NATIONAL PHARMACEUTICAL CONTROL BUREAU
MINISTRY OF HEALTH MALAYSIA

MALAYSIAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

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1. INTRODUCTION

Throughout the life of a pharmaceutical product, the product registration holder is responsible for the product that is placed in the market and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the pharmaceutical products to be manufactured and checked by means of generally accepted scientific methods. Such amendments have to be approved by National Pharmaceutical Control Bureau (NPCB).

This guidance document is adopted from the ASEAN Variation Guideline for Pharmaceutical Products 2012 incorporating Malaysia's specific requirements. It is intended to provide supportive information on the requirements for submission of a variation application to implement a change to a pharmaceutical product. Variation applications are categorized into major variation, minor variation (prior approval) and minor variation (notification). 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 pharmaceutical products for human use only.
For biologics, some of the variations are applicable. However, more extensive data may be required.

3. DEFINITION

3.1 Major variation (MaV)

Variation to a registered pharmaceutical finished product that may affect significantly and/or directly the aspects of quality, safety and efficacy 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 pharmaceutical finished product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy, quality, and safety.

4. PROCEDURE AND TIMELINE

4.1 Minor Variation – Notification

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 20 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 45 working days following receipt of an application.	Within 60 working days following receipt of an application.

Approval or correspondence	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 20 working days. After third correspondence, application may be rejected if still does not fulfill requirements.	Approval or first correspondence shall be issued to product registration holder within 60 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 third correspondence, application may be rejected if still does not fulfill requirements.
Timeline for product registration holder to reply	Within 20 working days failing which application will be rejected. Auto-reminder will be sent 10 working days before the deadline.	Within 30 working days failing which application will be rejected. Auto-reminder will be sent 15 working days before the deadline.
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 correct category.

4.3.2 Variation application is submitted along with a declaration letter which is undersigned by the product registration holder that declares

- There is no other change except for the proposed variation;
- The change will not adversely affect the quality, efficacy and safety of the product;
- All conditions for the variation concerned are fulfilled;
- The required supporting documents as specified for the variation have been submitted; and
- The proposed change has been checked in reference with the currently approved data in the system.

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) and Circulars from NPCB.

4.3.4 NPCB reserves the right to request for additional information, when deemed necessary or reject the application when the submission is incomplete.

5. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

The following changes are considered as new product registration.

5.1 Changes to the Active Pharmaceutical Ingredient (API).
- Change of the API to a different API including change in the salt or isomer form of the API.
- Inclusion of an additional API to a multicomponent product.
- Removal of one API from a multicomponent product.
- Change in the strength of one or more APIs.
- Increase in overage (exception for vitamins and minerals as per pharmacopoeia).

5.2 Changes to the pharmaceutical form/dosage form.

5.3 Changes in the route of administration (exception for parenteral route).

5.4 Changes in the manufacturing site of drug product.
- Addition of a new manufacturing site to the currently approved site for the same manufacturing process.
- Change from a currently approved contract manufacturer or own plant to another contract manufacturer not under crisis situation.

6. OTHERS

6.1 **Lead compendium** refers to British Pharmacopeia (BP), European Pharmacopeia (EP), Japan Pharmacopoeia (JP) and United States Pharmacopeia (USP).

6.2 This list of variations is not exhaustive and will be amended from time to time as and when the need arises. Any variations not yet listed in this guideline should be justified and decided by NPCB. Appropriate reference can be made to:

i. ASEAN Variation Guideline for Pharmaceutical Products 2012
ii. EMA Classification Guidance On Minor Variations of Type IA, Minor Variations of Type IB And Major Variations of Type II.
iii. SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up And Post-Approval Changes: Chemistry, Manufacturing And Controls, In Vitro Dissolution Testing, And In Vivo Bioequivalence Documentation.
iv. SUPAC-MR: Modified Release Solid, Oral Dosage Forms, Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation.
v. WHO Guidance On Variations To A Prequalified Product Dossier.

6.3 **Abbreviations:**

C	=	Conditions to be fulfilled
D	=	Documents to be submitted
MaV	=	Major Variation
MiV-N	=	Minor Variation (Notification)
MiV-PA	=	Minor Variation (Prior Approval)

7. MAJOR VARIATION

Major Variation (MaV)	
MaV-1	**Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product**
C	1. Product labeling refers to Package Insert(PI), unit carton label, inner label and/or blister strips. 2. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI). 3. Not applicable to new / additional indication / extension of patient population / parenteral route of administration for new chemical entity (NCE). Please refer to Section 16.4 of Drug Registration Guidance Document for new or additional indication for NCE products.
D	1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4. Justifications for the changes proposed. 5. Approval letters from reference countries or country of origin which have approved the new indication or dosing regimen (where applicable). 6. Clinical expert reports and/or clinical trial reports (where applicable). 7. Clinical documents as per ASEAN Common Technical Dossier (ACTD) part IV (where applicable).
MaV-2	**Change of content of product labeling**
C	1. Product labeling refers to Package Insert (PI), unit carton label, inner label and/or blister strips. 2. The change is not a minor variation and not within the scope of MaV-1. 3. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4. Justifications for the changes proposed and supporting clinical documents when applicable.

