MAJOR VARIATION (MaV)

- 17 types of MaV excluding MaV-3 & MaV-4
- Quest 2 system : online submission
- Quest 3 system : manual submission
- ASEAN Guideline On Stability Study Of Drug Product : Annexe 5
    - Objective, packaging, batch size, drug formulation, stability data, discussion/conclusion
    - Quest system is an overwrite system : please combine old and new stability report where applicable

PACKAGE INSERT

MaV-1: **Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product**

- Amendments to A6 and A7: Includes rephrasing of indication, rephrasing of recommended dose (including additional data on hepatic, renal and amendments to dosing regimen).
- Amendments of indication and recommended dose for generic products based on DCA approved innovator package insert.

MaV-2 : Change of content of product labeling

- Amendments to A5.1 (pharmacology), A5.2 (pharmacokinetics), A12 (pregnancy & lactation), A14 (symptoms and treatment of overdose) and updates of clinical information on already approved indication and recommended dose.
- Amendments to A4 (product description)
- Removal of safety information

PACKAGE INSERT

MiV-PA2 (will be presented by Mr. Chai):

- **Change of product labeling (in accordance to country specific labeling requirement) Includes:**
- Change of the layout/artwork without altering meaning.
- Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts that do not imply an unapproved indication.
- Addition/strengthening of warnings, precautions, contraindications and/or adverse events/effects to the approved product labeling **(amendments to A9, A10, A11, A13)**
- Tightening of product's target population.
- Deletion of indication.
- Change of distributor's details
- **Editorial changes.**
- **Directives from Pharmacovigilance Section to amend safety information**
- **DCA directives and compulsory warning (refer Drug Registration Guidance Document - DRGD)**

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

MaV-2: Change of content of product labeling	
C	1.Product labeling refers to Package Insert (PI), unit carton label, inner label and/or blister strips. 2.The change is not a minor variation and not within the scope of MaV-1. 3.As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1.Currently approved product labeling. 2.Proposed product labeling, a clean and annotated version highlighting the changes made. 3.Approved PI/SmPC from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4.Justifications for the changes proposed and supporting clinical documents when applicable.

MaV-1 and MaV-2 for Innovator products

Documentations required:

- 1. Currently approved product labelling **(already in the Quest 2 or Quest 3 system)**

- 2. Proposed package insert **(submit under D3)** or proposed labels **(submit under D1 and/or D2)**:
  - a) annotated version highlighting the changes made
  - b) clean copy version

- 3. Supporting documents **(submit under D3 or E7 or E12):** approved SmPC or equivalent documents (eg USPI) from reference country or country of origin

- 4. Documents no 4 – 7 for MaV-1 and no. 4 for MaV-2 **(submit under D3 or E12)**

MaV-1 and MaV-2 for Generic products

Documentations required:

- 1. Currently approved product labelling **(already in the Quest 2 or Quest 3 system)**

- 2. Proposed package insert **(submit under D3)** or proposed labels **(submit under D1 and/or D2)**:
  - a) annotated version highlighting the changes made
  - b) clean copy version

- 3. Supporting documents **(submit under D3 or E12):**
  - a) DCA approved innovator products package insert
  - b) Other DCA approved generic products package insert
  - c) Martindale or other relevant documents

- 4. Documents no 4 – 7 for MaV-1 and no. 4 for MaV-2 **(submit under D3 or E12)**

Other important points:

1. Please check all of the information in the package insert against the registered information in Quest 2 or Quest 3 including pack sizes, manufacturer's details.
2. For all amendments made, please apply variation to relevant fields for example changes to indication , please apply variation to A6, Quest 2.
3. Please refer to **Appendix 9: SECTION D: LABELING REQUIREMENTS : DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)** – all of the information need to be included on the package insert and labels.
4. The annotated package insert must clearly highlight the amendments made and for the new data, please state which supporting document is used (if used more than one supporting document).
5. For sharing package insert:

- please ensure all information in the proposed package insert tally in all of the products stated in the proposed package insert, or else, please amend accordingly with supporting document.
- remove all information on unregistered product or expired/terminated products

The following information is required to be included in the PI:

- a) Brand or Product Name = **as per registered with DCA**
- b) Name and Strength of Active Substance(s) = **as per registered with DCA**
- c) Product Description = **A4**
- d) Pharmacodynamics = **A5.1**
  Pharmacokinetics = **A5.2**
- e) Indication = **A6**
- f) Recommended Dosage = **A7**
- g) Route of Administration = **A8**
- h) Contraindications = **A9**
- i) Warnings and Precautions = **A10**
- j) Interactions with Other Medicaments = **A11**
- k) Statement on usage during pregnancy and lactation = **A12**
- l) Adverse Effects/ Undesirable Effects = **A13**
- m) Overdose and Treatment = **A14**
- n) Incompatibilities (For injections only) = **A8 or A15**
- o) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels) = **A15**
- p) Dosage forms and packaging available = **Part C**
- q) Name and address of manufacturer/ product registration holder = **E13 and/or applicant details, if other manufacturers mentioned, need to tally with E14**
- r) Date of revision of PI = **Date of the amendments made**

- * Fields referred to Quest 2, system.

Example of annotated package insert

Recommended dose:

Oral Administration only

Do not exceed the stated dose or frequency of dosing

Adults and children 12 years and over:

1 tablet (4mg) every 4 to 6 hourly (daily maximum dosage 6 tablets (24mg)

Hepatic impairment

Used with caution in patients with hepatic impairment and contraindicated in patients with active liver disease.

