



ASEAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

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ASEAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

1. INTRODUCTION

Throughout the life of a pharmaceutical product, the marketing authorization 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 the Drug Regulatory Authority.

This guidance document 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 ASEAN Variation Guideline concerns the variation applications submitted by the marketing authorization holder for pharmaceutical products for human use only and not including biologics.

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

Variation application is submitted along with a declaration letter undersigned by the Head of Regulatory Officer that declares there is no other change except for the proposed variation

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, the Drug Regulatory Authority shall acknowledge receipt of a valid notification.
Timeline for the Drug Regulatory Authority to acknowledge the variation notification	Within a duration subject to country specific proposal, following receipt of a valid notification.

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, the Drug Regulatory Authority 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, the Drug Regulatory Authority shall issue an approval for the proposed change.
Timeline for the Drug Regulatory Authority to evaluate the variation application	Within a duration subject to country specific proposal following receipt of a valid application.	Within a duration subject to country specific proposal following receipt of a valid application.

Implementation of the variation	Within a duration subject to country specific proposal after the marketing authorization holder has been informed of the approved variations.
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Note:

1. The 'timeline' and 'implementation of the variation' is subject to country specific proposals and be made publicly available.
2. The Drug Regulatory Authority reserves the right to re-categorize the application type, where deemed appropriate. Subject to country specific procedure, re-categorization may require the marketing authorization holder to withdraw the original application and resubmit a new application according to the correct category.

5. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

Changes requiring a new product registration may vary from country to country. Certain variations described in this guideline may require a new product registration in certain countries. Applicants are advised to check with individual country on the applicability of this variation guideline

6. OTHERS

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

6.2 Any variations not yet listed in this guideline should be justified and decided by the Drug Regulatory Authority. Appropriate reference can be made to:

- i. EMA Classification Guidance On Minor Variations of Type IA, Minor Variations of Type IB And Major Variations of Type II.
- ii. 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.
- iii. SUPAC-MR: Modified Release Solid, Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation.
- iv. WHO Guidance On Variations To A Prequalified Product Dossier.

6.3 The Drug Regulatory Authority reserves the right to request for additional information, when deemed necessary.

6.4 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	<ol style="list-style-type: none"> 1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), 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).
D	<ol style="list-style-type: none"> 1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justifications for the changes proposed. 4. Clinical expert reports and/or clinical trial reports (where applicable). 5. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 6. Approval letters from reference countries or country of origin which have approved the new indication or dosing regimen (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	<ol style="list-style-type: none"> 1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), 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	<ol style="list-style-type: none"> 1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justifications for the changes proposed and supporting clinical documents when applicable. 4. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where 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	<ol style="list-style-type: none"> 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-PA4.
D	<ol style="list-style-type: none"> 1. Complete ACTD section S1-S7, or both the open and closed part of the Drug Master File (closed part may be provided directly by manufacturer) with the Letter of Access or equivalent audit document/certification from reference country which is deemed appropriate by the Drug Regulatory Authority. 2. Comparative tabulated format of the currently registered and revised drug substance manufacture information (where applicable). 3. 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 marketing authorization 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.

MaV-4	Addition or replacement of the manufacturing site of the drug product
C	<ol style="list-style-type: none"> 1. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. 2. For addition or replacement of the company or party responsible for batch release, please refer to MiV-PA3. 3. If there are changes to the manufacturing process, MaV-9 is also applicable.
D	<ol style="list-style-type: none"> 1. Proof that the proposed site is appropriately authorized for the pharmaceutical form concerned such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. 2. 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 full production batches should be available upon request or reported if outside specifications (with proposed action). 3. 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). 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 6. Comparative dissolution profile data manufactured in the currently approved and proposed manufacturing site for oral solid dosage forms as per compendium and validated dissolution test method. 7. Product formula. 8. Release and shelf-life specifications of drug product. 9. Batch numbering system (where applicable). 10. Specification of drug substance. 11. Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 12. In case of a contract manufacturer, letter of appointment and letter of acceptance for the proposed site to manufacture the product and stating the types of activity to be performed (where applicable).