MaV-3	**Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. Specifications of drug substances remain unchanged. 2. For Change and/or addition of alternative manufacturer/site of drug substance where European Pharmacopoeial Certificate of Suitability (CEP) is available, please refer to MiV-PA5.
D	1. Either one of the following options is applicable; a) Option 1 (DMF) i. DMF (Open and Closed part) ii. Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and, iii. Letter of Access. or b) Option 2 (Full ACTD) i. Full details of Part II S ACTD (S1-S7) ii. Current GMP certificate or any other evidence of GMP compliance from a regulatory authority. 2. Comparative tabulated format of the currently registered and revised drug substance manufacture information (where applicable). 3. Certificate of analysis and batch analysis data (in a comparative tabular format) for at least two pilot batches of the drug substance from the current and proposed manufacturing sites. 4. 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. 5. 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 guideline.

MaV-4	**Major change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. The synthetic route is different. Refer to MiV-PA8 if the synthetic route remains unchanged. 3. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety. 4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 5. Specifications and stability performance of drug substance remain unchanged. 6. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	1. Either one of the following options is applicable; a) Option 1 (DMF) i. DMF (Open and Closed part); and, ii. Letter of Access. or b) Option 2 (Full ACTD) i. Full details of Part II S ACTD (S1-S7) 2. Comparative tabulated format of the currently registered and revised manufacturing process of the drug substance. 3. Certificate of analysis and batch analysis data (in a comparative tabular format) for at least two pilot batches of the drug substance from the current and proposed manufacturing process. 4. 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 synthesized from the proposed manufacturing process, and report if any results fall outside shelf-life specifications (with proposed action) or when requested. 5. 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 guideline.

MaV-5	Change of the manufacturing site of the drug product
C	1. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. 2. For replacement of the company or party responsible for batch release, please refer to MiV-PA4. 3. If there are changes to the manufacturing process, MaV-10 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.

APPENDIX 13:

SUPPORTING DOCUMENTS REQUIRED FOR CHANGE OF MANUFACTURING SITE (COS) APPLICATION

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
1.	Letter of authorization/ appointment from the product owner to authorize Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.	√	√	√	√	√
2.	Letter from the manufacturer/ product owner to clarify/ explain the need to change site of manufacture. ***For Type I:*** Letter of declaration stating the reason(s) for change of manufacturing site and clearly state the proposed and current name and address of manufacturer	√	√	√	√	√
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry specifications of the product as the same as already approved. *OR* If there are minor changes, to declare the 'minor changes' & justify the need for such changes.	√	√	√	√	√
4.	'Release' and 'end-of-shelf life' specifications from proposed site.	√	√	√	√	√
5.	Original copy of the Certificate of Free Sale (CFS) and Good Manufacturing Practice (GMP)/ Certificate of Pharmaceutical Product (CPP) from the source country of the new manufacturing site in the case of an imported product *OR* Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.	√	√	√	√	√
6.	Specification of the drug substance	√	√	√	√	√
7.	Product formula	√	√	√	√	√
8.	Original copy of Certificate of Analysis (CoA) from the new manufacturing site.		√	√	√	
9.	Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two		√	√	√	

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
	full production batches should be available upon request or reported if outside specifications (with proposed action).					
10.	"Accelerated" and on-going stability data as per ASEAN Guideline on Stability Study of Drug Product and a letter of commitment to submit real time stability data. ***For Type I:*** Letter of commitment to submit stability data report.	√	√	√	√	
11.	Amended immediate label, outer label and package insert for the product from the proposed site.	√	√	√	√	√
12.	Process validation report as per ASEAN Guideline On Submission Of Manufacturing Process Validation Data For Drug Registration. ***For Type I:*** Letter of commitment to submit process validation report, if applicable	√	√	√	√	
13.	Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).		√	√	√	
14.	Declaration and commitment that the manufacturer will carry out continuous quality monitoring on the post change products	√				
15.	Letter of commitment to submit stability data, certificate of analysis, process validation report (where applicable) and sample for laboratory testing within 6 months of approval of site change.					√
16.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.	√	√		√	

