ASEAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

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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 the valid notification.
Anticipated implementation time	Implementation timeline is subject to country specific proposal & existing procedures
Timeline for the Drug Regulatory Authority to acknowledge the variation notification	Within a duration subject to country specific proposal

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.

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 Post-Approval 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	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	1. Approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC/PIL 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 proposed 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), 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	1. Approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC/PIL 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	**Addition or replacement 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-PA4.
D	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 approved and proposed drug substance manufacture information (where applicable). 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. 4. A letter of commitment from marketing authorization holder to conduct long term 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	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/MiV-PA20/MiV-N11 is also applicable.
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 pharmaceutical form concerned such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. 3. Batch numbering system (where applicable). 4. 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). 5. Specification of drug substance. 6. Product formula and/or batch manufacturing formula. 7. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing site for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines. 8. 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. 9. Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 10. Release and shelf-life specifications of drug product. 11. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) 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 approved site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action). 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-5	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product, please refer to MiV-PA36.
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. 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-6	**Change of the specification of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available] and/or drug product** **a) Specification limits are widened** **b) Deletion of test parameter and limits**
C	1. Test procedures remain unchanged, 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; unless otherwise justified. 4. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	**(a) <u>Specification limits are widened</u>** 1. Revised specification of drug substance / drug product. 2. Comparative tabulated format of the approved and proposed specification of drug substance/drug product with changes highlighted. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of the drug substance/drug product for all tests in the proposed specification for two pilot or production scale batches. 4. Justification for change substantiated with scientific data to be provided. 5. For change of drug substance specification that involved stability-indicating parameters: stability data of drug substances and report if any results fall outside re-test/shelf-life specifications (with proposed action). 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). **(b) <u>Deletion of test parameter and limits</u>** All of the above documents except D5 & D6.
MaV-7	**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 approved and proposed 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/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to 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-8	**Change of batch size of non-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. 5. This is applicable to change of batch size more than 10-fold compared to the approved batch size. For change of batch size up to 10-fold compared to the approved batch size, please refer MiV-PA13.
D	1. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed batch size for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines (where applicable). 2. Comparative tabulated format of approved and proposed 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/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to approved and proposed batch sizes and letter of undertaking to submit batch analysis 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-9	**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 manufacturing site remains unchanged. If there is a change in manufacturing site, MaV-4 is also applicable. 3. For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA20/MiV-N11.
D	1. Description of the proposed manufacturing process and technical justification for the change. 2. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines. 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 approved release and shelf-life specifications. Or, alternatively, copy of proposed release and shelf-life specifications that supports that the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product for a minimum of one production batch manufactured according to approved 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-10	**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 unchanged, excluding product description except for update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 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 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 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-PA15.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration that the proposed 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 approved and proposed 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 pilot/production batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms as US FDA SUPAC IR or MR Guidelines (where applicable). 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. 8. Revised ACTD Section P3.1 to P3.4 (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 authority of the issuing country and/or documentary evidence from the supplier (where applicable). 11. Drug product release and shelf-life specifications. 12. Certificate of analysis and/or 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 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 ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 15. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).

MaV-11	**Quantitative change in coating of tablets 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 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 of tablets or weight and/or size of capsule shell for immediate release oral solid dosage forms, please refer to MiV-PA16.
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 manufactured in the approved and proposed composition for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines (where applicable). 4. Approved and proposed product and batch manufacturing formula. 5. Revised release and shelf-life specifications of the drug product. 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 the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

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	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	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Appropriate scientific data on proposed 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 approved and proposed 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-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	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 unchanged. 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-PA30.
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-14	**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-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	1. Revised drafts of the package insert and labeling incorporating the proposed variation. 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. A declaration from the marketing authorization holder that the release and shelf-life specifications of drug product are not affected. 6. In addition to section P for the solvent/diluent and reconstitution stability data, section S is also required (where applicable).

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	1. For (a) & (b) - The studies must show conformance to the approved shelf-life specification. 2. For (c)–The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For reduction of shelf-life, please refer to MiV-PA34.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change (where applicable). 3. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 4. Results of appropriate long term stability studies covering the duration of proposed shelf-life 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-16	**Change of storage conditions of the drug product (Lowering from the 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 approved shelf-life specification. 2. For (c) – The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For change of storage condition (Increasing from the approved storage condition), please refer to MiV-PA35.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long term stability studies covering the duration of approved shelf-life (at proposed storage condition) of the product and 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 microbiological testing should be included (where appropriate).