MaV-5	Addition or replacement of alternative site for primary packaging (direct contact with drug product)
C	<ol style="list-style-type: none"> 1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product).
D	<ol style="list-style-type: none"> 1. 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. 2. 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). 3. 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. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (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). 6. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable).

<p>MaV-6</p>	<p>Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]</p> <p>a) Specification limits are widened b) Deletion of test parameter and limits</p>
<p>C</p>	<ol style="list-style-type: none"> 1. Test procedures remain the same, or changes in the test procedure are minor. 2. Not applicable to compendial drug substances/drug products. 3. Refer to MiV-PA12 if this change resulted in revision of CEP. 4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
<p>D</p>	<p>(a) <u>Specification limits are widened</u></p> <ol style="list-style-type: none"> 1. Justification for change substantiated with scientific data to be provided. 2. Comparative tabulated format of the currently approved and revised specification of drug substance/drug product with changes highlighted. 3. Revised specification of drug substance / drug product. 4. Batch analysis data of the drug substance/drug product for all tests in the new specification for two pilot or production scale batches. 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). <p>(b) <u>Deletion of test parameter and limits</u></p> <p>In addition to the above documents except D5,</p> <ol style="list-style-type: none"> 6. Certificate of analysis of the drug substance/drug product for all tests with the new specification.

MaV-7	Change of batch size of sterile drug product
C	<ol style="list-style-type: none"> 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. The product formulation remains unchanged.
D	<ol style="list-style-type: none"> 1. 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. 2. Comparative tabulated format of proposed and currently approved batch manufacturing formula. 3. 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. 4. Release and shelf-life specifications of the drug product. 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-8	Change of batch size of non-sterile drug product
C	<ol style="list-style-type: none"> 1. 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-PA13. 2. The change does not affect consistency of production. 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	<ol style="list-style-type: none"> 1. 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. 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. 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. 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). 5. Release and shelf-life specifications of the drug product. 6. For oral solid dosage forms, comparative dissolution profile for at least one production batch (where applicable).

MaV-9	Major change in the manufacturing process for drug product
C	<ol style="list-style-type: none"> 1. The same currently approved manufacturing site. If there is a change in manufacturing site, MaV-4 is also applicable. 2. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 3. For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA20.
D	<ol style="list-style-type: none"> 1. Description of the new manufacturing process and technical justification for the change. 2. 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. 3. 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. 4. Comparative batch analysis data of drug product for a minimum of one production batch manufactured according to currently registered and proposed processes. 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). 6. 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. 7. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

<p>MaV-10</p>	<p>Qualitative or quantitative change of excipient</p> <p>a) For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)</p> <p>b) For modified release oral dosage forms</p> <p>c) For other critical dosage forms such as sterile preparations.</p>
<p>C</p>	<ol style="list-style-type: none"> 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. 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. 3. The dissolution profile of the proposed product is comparable to that of the current approved product. 4. Replacement of an excipient with a comparable excipient of the same functional characteristics. 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-PA15.
<p>D</p>	<ol style="list-style-type: none"> 1. Justification for the change must be given by appropriate development of pharmaceuticals. 2. 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). 3. 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). 4. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 5. 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). 6. Drug product release and shelf-life specifications. 7. 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. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (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. Revised batch manufacturing formula. 12. 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. 13. Revised ACTD Section P3.1 to P3.4 (where applicable).

MaV-11	Quantitative change in coating weight of tablets or weight and/or size of capsule shell-for modified release oral dosage form
C	<ol style="list-style-type: none"> 1. The dissolution profile of the proposed product is comparable to that of the current approved product. 2. The product release and shelf-life specifications have only been updated in respect of product description (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-PA16.
D	<ol style="list-style-type: none"> 1. Comparative dissolution profile data of at least one pilot/production batch of the drug product between the currently approved and proposed composition. 2. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable). 3. Revised release and shelf-life specifications of the drug product. 4. A declaration that the change does not interfere with the drug product release and shelf-life specifications test method. 5. Current and proposed product and batch manufacturing formula. 6. Revised draft of product label incorporating the proposed change (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-12	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	<ol style="list-style-type: none"> 1. Release and shelf-life specifications of the drug product remain unchanged. 2. For change in the primary packaging material for non-sterile drug product, please refer to MiV-PA28.
D	<ol style="list-style-type: none"> 1. 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. 2. 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). 3. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 4. Comparative tabulated format of specifications of the proposed and current primary packaging material. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 6. Revised ACTD Sections P3 and/or P7 (where applicable). 7. Appropriate scientific data on new packaging (comparative data on permeability, e.g. moisture, O₂, CO₂).