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
17.	Comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer circular:* Bil (31) dlm. BPFK/PPP/01/03 *OR* Report of bioavailability and bioequivalence studies for generic products. *OR* Comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. (*Please refer to ASEAN Guidelines and list of products requiring BA and BE study).*		√	√		
18.	Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer circular:* Bil (31) dlm. BPFK/PPP/01/03 *OR* Letter of commitment to submit report of bioavailability and bioequivalence studies for generic products. *OR* Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. *(Please Refer to ASEAN Guidelines and list of products requiring BA and BE study).*	√				√

MaV-6	**Replacement of alternative site for primary packaging (direct contact with drug product)**
C	1. No other changes except for the replacement of alternative site for primary packaging (direct contact with drug product).
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned such as a valid GMP Certificate and/or a CPP which covers GMP certification. 3. 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). 4. For sterile product, validation scheme and/or report on primary packaging processes as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-7	**Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]** **a) Specification limits are widened and/or deletion of test parameter and limits of drug substance** **b) Specification limits are widened and/or deletion of test parameter and limits of drug product**
C	1. Test procedures remain the same, or changes in the test procedure are minor. 2. Not applicable to compendial drug substances/drug products. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 4. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	**For both (a) and (b)** 1. Revised specification of drug substance / drug product. 2. Comparative tabulated format of the currently approved and revised specification of drug substance/drug product with changes highlighted. 3. Certificate of analysis and batch analysis data of the drug substance/drug product for all tests in the new specification for two pilot or production scale batches. 4. Justification for change substantiated with scientific data to be provided. **In addition of D1 to D4, this is applicable for (b) only** 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action); (where applicable).

MaV-8	Change of batch size of sterile drug product
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 3. Release and shelf-life specifications of drug product remain unchanged. 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 appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration.
D	1. Comparative tabulated format of proposed and currently approved batch manufacturing formula. 2. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration of the proposed batch size should be provided upon submission. 3. Release and shelf-life specifications of the drug product. 4. Certificate of analysis and batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to currently approved and proposed batch sizes. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-9	Change of batch size of non-sterile drug product
C	1. The change does not affect consistency of production. 2. Release and shelf-life specifications of drug product remain unchanged. 3. 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 appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 4. This is applicable to change of batch size more than 10-fold compared to the currently registered batch size. For change of batch size up to 10-fold compared to the currently registered batch size, please refer MiV-PA14.
D	1. For oral solid dosage forms, comparative dissolution profile for at least one production batch (where applicable). 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration the proposed batch size should be provided upon submission. 4. Release and shelf-life specifications of the drug product. 5. Certificate of analysis and batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to currently approved and proposed batch sizes and letter of undertaking to submit batch data on the next one full production batch. 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-10	Major change in the manufacturing process for drug product
C	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. If there is a change in manufacturing site, MaV-5 is also applicable. 3. For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA21.
D	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 ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 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. Certificate of analysis and 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 ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 7. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-11	**Qualitative or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)** **b) For modified release oral dosage forms** **c) For other critical dosage forms such as sterile preparations.**
C	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 in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 5. For other qualitative or quantitative changes of excipient for immediate release oral dosage forms and other non-critical dosage forms, please refer to MiV-PA16. 6. For Quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form, please refer to MaV-12.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification for the change must be given by appropriate development of pharmaceutics. 3. 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). 4. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation (where applicable). 5. Revised batch manufacturing formula. 6. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission. 7. Revised ACTD Section P3.1 to P3.4 (where applicable). 8. Specifications of the proposed excipient. 9. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant veterinary authority of the issuing country (where applicable). 10. Drug product release and shelf-life specifications. 11. Certificate of analysis and 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. 12. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 13. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-12	**Quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the current approved product. 2. The release and shelf-life specifications of the drug product remain unchanged except for the weight and/or size(where applicable). 3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage forms, please refer to MiV-PA17.
D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. A declaration that the change does not interfere with the drug product release and shelf-life specifications test method. 3. Comparative dissolution profile data of at least one pilot/production batch of the drug product between the currently approved and proposed composition. 4. Current and proposed product and batch manufacturing formula. 5. Revised release and shelf-life specifications of the drug product. 6. Certificate of analysis and batch analysis data for two production/pilot scale batches of the drug product. 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 8. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-13	**Change in primary packaging material for sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. Release and shelf-life specifications of the drug product remain unchanged. 2. The change includes the same packaging type (for example from amber glass ampoule to clear glass ampoule). 3. For change in the primary packaging material for non-sterile drug product, please refer to MiV-PA29.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Appropriate scientific data on new packaging (comparative data on permeability, e.g. moisture, O_2, CO_2). 3. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 4. Validation scheme and/or report of the manufacturing and sterilization process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in primary packaging material should be provided upon submission. 5. Comparative tabulated format of specifications of the proposed and current primary packaging material. 6. Revised ACTD Sections P3 and/or P7 (where applicable). 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-14	**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**
C	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. 4. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile drug product, please refer to MiV-PA31.
D	1. Revised drafts of the package insert and labeling 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 ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-15	**Inclusion or replacement of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product. 2. For deletion of the solvent/diluent, please refer to MiV-PA19. 3. For change of shelf-life and/or storage condition of the drug product after first opening and/or after dilution/reconstitution, please also refer to MaV-16/MiV-PA35 and/or MaV-17/MiV-PA36 (where applicable).
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation. 2. Approved PI/SmPC from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 3. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 4. A letter of authorization from product owner to authorize the manufacturing site to manufacture and package the solvent/diluent (where applicable). 5. A declaration from the product registration holder that the release and shelf-life specifications of drug product are not affected. 6. Revised section P for the solvent/diluent and reconstitution stability data(where applicable).