MaV-17	**Major change in the manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. The synthetic route is different with potential change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. Refer to MiV-PA7 if the synthetic route remains unchanged. 2. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety; unless otherwise justified. 3. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 4. Stability performance of drug substance remain unchanged. 5. If there are changes to the specification of drug substance, MiV-PA8 is also applicable.
D	1. Relevant 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 approved and proposed processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. 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. 5. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed (where applicable). 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed process. 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 will be started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Certificate of analysis and/or 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 approved and proposed processes.

8. MINOR VARIATION PRIOR 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 proposed 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 marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 4. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the change of drug product name. 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), 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 labeling, please refer to MaV-2.
D	1. 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	1. Only applicable for batch release. 2. The manufacturer of the drug product remains unchanged. 3. Method transfer from the 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-PA4	**Addition or replacement 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 marketing authorization holder to conduct long term 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/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. 4. If the re-test period is not stated in the CEP, long term 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-PA5	**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. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
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/or 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 approved and proposed batch sizes. Batch analysis 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-PA6	**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 new tests are added. 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. 5. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
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 approved and proposed in-process controls and the relevant changes. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of two production batches of the drug substance for all tests in the proposed specification (where applicable).

MiV-PA7	**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 unchanged (for example, intermediates remain unchanged). Refer to MaV-17 if 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.
D	1. Drug Master File (DMF), or relevant updated drug substance (DS) section or equivalent/audit document. 2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. 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. 5. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for two batches of the drug substance. 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. Certificate of analysis and/or 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 approved and proposed processes.

MiV-PA8	**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; unless otherwise justified. 3. Test procedures remain unchanged, or changes in the test procedure are minor. 4. For (b) - applicable to non-compendial method only. 5. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12. 6. For widening of specification limits and deletion of test parameter and limits of drug substance, please refer to MaV-6.
D	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed specification of drug substance with changes highlighted. 3. Comparative batch analysis data of the drug substance for all tests in the proposed 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. 5. For change of drug substance specification that involved stability-indicating parameters: stability data of drug substances and report if any results fall outside re-test/shelf-life specifications (with proposed action).

MiV-PA9	**Change of the test procedure of non-compendial drug substance**
C	1. Results of method validation show proposed test procedure to be at least equivalent to the approved procedure. 2. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. Description of the proposed test procedure with a summary of change(s) from the approved test procedure. 2. Appropriate verification/validation data of the proposed test procedure. 3. Specification of the drug substance. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed test procedure.

MiV-PA10	**Change of shelf-life or re-test period for drug substance**
C	1. The stability studies must show compliance with specification. 2. There is no change in storage condition. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
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 proposed shelf-life or retest period.

MiV-PA11	**Change of storage condition for drug substance**
C	1. The stability studies must show compliance with specification. 2. There is no change in shelf-life/re-test period. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
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 proposed storage condition.

MiV-PA12	**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). 3. Specifications of drug substance (where applicable). 4. Certificate of analysis and/or results of batch analysis data (in a comparative tabulated format) 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), if 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-PA13	**Change of batch size of non-sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains 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 at the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 4. Release and shelf-life specifications of drug product remain unchanged. 5. This is applicable to change of batch size up to 10-fold compared to the approved batch size. 6. 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 approved batch size, please refer MaV-8.
D	1. Comparative tabulated format of approved and proposed 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/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to approved and proposed batch sizes and letter of undertaking to submit batch analysis 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).
MiV-PA14	**Reduction or removal of overage**
C	1. Changes of approved manufacturing overages of drug substance only. 2. Release and shelf-life specifications of drug product remain unchanged.
D	1. Justification for the change. 2. Comparative tabulated format of approved and proposed batch manufacturing formula. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) 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	1. Replacement of an excipient with a comparable excipient of the same functional characteristics (where applicable). 2. The dissolution profile of the proposed product is comparable to that of the 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; except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 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-10.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration that the proposed 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 approved and proposed 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 pilot/production batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines (where applicable). 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 authority of the issuing country and/or documentary evidence from the supplier (where applicable). 11. Release and shelf-life specifications. 12. Certificate of analysis and/or 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 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. 15. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).