MaV-13	Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product
C	<ol style="list-style-type: none"> 1. Release and shelf-life specifications of the drug product are not affected, except pack size/fill volume specification. 2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. The packaging material remains the same. 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-PA30.
D	<ol style="list-style-type: none"> 1. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. Validation data of the manufacturing process, sterilization and container closure system (where applicable). 3. 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). 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MaV-14	Inclusion or replacement of the solvent/diluent for the drug product
C	<ol style="list-style-type: none"> 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-PA18. 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-15/MiV-PA34 and/or MaV-16/MiV-PA35 (where applicable)
D	<ol style="list-style-type: none"> 1. In addition to section P for the solvent/diluent and reconstitution stability data, section S is required (where applicable). 2. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 3. Batch numbering system (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. Revised artworks for the drug product labels incorporating the changes. 6. A declaration from the marketing authorization holder that the release and shelf-life specifications of drug product are not affected.

MaV-15	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	<ol style="list-style-type: none"> 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-PA34.
D	<ol style="list-style-type: none"> 1. 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 <ol style="list-style-type: none"> 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). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf-life of the drug product (where applicable). 4. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).
MaV-16	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	<ol style="list-style-type: none"> 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-PA35.
D	<ol style="list-style-type: none"> 1. 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. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Technical justification for the change.

8. MINOR VARIATION PRIOR APPROVAL

Minor Variation (MiV-PA)	
Prior Approval	
MiV-PA1	Change of drug product name
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Official letter from product owner or marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 2. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the drug product name change. 3. Revised draft package insert and labeling incorporating the proposed variation. 4. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 5. Trademark certificate (where applicable).
MiV-PA2	Change of product labeling (in accordance to country specific labeling requirement)
	<p>Includes:</p> <ol style="list-style-type: none"> 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 labelling. d) Tightening of product's target population. e) Deletion of indication. f) Change of distributor's details.
C	<ol style="list-style-type: none"> 1. Product labeling refers to Package Insert (PI), Patient Information Leaflet (PIL), 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 labelling, please refer to MaV-2.
D	<ol style="list-style-type: none"> 1. Current approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Letter of declaration from the marketing authorization 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	Addition or replacement of the company or party responsible for batch release
C	<ol style="list-style-type: none"> 1. Only applicable for batch release. 2. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed. 3. The manufacturer of the drug product remains the same.
D	<ol style="list-style-type: none"> 1. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (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. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV-PA4	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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. 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. 3. 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. 4. A letter of commitment from marketing authorization 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.

MiV-PA5	Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. The change does not affect the reproducibility of the process. 2. Specifications of drug substance remain unchanged. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	<ol style="list-style-type: none"> 1. 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). 2. 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. 3. Amended relevant ACTD Section S (where applicable).
MiV-PA 6	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	<ol style="list-style-type: none"> 1. In-process limits are tightened or addition of new tests. 2. Refer to MiV-PA12 if this change resulted in revision of CEP. 3. The change is not a consequence of any commitment from previous assessments to review specification limits. 4. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	<ol style="list-style-type: none"> 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-PA7	Change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. Specifications and stability performance of drug substance remain unchanged. 3. The synthetic route remains the same (for example, intermediates remain the same). 4. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety. 5. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 6. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	<ol style="list-style-type: none"> 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. Certificate of analysis for two batches of the drug substance. 4. Batch analysis data (in a comparative tabulated format) of drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the currently approved and proposed processes. 5. A letter of declaration from marketing authorization holder stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies. 6. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed or if there is any change to the specification (for example, tightening), the texts of the currently approved and proposed specifications should be provided (in a comparative tabulated format where possible). 7. A declaration from the marketing authorization 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. For sterile drug substance, process validation report (where applicable).