MaV-16	**Extension of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c)–The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For reduction of shelf-life, please refer to MiV-PA35.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification letter for the change of shelf-life of the drug product (where applicable). 3. A letter of commitment from product owner or product registration holder to inform users of the relevant change (where applicable). 4. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate).
MaV-17	**Change of storage conditions of the drug product (Lowering from the current approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For change of storage condition (Increasing from the current approved storage condition), please refer to MiV-PA36.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the change. 3. Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product.

8. MINOR VARIATIONPRIOR APPROVAL

Minor Variation (MiV-PA)	
Prior Approval	
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. No confusion with another drug product either when spoken or written. 3. The new name does not (i) suggest greater safety or efficacy than supported by clinical data (ii) imply a therapeutic use (iii) imply superiority over another similar product and (iv) imply the presence of substance(s) not present in the product.
D	1. Revised draft package insert and labeling incorporating the proposed variation. 2. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 3. Official letter from product owner or product registration holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 4. A declaration from the product registration holder that there is no other changes to the product/label except for the drug product name change. 5. Trademark certificate (where applicable).
MiV-PA2	**Change of product labeling (in accordance to country specific labeling requirement)** Includes: a) Change of the layout/artwork without altering meaning. b) Addition/deletion/replacement of pictures, diagrams, bar code, logos 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) Tightening of product's target population. e) Deletion of indication. f) Change of distributor's details.
C	1. Product labeling refers to Package Insert (PI), unit carton label, inner label and/or blister strips. 2. The change is not a MaV and does not contain promotional information. For major change in product labeling, please refer to MaV-2.
D	1. Current approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Letter of declaration from the product registration holder stating that no other changes on the label except for the intended change. 4. Relevant document/reference to support the changes (where applicable).

MiV-PA3	**Change of patient information leaflet**
C	1. Changes to the content (eg. Section A, C) has been approved in the system.
D	1. Proposed patient information leaflet, a clean and annotated version highlighting the changes made.
MiV-PA4	**Replacement of the company or party responsible for batch release**
C	1. Only applicable for batch release. 2. The manufacturer of the drug product remains the same. 3. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized (accredited by the authority) to be responsible for batch release such as a valid GMP certificate or CPP which covers the GMP certification. 3. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable).
MiV-PA5	**Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]**
C	1. Specifications of drug substances remain unchanged. 2. For change and/or addition of alternative manufacturer/site of drug substance where CEP is not available, please refer to MaV-3.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by the European Directorate for the Quality of medicines (EDQM). 2. 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. 3. Certificate of analysis and batch analysis data (in a comparative tabular format) of at least two pilot batches of the drug substance from the current and proposed manufacturing sites. 4. If the re-test period is not stated in the CEP, real time and accelerated stability data up to the proposed re-test period on two pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided.

MiV-PA6	**Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. The change does not affect the reproducibility of the process. 2. Specifications of drug substance remain unchanged. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	1. A letter of declaration from marketing authorized holder that the specifications of drug substance have not changed and the reproducibility of the process has not been affected 2. Certificate of analysis and comparative batch analysis data with specification and results (in a comparative tabulated format)on a minimum of one production or pilot batch manufactured to both the currently approved and proposed batch sizes. Batch data on the next two full production batches should be available on request or reported if outside specification (with proposed action). 3. Amended relevant ACTD Section S (where applicable).
MiV-PA7	**Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. In-process limits are tightened or addition of new tests. 2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 4. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	1. A description of the analytical method and summary of validation data must be provided for all new analytical methods (where applicable). 2. Comparative tabulated format of the proposed and current in-process controls and the relevant changes. 3. Comparative batch analysis data of two production batches of the drug substance for all tests in the proposed specification (where applicable).