MiV-PA16	**Quantitative change in coating of tablets 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 approved product. 2. The product release and shelf-life specifications of the drug product remain unchanged except for the weight and/or size. 3. For quantitative change in coating of tablets and/or size of capsule shell for modified release oral solid dosage forms please refer to MaV-11.
D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. A declaration from marketing authorization holder that the change does not interfere with the drug product release and shelf-life specifications test method. 3. Comparative tabulated format of approved and proposed product and batch manufacturing formula. 4. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines (where applicable). 5. Revised release and shelf-life specifications of the drug product. 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). 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. 7. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV-PA17	**Change of the colouring agent/flavouring agent/capsule shell colour of the product**
C	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring agents /flavouring agents/capsule shell must not have been rejected for pharmaceutical use. 3. The release and shelf-life specifications of the drug product remain unchanged, except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 4. If there is a change to the source of capsule shell, MiV-PA23 is also applicable.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. A declaration that the proposed colouring agent/flavouring agent/capsule shell colour does not interfere with the drug product release and shelf-life specifications test method. 3. A letter of commitment from product owner or marketing authorization 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 approved and proposed colouring agent/flavouring agent/capsule shell colour 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 authority of the issuing country and/or documentary evidence from the supplier (where applicable). 7. Revised release and shelf-life specifications 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). 9. Certificate of Analysis of proposed coloring agent/flavoring agent/capsule shell (where applicable).

MiV-PA18	**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-PA19	**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 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	1. Comparative tabulated format of 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. Proposed in-process specifications together with justification and relevant process validation data. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production/pilot batches.

MiV-PA20	**Minor change of the manufacturing process for non-sterile product**
C	1. The manufacturing site remains unchanged. 2. The overall manufacturing principle remains unchanged. 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 approved product. 5. Release and shelf-life specifications of drug product remain unchanged. 6. For major change in the manufacturing process for drug product, please refer to MaV-9 7. For minor change in the manufacturing process of an immediate release solid oral dosage form, semi solid or oral solutions, please refer to MiV-N11
D	1. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines (where applicable). 2. Description of the proposed manufacturing process and technical justification for the change. 3. Comparative tabulated format of approved 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 approved release and shelf-life specifications. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one batch manufactured to both the approved and the proposed process; batch analysis 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. Justification for not submitting a new bioequivalence study according to the current Bioavailability and Bioequivalence guidance (where applicable).

MiV-PA21	**Change of specifications of non compendial excipient** **a) Specification limits are tightened/widened** **b) Addition/replacement/deletion of test parameter and limits**
C	1. Release and 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; unless otherwise justified. 3. Applicable to non compendial excipients. For compendial excipients, please refer to MiV-N9.
D	1. Description of new method and summary of analytical validation (applicable for addition/replacement of new parameter). 2. Comparative tabulated format of the approved and proposed specification of the excipient with changes highlighted. 3. Certificate of analysis of the excipient for all tests in the proposed specification.

MiV-PA22	**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 proposed test procedure to be at least equivalent to the approved procedure. 3. The change does not result in changes of the total impurity limits. 4. Only applicable to the approved test parameters and limits. For addition/replacement/deletion of test parameter and limits, please refer to MiV-PA21/MiV-N9. 5. No new unqualified impurities are detected. 6. This applies for non-compendial excipient. For compendial excipients, please refer to MiV-N9.
D	1. Description of the proposed analytical methodology with a comparative tabulation of the changes. 2. For quantitative test change, comparative analytical validation results showing that the approved and proposed tests are equivalent.