MiV-PA8	Change of the specification of drug substance a) Specification limits are tightened b) Addition of new test parameter and limits
C	<ol style="list-style-type: none"> 1. This is only applicable for drug substances which are non-compendial and generic drug substances without European Pharmacopoeial Certificate of Suitability (CEP) 2. For (b) - applicable to non-compendial method only. 3. Refer to MiV-PA12 if this change resulted in revision of CEP. 4. For widening of specification limits and deletion of test parameter and limits of drug substance, please refer to MaV-6. 5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 6. Test procedures remain the same, or changes in the test procedure are minor.
D	<p><u>(a) Specification limits are tightened</u></p> <ol style="list-style-type: none"> 1. Comparative tabulated format of the currently approved and revised specification of drug substance with changes highlighted. 2. Comparative batch analysis data of the drug substance for all tests in the new specification for two pilot or production scale batches. 3. Technical justification for the change. <p><u>(b) Addition of new test parameter and limits</u> In addition to the above documents,</p> <ol style="list-style-type: none"> 4. Description of any new analytical method and summary of the validation data.
MiV-PA9	Change of the test procedure of non-compendial drug substance
C	<ol style="list-style-type: none"> 1. Results of method validation show new test procedure to be at least equivalent to the former procedure. 2. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	<ol style="list-style-type: none"> 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-PA 10	Change of shelf-life or re-test period for drug substance
C	<ol style="list-style-type: none"> 1. The stability studies must show compliance with specification. 2. No change in storage condition. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	<ol style="list-style-type: none"> 1. 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. 2. Specifications of the drug substance.
MiV-PA 11	Change of storage condition for drug substance
C	<ol style="list-style-type: none"> 1. The stability studies must show compliance with specification. 2. No change in shelf-life/retest period. 3. Refer to MiV-PA12 if this change resulted in revision of CEP.
D	<ol style="list-style-type: none"> 1. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested storage condition. 2. Specifications of the drug substance.
MiV-PA 12	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
C	None
D	<ol style="list-style-type: none"> 1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. Specifications of drug substance (where applicable). 3. 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). 4. 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), if applicable. 5. If this change is due to drug substance specification change, a declaration from the applicant that the relevant stability studies of the <u>drug product</u> 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). <p>*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.</p>

MiV-PA13	Change of batch size of non-sterile drug product
C	<ol style="list-style-type: none"> 1. This is applicable to change of batch size up to 10-fold compared to the currently registered batch size. 2. The change does not affect consistency of production. 3. Release and end-of-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 at the proposed new batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 5. For change of batch size for sterile products, please refer to MaV-7 and for change of batch size more than 10-fold compared to the currently registered batch size, please refer MaV-8.
D	<ol style="list-style-type: none"> 1. 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. 2. Comparative tabulated format of proposed and current batch manufacturing formula. 3. 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. 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). 5. Release and shelf-life specifications of the drug product. 6. Revised ACTD Section P3.1-3.4 (where applicable).
MiV-PA14	Reduction or removal of overage
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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– PA15	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	<ol style="list-style-type: none"> 1. Release and shelf-life specifications of the drug product remain unchanged 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 of the proposed product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 3. The dissolution profile of the proposed product is comparable to that of the current approved product. 4. Replacement of an excipient with a comparable excipient of the same functional characteristics (where applicable). 5. For qualitative or quantitative change of excipient for immediate release and modified release oral dosage forms and other critical dosage forms, please refer to MaV-10.
D	<ol style="list-style-type: none"> 1. Justification for the change must be given by appropriate development of pharmaceuticals. 2. 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). 3. 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. 4. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies. 5. 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). 6. Release and shelf-life specifications. 7. 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. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (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. Revised batch manufacturing formula. 12. A declaration that the new excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 13. Revised ACTD Section P3.1-3.4 (where applicable). 14. 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).