MiV-PA8	**Minor change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. The synthetic route remains the same (for example, intermediates remain the same). Refer to MaV-4 if the synthetic route is different. 3. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety. 4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 5. Specifications and stability performance of drug substance remain unchanged. 6. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	1. Drug Master File (DMF), or relevant updated drug substance (DS) section or equivalent/audit document. 2. Comparative tabulated format of the currently approved and new processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. A declaration from product registration holder or DMF holder where applicable that there is no change in qualitative and quantitative impurity profile or in physicochemical properties that the synthesis route remains the same and that the specifications of active substance or intermediate are unchanged. 5. Certificate of analysis for two batches of the drug substance. 6. A declaration from the product registration holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).

MiV-PA9	**Change of the specification of drug substance** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. This is only applicable for drug substances which are non-compendial and generic drug substances without European Pharmacopoeial Certificate of Suitability (CEP) 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. Test procedures remain the same, or changes in the test procedure are minor. 4. For (b) - applicable to non-compendial method only. 5. Refer to MiV-PA13 if this change resulted in revision of CEP. 6. For widening of specification limits and deletion of test parameter and limits of drug substance, please refer to MaV-7.
D	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the currently approved and revised specification of drug substance with changes highlighted. 3. Certificate of analysis and comparative batch analysis data of the drug substance for all tests in the new specification for two pilot or production scale batches. **(b) Addition of new test parameter and limits** In addition to the above documents, 4. Description of any new analytical method and summary of the validation data.

MiV-PA10	**Change of the test procedure of non-compendial drug substance**
C	1. Results of method validation show new test procedure to be at least equivalent to the former procedure. 2. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	1. Description of the analytical methodology, a summary of validation data, and comparative analytical results between the currently approved and proposed test (where applicable). 2. Specification of the drug substance.

MiV-PA11	Change of shelf-life or re-test period for drug substance
C	1. The stability studies must show compliance with specification. 2. No change in storage condition. 3. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	1. Specifications of the drug substance. 2. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested shelf-life or retest period.

MiV-PA12	Change of storage condition for drug substance
C	1. The stability studies must show compliance with specification. 2. No change in shelf-life/retest period. 3. Refer to MiV-PA13 if this change resulted in revision of CEP.
D	1. Specifications of the drug substance. 2. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested storage condition.

MiV-PA13	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
C	None
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. If this change is due to drug substance specification change, a declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action); (where applicable). 3. Specifications of drug substance (where applicable). 4. Certificate of analysis and results of batch analysis from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP (where applicable). 5. Additional data to address any relevant parameter(s) not addressed in the CEP such as stability data (S7), if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc), (where applicable). * If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.

MiV-PA14	Change of batch size of non-sterile drug product
C	1. The change does not affect consistency of production. 2. 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 at the proposed new batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 3. Release and end-of-shelf-life specifications of drug product remain unchanged. 4. This is applicable to change of batch size up to 10-fold compared to the currently registered batch size. 5. For change of batch size for sterile products, please refer to MaV-8 and for change of batch size more than 10-fold compared to the currently registered batch size, please refer MaV-9.
D	1. Comparative tabulated format of proposed and current batch manufacturing formula. 2. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed batch size should be provided upon submission. 3. Revised ACTD Section P3.1-3.4 (where applicable). 4. Release and shelf-life specifications of the drug product. 5. Certificate of analysis and 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. 6. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA15	Reduction or removal of overage
C	1. Changes of previously approved manufacturing overages of drug substance only. 2. Release and end-of-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. Certificate of analysis for two batches of the finished product. 4. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA16	**Qualitative and/or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline)** b) **For other non-critical dosage forms eg. oral liquid, external preparation.**
C	1. Replacement of an excipient with a comparable excipient of the same functional characteristics. 2. The dissolution profile of the proposed product is comparable to that of the current approved product. 3. 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 product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 4. Release and shelf-life specifications of the drug product remain unchanged 5. For qualitative or quantitative change of excipient for immediate release(Level 2 and 3 change as per SUPAC) and modified release oral dosage forms and other critical dosage forms, please refer to MaV-11. 6. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage form, please refer MiV-PA17.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration that the new excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 3. Justification for the change must be given by appropriate development of pharmaceutics. 4. 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). 5. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation. 6. Revised batch manufacturing formula. 7. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission (where applicable). 8. Revised ACTD Section P3.1-3.4 (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant veterinary authority of the issuing country (where applicable). 11. Release and shelf-life specifications. 12. Certificate of analysis and batch analysis data (in a comparative tabulated format) of drug product of at least two production (or one production batch and two pilot batches) according to currently approved and proposed product formula. 13. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 14. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies.

