB covering the duration of proposed shelf-life of two pilot scale batches of the product in the authorized packaging material as a package for sale and after first opening (where applicable).

MaV-13	Change of storage conditions of the drug product
C	1. It is applicable to increasing or lowering from the currently approved storage temperature. 2. The studies must show conformance to the currently approved shelf-life specification. 3. Stability studies should have been conducted for drug product in the authorized packaging material as a package for sale and/or after first opening (where applicable)
D	1. Proposed storage conditions. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification for the change. 4. Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of two pilot scale batches of the product and in the authorized packaging material as a package for sale and after the first opening (where applicable).

Note: * Condition and supporting document are not implemented for the interim period to accommodate variation workflow in the QUEST2 system.

8. MINOR VARIATION PRIOR APPROVAL

Minor Variation (MiV)	
MiV-PA1	Change of drug product name
C	1. There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the product name change. 2. Change of product name comply to the current DRGD
D	1. Proposed new product name. 2. Revised draft package insert and labeling incorporating the proposed variation. 3. Letter from product registration holder authorizing the change of product name.
MiV-PA2	Change of Consumer Medication Information Leaflet (RiMUP)
C	1. Changes to the content have been approved in the system. 2. This includes submission of a new RiMUP.
D	1. Proposed RiMUP, a clean and annotated version highlighting the changes made.
MiV-PA3	Change and/or addition of manufacturer/ manufacturing site/ supplier of (a) drug substance(active ingredient) (b) excipients in premixed form
C	1. Specifications and composition of the drug substance/excipients in premixed form remain unchanged. 2. Specifications of drug product remain unchanged. 3. For deletion of a drug substance manufacturer, an alternative manufacturer must be registered. 4. Refer MaV-8 if composition of premixed excipients is changed. 5. For withdrawal/deletion of alternative manufacturer(s) for drug substance, refer MiV-N7.
D	1. For (a) only, certificate of analysis for at least one commercial batch of the drug substance from the proposed manufacturer/manufacturing site/supplier. 2. For (a) only, if active ingredients in premixed form are involved, GMP certificate for the manufacturer of the premix. 3. For (b) only, certificate of analysis of the excipients available in premixed form from the proposed manufacturer/supplier. 4. Proposed product labeling, a clean and annotated version highlighting the changes made (where applicable). 5. A letter of commitment from product registration holder to conduct real time and accelerated stability studies for the drug product manufactured with the

drug substance from the proposed manufacturing site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.	
Change of the specification of drug substance (active ingredient)	
MiV-PA4	a) Tightening of limits b) Addition/replacement of new test parameter
C	1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns unless otherwise justified. 2. Specifications of drug product remain unchanged. Refer MaV-7 or MiV-PA6 if there is a change in specifications of drug product. 3. For widening of limits and/or removal of test parameter, refer to MaV-3.
D	1. Description of any new analytical method (where applicable). 2. Technical justification for the change. 3. Certificate of analysis of the drug substance of one commercial batch for all tests in the new specification. 4. For compendial specifications, a copy of the relevant monograph from the compendium. 5. Tabulation of the current and revised specifications of the drug substance with changes highlighted.
Replacement of the company or party responsible for batch release	
MiV-PA5	
C	1. Only applicable for site that is solely responsible for batch release. 2. The manufacturer of the drug product remains the same.
D	1. Proposed name and address of batch release site. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Proof that the proposed site is appropriately authorized (accredited by the authority) to be responsible for batch release such as a valid GMP certificate. 4. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable).

MiV-PA6	Change of the specification of drug product a) Tightening of limits b) Addition/replacement of new test parameter
C	1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns unless otherwise justified. 2. Test procedures remain the same, or changes in the test procedure are minor. 3. For widening of limits and/or removal of test parameter, refer MaV-7.
D	1. Description of any new analytical method (where applicable). 2. Revised specifications of drug product. 3. Tabulation of the current and revised release and shelf-life (where applicable) specifications of the drug product with changes highlighted. 4. Certificate of analysis of the drug product for all tests in the new specification for at least one pilot scale batch. 5. For compendial specifications, copy of the relevant monograph from the compendium. 6. Stability data (at least 3 months of accelerated stability data and 3 months of real time stability data, with a letter of commitment to complete the stability study) of one batch of the drug product of at least pilot scale manufactured according to the proposed specification of drug product and report if any results fall outside shelf-life specifications (with proposed action).
MiV-PA7	Change of the specification of drug substance (active ingredient)/drug product within compendial limits
C	1. It is applicable for widening or tightening of limits within the compendial specification. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns unless otherwise justified.
D	1. Revised specifications of drug substance/drug product. 2. Tabulation of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 3. Certificate of analysis of the drug substance for at least one commercial batch for all tests in the new specification (where applicable). 4. Certificate of analysis of the drug product for at least one pilot scale batch for all tests in the new specification (where applicable). 5. Copy of the relevant monograph from the compendium.
MiV-PA8	Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)
C	1. Release and shelf-life specifications of drug product remain unchanged. 2. The change does not result from unexpected events arising during manufacture.
D	1. Revised in-process specifications together with justification 2. Comparative tabulated format of currently approved and proposed in-process controls. 3. A description of the analytical methodology (where applicable).