MiV-PA23	**Change in the source of empty hard capsule**
C	1. The change is from TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa. 2. The formulation and manufacturing process of drug product remain unchanged. 3. Not applicable to change from hard capsule to soft gel. 4. Excipient and finished product release and shelf-life specifications remain unchanged.
D	1. 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. 2. Technical specifications and composition of the empty hard capsule of the proposed source. 3. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant authority of the issuing country and/or documentary evidence from the supplier. 4. Comparative dissolution profile data of at least one pilot/production batch of the drug product using hard capsule between the two sources for oral solid dosage as per US FDA SUPAC IR or MR Guidelines (where applicable). 5. Certificate of Analysis of the empty hard capsule of the proposed source. 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-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	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; unless otherwise justified. 3. The test methods remain unchanged 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	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed release and shelf-life specifications of the drug product with changes highlighted. 3. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the drug product for all tests in the proposed 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-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	**(a) Except score/break-line** 1. Proposed 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 marketing authorization holder to inform users of the relevant change (where applicable). 3. Details and specifications of the proposed inks (where applicable). 4. Detailed drawing or written description of the approved 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 proposed 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 as conformed to compendial requirement. 9. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the drug product of two production/pilot scale batches.

MiV-PA26	**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 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 approved and proposed appearance. 3. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed dimensions/shape for oral solid dosage forms as per US FDA SUPAC IR or MR Guidelines (where applicable). 4. For scored tablets, data on test of uniformity of the subdivided parts of tablets at release as conformed to compendial requirement. 5. Release and shelf-life specifications of the drug product with proposed dimension and/or shape. **(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-PA27	**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 proposed test procedure to be at least equivalent to the approved procedure. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified.
D	1. Justification for the proposed change. 2. Comparative tabulated format of the 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 approved and proposed test. 5. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the finished product of two production batches when made available.
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	1. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 2. Release and shelf-life specifications of drug product remain unchanged. 3. For change in the primary packaging material for sterile drug product, please refer to MaV-12.
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 proposed 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 approved and proposed specifications of the primary packaging material (where applicable). 5. Revised ACTD Sections P3 and/or P7 (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).

MiV-PA29	**Addition or 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 proposed manufacturer or packager to perform secondary packaging (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	1. The change only concerns the same packaging type and material. 2. The proposed pack 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 (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-13.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification for the proposed pack size. 3. Revised ACTD Sections P3 and/or P7 (where applicable). 4. 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	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 marketing authorization holder stating that no other changes except for the change of outer carton pack sizes for a drug product.

MiV-PA32	**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 proposed 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. 5. Data on test of uniformity of delivered dose as per compendium.

MiV-PA33	**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 approved shelf-life specification. 2. For (c) – The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For extension of shelf-life, please refer to MaV-15.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change(where applicable). 3. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 4. Results of appropriate long term stability studies covering the duration of proposed shelf-life 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-PA34	**Change of storage conditions of the drug product (Increasing from the 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 approved shelf-life specification. 2. For (c) – The studies must show conformance to the approved shelf-life specification for the reconstituted product. 3. For change of storage condition (lowering from the approved storage condition), please refer to MaV-16. 4. General precautionary statements on storage conditions in product labeling may be included but should not be used due to stability concerns.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long term stability studies covering the duration of approved shelf-life (at proposed storage condition) of the product and 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 microbiological testing should be included (where appropriate). 4. Data on photosensitivity and/or moisture sensitivity test on drug product (where applicable).

MiV-PA35	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product, please refer to MaV-5.
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. 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 of alternative site for primary packaging (where applicable). 5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6. A letter of commitment from marketing authorization holder to conduct long term and accelerated stability studies for the drug product packed at the proposed site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.

MiV-PA36	**Addition or replacement of the company or party responsible for quality control testing site**
C	1. Only applicable for quality control testing site. 2. The manufacturer and primary packager of the drug product remains unchanged. 3. Method transfer from the approved to the proposed site or test laboratory has been successfully completed.
D	1. Declaration from the drug product manufacturer / product owner on the following: a) The change does not affect the release and shelf life specifications of the drug product. b) The tests used by the proposed QC testing site are equivalent to the registered methods. c) List of tests used by the proposed QC testing site with indication if the method suitability / transfer / validation has been completed for each test. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Documentary evidence that the proposed quality control testing site is appropriately accredited. 4. Official letter from product owner authorizing the company to be responsible for quality control testing site (where applicable). 5. Analytical method transfer data/verification data (where applicable). 6. Revised ACTD Sections S2 or P3.