MiV-PA17	Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage form
C	1. The dissolution profile of the proposed product is comparable to that of the current approved product. 2. The product release and end-of-shelf-life specifications of the drug product remain unchanged except for the weight and/or size. 3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral solid dosage forms please refer to MaV-12.
D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. A declaration from product registration holder that the change does not interfere with the drug product release and shelf-life specifications test method. 3. Comparative tabulated format of current and proposed product and batch manufacturing formula. 4. Comparative dissolution profile data of at least one pilot/production batch of the drug product between the currently approved and proposed composition. 5. Revised release and shelf-life specifications of the drug product. 6. Certificate of analysis and batch analysis data for two production/pilot scale batches of the drug product. 7. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). Except for the change in weight and/or size of capsule shell, a letter of declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline on Stability Study of Drug Product have been started will suffice. 8. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV-PA18	**Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]**
C	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring/flavouring agents must not have been rejected for pharmaceutical use. 3. The release and shelf-life specifications of the drug product remain unchanged except for the change in colour/flavour.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration from product registration holder that the change does not interfere with the drug product release and shelf-life specifications test method. 3. A letter of commitment from product owner or product registration holder to inform users of the relevant change (where applicable). 4. Revised product formulation and batch manufacturing formula. 5. Qualitative and quantitative information of the current and proposed colouring/flavouring agent in a comparative table. 6. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant veterinary authority of the issuing country (where applicable). 7. Revised release and shelf-life specifications of the drug product. 8. Certificate of analysis and batch analysis data for two production/pilot scale batches of the drug product. 9. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA19	**Deletion of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent. 3. Amended relevant ACTD Section P (where applicable).

MiV-PA20	**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 e.g. new unqualified impurity; change in total impurity limits. 3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	1. Comparative tabulated format of currently approved and proposed in-process controls. 2. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 3. Revised in-process specifications together with justification and relevant process validation data. 4. Certificate of analysis and comparative batch analysis data of drug product of at least two production/pilot batches.

MiV-PA21	Minor change of the manufacturing process for non-sterile product
C	1. The same currently approved manufacturing site. 2. The overall manufacturing principle remains the same. 3. The change does not cause negative impact on the quality, safety and efficacy of the drug product. 4. The dissolution profile of the proposed product is comparable to that of the current approved product. 5. Release and end-of-shelf-life specifications of drug product remain unchanged. 6. For major change in the manufacturing process for drug product, please refer to MaV-10.
D	1. For solid oral dosage forms, comparative dissolution profile data of at least one representative production batch of the drug product between the currently approved and proposed solid oral dosage forms formulation. 2. Description of the new manufacturing process and technical justification for the change. 3. Comparative tabulated format of present and proposed process with changes highlighted. 4. For semi solid and suspension products, validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 5. Copy of currently approved release and shelf-life specifications. Or, alternately, copy of revised 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. 6. Certificate of analysis and batch analysis data (in a comparative tabulated format) of drug product on a minimum of one batch manufactured to both the currently approved and the proposed process; batch data on the next two full production batches should be made available upon request. 7. A declaration from the product registration holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Justification for not submitting a new bioequivalence study according to the current Bioavailability and Bioequivalence guidance (where applicable).

MiV-PA22	**Change of specifications of an excipient** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. Release and end-of-shelf-life specifications of drug product remain unchanged. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. Applicable to non compendial excipients. For compendial excipients, please refer to MiV-N10.
D	1. Description of new method and summary of analytical validation (applicable for addition of new parameter). 2. Comparative tabulated format of the current and revised specification of the excipient with changes highlighted. 3. Batch analysis data of the excipient for all tests in the new specification.
MiV-PA23	**Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure**
C	1. Appropriate method validation studies have been performed in accordance with the ASEAN Guidelines For Validation of Analytical Procedures. 2. Results of method validation show new test procedure to be at least equivalent to the former procedure. 3. There have been no changes of the total impurity limits. 4. Only applicable to the currently approved test parameters. 5. No new unqualified impurities are detected. 6. This applies for non-compendial excipient.
D	1. Description of the analytical methodology with a comparative tabulation of the changes. 2. For quantitative test change, comparative analytical validation results showing that the current and proposed tests are equivalent.

MiV-PA24	Change in the source of empty hard capsule
C	1. From TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa. 2. No change in the formulation and manufacturing process of drug product. 3. Not applicable to change from hard capsule to soft gel. 4. Excipient and finished product release and end of shelf-life specifications remain unchanged.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A letter of declaration from the manufacturer or the product registration holder stating that the material is purely of vegetable, animal or synthetic origin. 3. Technical specifications and composition of the empty hard capsule of the new source. 4. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued by a competent authority of the issuing country. 5. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product using hard capsule between the two sources (where applicable). 6. Certificate of Analysis of the empty hard capsule of the proposed new source. 7. Certificate of analysis and batch analysis data for two production/pilot scale batches of the drug product. 8. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA25	**Change of release and shelf-life specifications of the drug product** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. Applicable to non-compendial method. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. The test methods remain the same or changes in the test methods are minor. 4. If there are changes to the test procedure, MiV-PA28 is also applicable. 5. For widening of specification limits and deletion of test parameter and limits of drug product, please refer to MaV-7.
D	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 3. Certificate of analysis and comparative batch analysis data of the drug product for all tests in the new specification of at least two batches. **(b) Addition of new test parameter and limits** In addition to the above documents: 4. Description of any new method and summary of analytical validation data for non-compendial method. 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). (where applicable).