MiV-PA9	Change of batch size of drug product
C	1. The change does not affect consistency of production. 2. Release and shelf-life specifications of drug product remain unchanged.
D	1. Revised batch manufacturing formula. 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. Certificate of analysis of drug product on a minimum of one production batch manufactured according to proposed batch size and letter of undertaking to submit batch data on the next one full production batch.
MiV-PA10	Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking
C	<u>(a) Except score/break-line</u> 1. New markings do not cause confusion with other registered products. 2. Any ink proposed must comply to relevant pharmaceutical legislation or of food grade and not a listed banned substance. 3. Release and shelf-life specifications of the drug product remain unchanged except for appearance. <u>(b) On score/break-line</u> In addition to the above conditions, 4. Score/break-line is not meant for cosmetic purpose. 5. Applicable to addition or removal of score/break-line.
D	<u>(a) Except score/break-line</u> 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Detailed drawing or written description of the proposed imprint/bossing/markings. Certificate of analysis of ink/printing material (either pharmaceutical grade or food grade) (where applicable). 3. Release and shelf-life specifications of the drug product with the new product description. <u>(b) On score/break-line</u> In addition to the above documents, 4. Justification for the change (i.e. change in dosing regimen). 5. Data on test of uniformity of the subdivided parts of the tablets at release should be submitted. 6. Certificate of analysis of drug product for at least one pilot scale batch and letter of undertaking to submit batch data on the next one full production batch.

MiV-PA11	Change in the test procedure of the drug product (including replacement or addition of a test procedure)
C	1. Drug product specifications are not adversely affected unless the specifications are tightened. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns unless otherwise justified.
D	1. Justification for the proposed change. 2. Proposed release and shelf-life specifications of the drug product. 3. Description of the analytical methodology. 4. Certificate of analysis of the finished product of at least one pilot batch when made available.
MiV-PA12	Replacement of a manufacturer for secondary packaging/repacker
C	1. No other changes except for the replacement of site for secondary packaging.
D	1. Proposed name and address of manufacturer for secondary packaging/repacker. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Proof that the proposed site is appropriately authorized (accredited by the authority) for the packaging activity concerned such as a valid GMP certificate. 4. Letter from product owner authorizing the new manufacturer for secondary packaging/repacker to perform secondary packaging (where applicable). 5. Letter of acceptance from the manufacturer for secondary packaging/repacker to perform secondary packaging of the product.
MiV-PA13	Change of pack size/ fill volume/ carton pack sizes and/ or change of shape or dimension of container or closure
C	1. The change only concerns the same packaging type and material. 2. The new size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. This also includes addition and/or deletion of pack size or change in the dimension of the primary packaging material (where applicable). 4. Release and shelf-life specifications of the drug product remain unchanged. 5. No processing fee is required for deletion of pack size. 6. For deletion of pack size, refer MiV-N8.
D	1. Proposed packing particulars. (eg: type of material use, colour of cap and bottle). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification for the proposed pack size/deletion of pack size. 4. Description of the container, e.g. actual picture of the container.

MiV-PA14	Change in secondary packaging or any part of the primary packaging material not in contact with the finished product formulation such as colour of flip-off caps
C	1. The change does not affect the delivery, use, safety or stability of the finished product.
D	1. Proposed packing particulars. (eg: type of material use, colour of cap and bottle) 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Description of the container, e.g. actual picture of the container.
MiV-PA15	Addition or replacement of measuring device for oral liquid dosage forms and other dosage form
C	1. The size and where applicable, the accuracy of the proposed measuring device must be compatible with the approved dosing regimen. 2. The new device is compatible with the drug product. 3. Size and accuracy of the device are adequate for the dosing regimen as approved in the product labeling
D	1. Revised draft of the package insert and labeling incorporating the proposed variation (where applicable). 2. Description of the device (including an actual picture; where applicable). 3. Justification that size and accuracy of the device are adequate for the dosing regimen as approved in the product labeling. 4. Revised dosage instructions (where applicable).
MiV-PA16	Change of dimensions and/or shape of tablets, suppositories or pessaries without change in qualitative and quantitative composition and mean mass
C	1. Release and shelf-life specifications of the drug product remain unchanged except for dimension and/or shape.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Detailed drawing or written description of the current and proposed appearance. 3. Release and shelf-life specifications of the drug product.

Note: * Condition and supporting document are not implemented for the interim period to accommodate variation workflow in the QUEST2 system.