MiV– PA16	Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage form
C	<ol style="list-style-type: none"> 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-11.
D	<ol style="list-style-type: none"> 1. Comparative dissolution profile data of at least one pilot/production batch of the drug product between the currently approved and proposed composition. 2. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable). 3. Revised release and shelf-life specifications of the drug product. 4. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 5. Comparative tabulated format of current and proposed product and batch manufacturing formula. 6. Revised draft of product label incorporating the proposed change (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). 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.

MiV-PA17	Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Qualitative and quantitative information of the current and proposed colouring/flavouring agent in a comparative table. 2. Revised product formulation and batch manufacturing formula. 3. Revised release and shelf-life specifications of the drug product. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (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). 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. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 8. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).
MiV-PA18	Deletion of the solvent/diluent for the drug product
C	<ol style="list-style-type: none"> 1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product.
D	<ol style="list-style-type: none"> 1. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Amended relevant ACTD Section P (where applicable).

MiV-PA19	Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)
C	<ol style="list-style-type: none"> 1. Release and shelf-life specifications of drug product remain unchanged. 2. The change is not a consequence of any commitment from previous assessments to review specification limits. 3. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 4. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	<ol style="list-style-type: none"> 1. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 2. Revised in-process specifications together with justification and relevant process validation data. 3. Comparative batch analysis data of drug product of at least two production/pilot batches. 4. Comparative tabulated format-change of the in-process controls.

MiV-PA20	Minor change of the manufacturing process for non-sterile product
C	<ol style="list-style-type: none"> 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. Release and end-of-shelf-life specifications of drug product remain unchanged. 5. The dissolution profile of the proposed product is comparable to that of the current approved product. 6. For major change in the manufacturing process for drug product, please refer to MaV-9.
D	<ol style="list-style-type: none"> 1. Description of the new manufacturing process and technical justification for the change. 2. 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. 3. 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. 4. 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. 5. Justification for not submitting a new bioequivalence study according to the current Bioavailability and Bioequivalence guidance (where applicable). 6. 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 marketing authorization 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. Comparative tabulated format of present and proposed process with changes highlighted.

MiV-PA21	Change of specifications of an excipient a) Specification limits are tightened b) Addition of new test parameter and limits
C	<ol style="list-style-type: none"> 1. Applicable to non compendial excipients. For compendial excipients, please refer to MiV-N9. 2. Release and end-of-shelf-life specifications of drug product remain unchanged. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
D	<ol style="list-style-type: none"> 1. Comparative tabulated format of the current and revised specification of the excipient with changes highlighted. 2. Batch analysis data of the excipient for all tests in the new specification. 3. Description of new method and summary of analytical validation (applicable for addition of new parameter).
MiV-PA22	Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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-PA23	Change in the source of empty hard capsule
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. 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). 2. Certificate of Analysis of the empty hard capsule of the proposed new source. 3. Technical specifications and composition of the empty hard capsule of the new source. 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). 5. 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. 6. A letter of declaration from the manufacturer or the marketing authorization holder of the material that it is purely of vegetable, animal or synthetic origin.
MiV-PA24	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	<ol style="list-style-type: none"> 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-PA27 is also applicable. 5. For widening of specification limits and deletion of test parameter and limits of drug product, please refer to MaV-6.
D	<p><u>(a) Specification limits are tightened</u></p> <ol style="list-style-type: none"> 1. Comparative tabulated format of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 2. Comparative batch analysis of the drug product for all tests in the new specification of at least two batches. 3. Technical justification for the change. <p><u>(b) Addition of new test parameter and limits</u></p> <p>In addition to the above documents:</p> <ol style="list-style-type: none"> 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-PA25	Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking
C	<p><u>(a) Except score/break-line</u></p> <ol style="list-style-type: none"> 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. <p><u>(b) On score/break-line</u> In addition to the above conditions,</p> <ol style="list-style-type: none"> 4. Score/break-line is not meant for cosmetic purpose. 5. Applicable to addition or removal of score/break-line.
D	<p><u>(a) Except score/break-line</u></p> <ol style="list-style-type: none"> 1. Details and specifications of the proposed new inks (where applicable). 2. Certificate of analysis of ink/printing material (pharmaceutical grade and of food grade) (where applicable). 3. Detailed drawing or written description of the current and proposed imprint/bossing/markings. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 5. Release and shelf-life specifications of the drug product with the new product description. 6. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). <p><u>(b) On score/break-line</u> In addition to the above documents,</p> <ol style="list-style-type: none"> 7. Justification for the change (i.e. change in dosing regimen). 8. Certificate of analysis of two production/pilot scale batches. 9. Data on test of content uniformity of the subdivided parts of the tablets at release should be submitted.