MiV-PA26	**Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking**
C	**(a) Except score/break-line** 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. **(b) On score/break-line** 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	**(a) Except score/break-line** 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A letter of commitment from product owner or product registration holder to inform users of the relevant change (where applicable). 3. Details and specifications of the proposed new inks (where applicable). 4. Detailed drawing or written description of the current and proposed imprint/bossing/markings. 5. Certificate of analysis of ink/printing material (pharmaceutical grade and of food grade) (where applicable). 6. Release and shelf-life specifications of the drug product with the new product description. **(b) On score/break-line** In addition to the above documents, 7. Justification for the change (i.e. change in dosing regimen). 8. Data on test of uniformity of the subdivided parts of the tablets at release should be submitted. 9. Certificate of analysis and batch analysis data of two production/pilot scale batches.

MiV-PA27	**Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass** **a) Immediate release oral solid dosage form, suppositories and pessaries** **b) Other than immediate release oral solid dosage forms, suppositories and pessaries.**
C	1. If appropriate, the dissolution profile of the proposed product is comparable to that of the current approved product. 2. Release and shelf-life specifications of the drug product remain unchanged except for dimension and/or shape.
D	**(a) Immediate release oral solid dosage form, suppositories and pessaries** 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. Comparative dissolution data on at least one pilot/production batch of the currently approved and proposed dimensions. 4. Data on test of uniformity of the subdivided parts of tablets at release as conformed to compendial requirement should be submitted (only applicable for drug product with score/break-line). 5. Release and shelf-life specifications of the drug product. **(b) Other than immediate release oral solid dosage forms, suppositories and pessaries** In addition to the above condition, 6. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV-PA28	**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. Results of method verification/validation show new test procedure to be at least equivalent to the former procedure. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	1. Justification for the proposed change. 2. Comparative tabulated format of the currently approved and proposed release and shelf-life specifications of the drug product. 3. Description of the analytical methodology. 4. Appropriate verification/validation data and comparative analytical results between the currently approved and proposed test. 5. Certificate of analysis and batch analysis data of the finished product of two production batches when made available.
MiV-PA29	**Change in primary packaging material for non-sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	1. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 2. The change includes the same packaging type (for example from blister to blister, from transparent glass bottle to amber glass bottle). 3. Release and end-of-shelf-life specifications of drug product remain unchanged. 4. For change in the primary packaging material for sterile drug product, please refer to MaV-13.
D	1. Revised drafts of the package insert incorporating the proposed variation (where applicable). 2. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 3. For semi-solid and liquid dosage forms, 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. Comparative tabulated format of the currently approved and proposed specifications of the primary packaging material (where applicable). 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MiV-PA30	**Replacement of a manufacturer for secondary packaging**
C	None
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized (accredited by the authority) for the packaging activity concerned such as a valid GMP certificate and/or CPP which covers the GMP certification. 3. Official letter from product owner authorizing the new manufacture or packager to perform secondary packaging (where applicable).
MiV-PA31	**Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product**
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. Change in the dimension of the primary packaging material (where applicable). 4. Release and shelf-life specifications of the drug product remain unchanged. 5. For change of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product, please refer to MaV-14.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification for the proposed pack size. 3. A declaration from the product registration holder that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action) (where applicable).

MiV-PA32	**Change of outer carton pack sizes for a drug product**
C	1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a drug product. 3. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of declaration from the product registration holder stating that no other changes except for the change of outer carton pack sizes for a drug product.
MiV-PA33	**Change in any part of the (primary)packaging material not in contact with the finished product formulation such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)**
C	1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
D	1. Amendment of the relevant section(s) of the dossier (presented in the ACTD format), including revised product labeling as appropriate.
MiV-PA34	**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 posology. 2. The new device is compatible with the drug product.
D	1. Revised draft of the package insert and labeling incorporating the proposed variation (where applicable). 2. Description of the device (including a drawing; where applicable). 3. The composition of the device material. Where applicable the materials should comply with the pharmacopoeia. 4. Justification that size and accuracy of the device are adequate for the posology as approved in the product labeling.

MiV-PA35	**Reduction of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For extension of shelf-life, please refer to MaV-16.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification letter for the change of shelf-life of the drug product (where applicable). 3. A letter of commitment from product owner or product registration holder to inform users of the relevant change (where applicable). 4. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate).
MiV-PA36	**Change of storage conditions of the drug product (Increasing from the current approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3. For change of storage condition (lowering from the current approved storage condition), please refer to MaV-17.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the change of storage condition. 3. Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product.