9. MINOR VARIATION NOTIFICATION

Minor Variation (MiV-N)	
Notification	
MiV-N1	Change of details of product registration holder
C	1. This is applicable only after the formal application to update product registration holder's details in the system has been approved. 2. This includes change of product registration holder, renaming of the company and updating of the address of product registration holder (for example: postal code, street name) in product labeling only. 3. Please refer to MaV-2 if other changes on label are involved.
D	1. Revised draft package insert and labeling incorporating the proposed variation (where applicable). 2. Letter by the product owner authorizing the new product registration holder to hold the product license.
MiV-N2	Change of importer and/or store address
C	1. The manufacturer of the drug product remains the same. 2. The batch release site remains the same. 3. Please refer to MaV-2 if other changes on label are involved.
D	1. Proposed importer and/or store address. 2. Valid business license. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

MiV-N3	Change of product owner
C	1. The product registration holder remains the same. 2. The manufacturing site remains the same. 3. This includes transfer of ownership/ renaming of the company and updating of the address of product owner (for example: postal code, street name). 4. Please refer to MaV-2 if other changes on label are involved.
D	1. Proposed name and address of product owner. 2. Revised draft package insert and labeling incorporating the proposed variation (where applicable). 3. A letter of declaration on the transfer of ownership between old product owner and new owner and counter-signed by both parties (where applicable). 4. Letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 5. a Letter by the new product owner authorizing the manufacturer to manufacture the drug product on its behalf, if the new product owner is not the manufacturer of the drug product, 6. A letter of acceptance from the manufacturer to manufacture the product, if the new product owner is not the manufacturer of the drug product,
MiV-N4	Change in ownership of manufacturer
C	1. This is applicable only after the formal application to update manufacturer's name in the database has been approved.* 2. This includes change in ownership of repacker. 3. The manufacturing site remains unchanged. 4. No other changes except for the change in ownership of manufacturer. 5. No changes in the product labeling. Please refer to MaV-2 if label contents are involved.
D	1. Letter of justification on the transfer of ownership such as a valid GMP certificate. 2. Official letter stating the transfer of ownership from old manufacturer to new manufacturer (where applicable). 3. In case of a contract manufacturer, official letter from product owner declaring the change and authorizing the new manufacturer to manufacture the drug products on its behalf. 4. In case of a contract manufacturer, letter of acceptance from the new manufacturer to manufacture the drug product.

MiV-N5	Change of the name or address (for example: postal code, street name) of the manufacturer of drug product
C	1. This is applicable only after the formal application to update manufacturer's details in the database has been approved.* 2. This includes change in packer/ repacker. 3. The manufacturing site remains the same. 4. No other changes except for the change of the name and/or address of a manufacturer of the drug product. 5. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N4. 6. For change in the manufacturer's details in product labeling only. Please refer to MaV-2 if other parts are involved.
D	1. Proposed name and address of the manufacturer. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. A valid GMP certificate or official document from relevant authority confirming the new name and/or address. 4. In case of a contract manufacturer, official letter from product owner declaring the change and authorizing the new manufacturer to manufacture the drug products on its behalf. 5. In case of a contract manufacturer, letter of acceptance from the new manufacturer to manufacture the drug product.
MiV-N6	Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release
C	1. This is applicable only after the formal application to update the details of the manufacturer responsible for batch release in the database has been approved. * 2. The manufacturer of the drug product remains the same. 3. The batch release site remains the same. 4. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N4. 5. For change on the part of batch releaser in product labeling only. Please refer to MaV-2 if other parts are involved.
D	1. Proposed name and address of batch release site. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. A valid GMP certificate or official document from relevant authority confirming the new name or address (where applicable). 4. Official letter from product owner authorizing company/manufacturer with new name/address responsible for batch release. 5. A declaration from the product registration holder that the change does not involve change of batch release site.

MiV-N7	Withdrawal/deletion of the alternative manufacturer/ manufacturing site/ supplier of drug substance (active ingredient)
C	1. At least one manufacturer of each drug substance remains to be registered. 2. For replacement or addition of manufacturer/ manufacturing site/ supplier of drug substance, refer MiV-PA3. 3. No changes in the product labeling. Please refer to MaV-2 if label contents are involved.
D	1. Certificate of analysis for at least one commercial batch of the drug substance from the remaining manufacturer/manufacturing site/supplier.
MiV-N8	Deletion of pack size for a drug product
C	1. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling. 2. Deletion of pack size does not involve any labelling on existing pack sizes (e.g: outer carton/ package insert) . Please refer to MaV-2 if label contents are involved. 3. For replacement or addition of pack size/ fill volume/ carton pack sizes and/ or change of shape or dimension of container or closure, refer MiV-PA13.
D	1. Reason for deletion.

Note: * Condition and supporting document are not implemented for the interim period to accommodate variation workflow in the QUEST2 system.

10. GLOSSARY

Refer to Glossary of Drug Registration Guidance Document.

11. REFERENCES

1. Malaysian Variation Guideline for Pharmaceutical Products 2013
2. Drug Registration Guidance Document
3. ASEAN Guideline on Stability of Drug Product