<p>MiV-PA26</p>	<p>Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass</p> <p>a) Immediate release oral solid dosage form, suppositories and pessaries</p> <p>b) Other than immediate release oral solid dosage forms, suppositories and pessaries.</p>
<p>C</p>	<ol style="list-style-type: none"> 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.
<p>D</p>	<p><u>(a) Immediate release oral solid dosage form, suppositories and pessaries</u></p> <ol style="list-style-type: none"> 1. Detailed drawing or written description of the current and proposed appearance. 2. Release and shelf-life specifications of the drug product. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Comparative dissolution data on at least one pilot/production batch of the currently approved and proposed dimensions. 5. Data on test of content 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). <p><u>(b) Other than immediate release oral solid dosage forms, suppositories and pessaries</u></p> <p>In addition to the above condition,</p> <ol style="list-style-type: none"> 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-PA27	Change in the test procedure of the drug product (including replacement or addition of a test procedure)
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Description of the analytical methodology. 2. Appropriate verification/validation data and comparative analytical results between the currently approved and proposed test. 3. Certificate of analysis of the finished product of two production batches when made available. 4. Justification for the proposed change. 5. Comparative tabulated format-of the currently approved and proposed release and shelf-life specifications of the drug product.
MiV-PA28	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	<ol style="list-style-type: none"> 1. Release and end-of-shelf-life specifications of drug product remain unchanged. 2. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 3. The change only concerns the same packaging type (for example from blister to blister). 4. For change in the primary packaging material for sterile drug product, please refer to MaV-12.
D	<ol style="list-style-type: none"> 1. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 2. For semisolid 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). 3. Comparative tabulated format of the currently approved and proposed specifications of the primary packaging material (where applicable). 4. Revised drafts of the package insert incorporating the proposed variation (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-PA 29	Addition or replacement of a manufacturer for secondary packaging
C	None
D	<ol style="list-style-type: none"> 1. 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. 2. Official letter from product owner authorizing the new manufacture or packager to perform secondary packaging (where applicable). 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV-PA30	Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product
C	<ol style="list-style-type: none"> 1. Release and shelf-life specifications of the drug product remain unchanged. 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. 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-13. 5. The change only concerns the same packaging type and material.
D	<ol style="list-style-type: none"> 1. Justification for the proposed pack size. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. A declaration from the marketing authorization 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-PA31	Change of outer carton pack sizes for a drug product
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter of declaration from the marketing authorization holder stating that no other changes except for the change of outer carton pack sizes for a drug product.
MiV-PA 32	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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Amendment of the relevant section(s) of the dossier (presented in the ACTD format), including revised product labeling as appropriate.
MiV-PA33	Addition or replacement of measuring device for oral liquid dosage forms and other dosage form
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Description of the device (including a drawing; where applicable). 2. The composition of the device material. Where applicable the materials should comply with the pharmacopoeia. 3. Justification that size and accuracy of the device are adequate for the posology as is approved in the product labeling. 4. Revised draft of the package insert and labeling incorporating the proposed variation (where applicable).

MiV-PA34	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	<ol style="list-style-type: none"> 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-15.
D	<ol style="list-style-type: none"> 1. 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 <ol style="list-style-type: none"> 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). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf-life of the drug product (where applicable). 4. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable).
MiV-PA35	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	<ol style="list-style-type: none"> 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-16..
D	<ol style="list-style-type: none"> 1. 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. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Technical justification for the change of storage condition.