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 and MiV-PA2 if other parts 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 name of product registration holder to hold the product license. 3. Official document from the relevant authority confirming the change with the new name and/or address (where applicable).
MiV-N2	**Change of importer and/or store address** **a) Updating of importer and/or store address in the system*** **b) Updating of product labeling after approval is granted on MiV-N2(a)***
C	1. MiV-N2(b) is applicable only after the application to update the details of the importer and store address in the system has been approved.* 2. The manufacturer of the drug product remains the same. 3. The batch release site remains the same. 4. For change on the importer and/or store address in product labeling only. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	**a) Updating of importer and/or store address in the system*** 1. Valid business license.* **b) Updating of product labeling after approval is granted on MiV-N2(a)*** 1. 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 renaming of the company and updating of the address of product owner (for example: postal code, street name).
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A letter of declaration on the transfer of ownership between old product owner and new owner and counter-signed by both parties (where applicable). 3. Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 4. If the new product owner is not the manufacturer of the drug product, an official letter by the new product owner authorizing the manufacturer to manufacture the drug product on its behalf. 5. If the new product owner is not the manufacturer of the drug product, letter of acceptance from the manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect 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. The manufacturing site remains unchanged. 3. No other changes except for the change in ownership of manufacturer. 4. For change on the part of manufacturer in product labeling only. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of justification on the transfer of ownership such as a valid GMP certificate. 3. Official letter stating the transfer of ownership from old manufacturer to new manufacturer (where applicable). 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 that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of 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. The manufacturing site remains the same. 3. No other changes except for the change of the name and/or address of a manufacturer of the drug product. 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 manufacturer in product labeling only. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A valid GMP certificate, CPP which covers the GMP certification or official document from relevant authority confirming the new name and/or address. 3. Official letter from product owner authorizing the manufacturer with new name/address 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 and MiV-PA2 if other parts are involved.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A valid GMP certificate, CPP which covers the GMP certification or official document from relevant authority confirming the new name or address (where applicable). 3. Official letter from product owner authorizing company/manufacturer with new name/address responsible for batch release. 4. A declaration from the product registration holder that the change does not involve change of batch release site.

MiV-N7	**Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance**
C	1. The manufacturing site of the drug substance remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug substance.
D	1. Updated information of the manufacturer of the drug substance. 2. Official document/evidence when required.
MiV-N8	**Withdrawal/deletion of the alternative manufacturer(s) (for drug substance**
C	1. An alternative manufacturer is registered.
D	1. Reason for withdrawal/deletion.
MiV-N9	**Renewal of European Pharmacopoeial Certificate of Suitability (CEP)**
C	1. Only applicable if the renewal of CEP does not involve any variation.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM.
MiV-N10	**Change of specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium**
C	1. Applicable to compendial specifications only. 2. Change is made exclusively to comply with an update of the relevant monograph of the compendium.
D	1. Revised release and shelf-life specifications. 2. Tabulation of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 3. Certificate of analysis and batch analysis data of the drug product for all tests in the new specification of at least two batches. 4. Copy of the relevant monograph from the compendium.

MiV-N11	Deletion of pack size for a product
C	1. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling. 2. For addition of pack size for sterile and non-sterile products, please refer to MaV-14 and MiV-PA31 respectively. For change in the outer carton pack size, please refer to MiV-PA32. 3. For change on the part of pack size in product labeling only. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. 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 ACTD/ACTR Glossary

11. REFERENCES

1. ASEAN Variation Guideline for Pharmaceutical Products 2012
2. European Medicine Agency Variation Guideline, 2008
3. Communication from the Commission — Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products - Official Journal of the European Union (C 17/1 of 22.01.2010)
4. Commission Regulation (EC) No 1234/2008 Official Journal of the European Union (L334 of 12 December 2008)
5. WHO Guidance on Variations To A Prequalified Product Dossier, 2007
6. SUPAC Guideline Immediate Release Solid Oral Dosage Forms, Scale-up and Post-approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, November 1995
7. SUPAC-MR: Modified Release Solid, Oral Dosage Forms, Scale-Up and Post - approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, September 1997
8. WHO Technical Report Series, No. 953, 2009
9. WHO Quality Assurance of Pharmaceuticals – A Compendium of Guidelines and Related Materials – Volume 1
10. ASEAN Guideline on Stability Study of Drug Product, 22 February 2005
11. ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration
12. ASEAN Guideline for Validation of Analytical Procedures
13. ASEAN Guideline for the Conduct of Bioavailability and Bioequivalence Studies, 21 July 2004