9. MINOR VARIATION NOTIFICATION

Minor Variation (MiV-N)	
Notification	
MiV-N1	**Change in name and/or address (for example: postal code, street name) of the marketing authorization holder** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	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 labeling only. 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 proposed name of marketing authorization holder to hold the product license. 3. Official document from the relevant authority confirming the change with the proposed name and/or address.
MiV-N2	**Change of product owner**
C	1. The marketing authorization holder remains unchanged. 2. The manufacturing site remains unchanged.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Declaration on the transfer of ownership between the approved and proposed product owner. 3. Official letter from the proposed product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 4. If the proposed product owner is not the manufacturer of the drug product, an official letter by the proposed product owner authorizing the manufacturer to manufacture the drug product on its behalf. 5. If the proposed 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-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	1. The manufacturing site remains unchanged. 2. No other changes except for the change in ownership of manufacturer.
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 to the proposed manufacturer (where applicable). 4. In case of a contract manufacturer, official letter from product owner declaring the change and authorizing the proposed manufacturer to manufacture the drug products on its behalf. 5. In case of a contract manufacturer, letter of acceptance from the proposed manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product.
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	1. The manufacturing site remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug product. 3. For change in ownership of manufacturer, please refer MiV-N3.
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 proposed name and/or address. 3. Official letter from product owner authorizing the manufacturer with proposed name/address to manufacture the drug product.

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	1. The manufacturer of the drug product remains unchanged. 2. The batch release site remains unchanged. 3. For change in ownership of manufacturer, please refer MiV-N3.
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 proposed name or address (where applicable). 3. Official letter from product owner authorizing company/manufacturer with proposed name/address responsible for batch release. 4. A declaration from the marketing authorization holder that the change does not involve 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	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 where applicable.
MiV-N7	**Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)**
C	1. An alternative manufacturer is registered.
D	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/or shelf-life/re-test specifications and/or test procedure of the drug product and/or drug substance and/or excipient, following the updates in the compendium**
C	1. Applicable to compendial specifications and/or test procedure only. 2. Change is made exclusively to comply with an update of the relevant monograph within the same compendium.
D	1. Tabulation of the approved and proposed release and/or shelf-life/re-test specifications and/or test procedure of the drug product with changes highlighted. 2. Batch analysis data (in comparative tabulated format) of the drug product for all tests in the proposed specification of at least two batches and/or certificate of analysis of excipient and/or drug substance. 3. Revised release and/or shelf-life/re-test specifications. 4. For change in test procedure, appropriate verification data of the proposed test procedure (where applicable).
MiV-N10	**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-13 and MiV-PA30 respectively. For change in the outer carton pack size, please refer to MiV-PA31.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Reason for deletion.

MiV-N11	**Minor change in the manufacturing process of an immediate release solid oral dosage form, semi solid or oral solutions**
C	1. The change, as per Level 1, Part VI Manufacturing, SUPAC Guideline. a) Change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients; b) Change to alternative equipment of the same design and operating principles of the same or of a different capacity. c) Process changes including changes such as mixing times and operating speeds within application/validation ranges. 2. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 3. The manufacturing principle for individual manufacturing steps remain unchanged, e.g. there are no changes in the processing intermediates and manufacturing solvent(s) used in the process. 4. The proposed process has to be controlled by relevant in-process controls used in the approved process and no changes (widening or deletion of limits) are required for these controls. 5. The specifications of the finished product and/or process intermediates remain unchanged. 6. The proposed process must lead to an identical product regarding all aspects of quality, safety and efficacy.
D	1. Amendment of the relevant section(s) of the dossier, as appropriate, including a direct comparison of the approved and proposed processes. 2. Copy of approved release and shelf life specifications. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the approved and the proposed process. Batch analysis data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action). 4. A declaration from the marketing authorization holder that the relevant stability studies of the drug product will be started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).

MiV-N12	**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-N13	**Change of the name or address (for example: postal code, street name) of the company or party responsible for quality control testing site** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturer of the drug product remains unchanged. 2. The quality control testing site remains unchanged. 3. For change in ownership of manufacturer, please refer MiV-N3.
D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Documentary evidence that the proposed quality control testing site is appropriately accredited (where applicable). 3. Official letter from product owner authorizing company with proposed name/address to be responsible for quality control testing. 4. A declaration from the marketing authorization holder that the change does not involve change of quality control testing site.

10. GLOSSARY

Refer to ACTD/ACTR Glossary

11. REFERENCES

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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 R1, 25th ACCSQ-PPWG
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, March 2015