9. MINOR VARIATION NOTIFICATION

Minor Variation (MiV-N)	
Notification	
MiV-N1	<p>Change in name and/or address (for example: postal code, street name) of the marketing authorization holder</p> <p>[Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]</p>
C	<ol style="list-style-type: none"> 1. The name change refers to the renaming of a company or organization. 2. The change does not include transfer of marketing authorization to another company. 3. For change on the part of marketing authorization holder in product labelling only. Please refer to MaV-2 and MiV-PA3 if other parts are involved.
D	<ol style="list-style-type: none"> 1. Letter by the product owner authorizing the new name of marketing authorization holder to hold the product license. 2. Official document from the relevant authority confirming the change with the new name and/or address. 3. Revised draft package insert and labeling incorporating the proposed variation (where applicable).
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MiV- N2	<p>Change of product owner</p>
C	<ol style="list-style-type: none"> 1. The marketing authorization holder remains the same. 2. The manufacturing site remains the same.
D	<ol style="list-style-type: none"> 1. Declaration on the transfer of ownership between old product owner and new owner. 2. Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 3. 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. 4. 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. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

MiV- N3	Change in ownership of manufacturer [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	<ol style="list-style-type: none"> 1. The manufacturing site remains unchanged. 2. No other changes except for the change in ownership of manufacturer.
D	<ol style="list-style-type: none"> 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 that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product. 5. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
MiV- N4	Change of the name or address (for example: postal code, street name) of the manufacturer of drug product [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	<ol style="list-style-type: none"> 1. The manufacturing site remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3. 3. No other changes except for the change of the name and/or address of a manufacturer of the drug product.
D	<ol style="list-style-type: none"> 1. Official letter from product owner authorizing the manufacturer with new name/address to manufacture the drug product. 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. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

MiV-N5	Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	<ol style="list-style-type: none"> 1. The manufacturer of the drug product remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3. 3. The batch release site remains the same.
D	<ol style="list-style-type: none"> 1. Official letter from product owner authorizing company/manufacturer with new name/address responsible for batch release. 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. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. A declaration from the marketing authorization holder that the change does not involve a change of batch release site.
MiV-N6	Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance
C	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Updated information of the manufacturer of the drug substance. 2. Official document/evidence when required.
MiV-N7	Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)
C	<ol style="list-style-type: none"> 1. An alternative manufacturer is registered.
D	<ol style="list-style-type: none"> 1. Reason for withdrawal/deletion.

MiV-N8	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-N9	Change of release and shelf-life specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium
C	<ol style="list-style-type: none"> 1. Applicable to compendial specifications only. 2. Change is made exclusively to comply with an update of the relevant monograph of the compendium.
D	<ol style="list-style-type: none"> 1. Tabulation of the current and revised release and shelf-life specifications of the drug product with changes highlighted. 2. Batch analysis of the drug product for all tests in the new specification of at least two batches. 3. Revised release and shelf-life specifications.
MiV-N10	Deletion of pack size for a product
C	<ol style="list-style-type: none"> 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-13 and MiV-PA30 respectively. For change in the outer carton pack size, please refer to MiV-PA31.
D	<ol style="list-style-type: none"> 1. Reason for deletion. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

10. GLOSSARY

Refer to ACTD/ACTR Glossary

11. REFERENCES

1. European Medicine Agency Variation Guideline, 2008
2. 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)
3. Commission Regulation (EC) No 1234/2008 Official Journal of the European Union (L334 of 12 December 2008)
4. WHO Guidance on Variations To A Prequalified Product Dossier, 2007
5. 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
6. 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
7. WHO Technical Report Series, No. 953, 2009
8. WHO Quality Assurance of Pharmaceuticals – A Compendium of Guidelines and Related Materials – Volume 1
9. ASEAN Guideline on Stability Study of Drug Product, 22 February 2005
10. ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration
11. ASEAN Guideline for Validation of Analytical Procedures
12. ASEAN Guideline for the Conduct of Bioavailability and Bioequivalence Studies, 21 July 2004