Please state the supporting document used

MaV-5 : Change of the manufacturing site of the drug product	
C	1.Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. 2.For replacement of the company or party responsible for batch release, please refer to MiV-PA4. 3.If there are changes to the manufacturing process, MaV-10 is also applicable.
D	Change of manufacturing site applications are categorised into 5 types with each requiring different set of documentations. Product registration holders are advised to refer to Appendix 13: Supporting Documents Required For Change Of Manufacturing Site Application Of Drug Registration Guidance Document for more details.

- **Type I , II, III, IV, V**
- **Manual submission for all products**
- **For Type II – V, please enclosed form (BPFK 415.3)**

Appendix 13: Supporting Documents Required For Change Of Manufacturing Site (COS) Application

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
1	Letter of authorization/ appointment from the product owner to authorize Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product. **Please check the registered product owner (E1) in Quest system.**	✓	✓	✓	✓	✓
2	Letter from the manufacturer/ product owner to clarify/ explain the need to change site of manufacture. ***For Type I:*** Letter of declaration stating the reason(s) for change of manufacturing site and clearly state the proposed and current name and address of manufacturer.	✓	✓	✓	✓	✓
3	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry specifications of the product as the same as already approved. ***OR*** If there are minor changes, to declare the 'minor changes' & justify the need for such changes. **Please declare all of the changes made as compared to the existing manufacturing site which may includes change in batch size, pack sizes or new primary packaging materials . All of these changes need to be supported by relevant documents.**	✓	✓	✓	✓	✓
4	'Release' and 'end-of-shelf life' specifications from proposed site. **Need to tally with the new COA and stability report.**	✓	✓	✓	✓	✓

Appendix 13: Supporting Documents Required For Change Of Manufacturing Site (COS) Application

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
5	Original copy of the Certificate of Free Sale (CFS) and Good Manufacturing Practice (GMP)/ Certificate of Pharmaceutical Product (CPP) from the source country of the new manufacturing site in the case of an imported product. **Refer to circulars on PiCS country requirement:** **For sterile products – need to come from PiCS country** **For non-sterile products – starting from 1.1.2014, need to come from PiCS country.** *OR* Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site. **For local manufacturers only.**	✓	✓	✓	✓	✓
6	Specification of the drug substance. **In case, the drug substance from new drug substance manufacturer is used, please declare and provide supporting documents.**	✓	✓	✓	✓	✓
7	Product formula. **To declare all of the excipients used including the coating materials.**	✓	✓	✓	✓	✓
8	Original copy of Certificate of Analysis (CoA) from the new manufacturing site. **Please ensure to state the batch number, batch size and place of manufacture (if different letterhead used on CoA).**		✓	✓	✓	

Appendix 13: Supporting Documents Required For Change Of Manufacturing Site (COS) Application

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
9	Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action).		✓	✓	✓	
10	"Accelerated" and on-going stability data as per ASEAN Guideline on Stability Study of Drug Product and a letter of commitment to submit real time stability data. ***For Type I:*** Letter of commitment to submit stability data report.	✓	✓	✓	✓	
11	Amended immediate label, outer label and package insert for the product from the proposed site. **Please check all of the information on the package insert against the registered information for example under Part A and Part C in Quest system** **Please refer to Appendix 9: SECTION D: LABELLING REQUIREMENTS (DRGD)**	✓	✓	✓	✓	✓
12	Process validation report as per ASEAN Guideline On Submission Of Manufacturing Process Validation Data For Drug Registration. ***For Type I:*** Letter of commitment to submit process validation report, if applicable	✓	✓	✓	✓	

Appendix 13: Supporting Documents Required For Change Of Manufacturing Site (COS) Application

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
13	Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).		✓	✓	✓	
14	Declaration and commitment that the manufacturer will carry out continuous quality monitoring on the post change products	✓				
15	Letter of commitment to submit stability data, certificate of analysis, process validation report (where applicable) and sample for laboratory testing within 6 months of approval of site change.					✓
16	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.	✓	✓		✓	

Appendix 13: Supporting Documents Required For Change Of Manufacturing Site (COS) Application

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

MaV-6: Replacement of alternative site for primary packaging (direct contact with drug product)	
C	1.No other changes except for the replacement of alternative site for primary packaging (direct contact with drug product).
D	1.Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2.Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned such as a valid GMP Certificate and/or a CPP which covers GMP certification. 3.In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 4.For sterile product, validation scheme and/or report on primary packaging processes as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site should be provided upon submission. 5.Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6.Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

MaV-7: Change of the specification of drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available] (a) Specification limits are widened and/or deletion of test parameter and limits of drug substance (b) Specification limits are widened and/or deletion of test parameter and limits of drug product	
C	1.Test procedures remain the same, or changes in the test procedure are minor. 2.Not applicable to compendial drug substances/drug products. 3.The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 4.Refer to MiV-PA13 if this change resulted in revision of CEP.
D	**For both (a) and (b)** 1.Revised specification of drug substance / drug product. 2.Comparative tabulated format of the currently approved and revised specification of drug substance/drug product with changes highlighted. 3.Certificate of analysis and batch analysis data of the drug substance/drug product for all tests in the new specification for two pilot or production scale batches. 4.Justification for change substantiated with scientific data to be provided. **In addition of D1 to D4, this is applicable for (b) only** 5. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action); (where applicable).

Change of Batch Size

MaV-8 : Change of batch size of sterile drug product.

- Applicable for all type of change of batch size of sterile drug products.

MaV-9 : Change of batch size of non-sterile drug product.

- Applicable to change batch size more than 10-fold compared to the currently registered batch size for non-sterile drug product.

MiV-PA14 (will be presented by Mr Chai): Change of batch size of non-sterile drug product.

- For change of batch size up to 10-fold compared to the currently registered batch size for non-sterile drug product.

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

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

MaV-10 : Major change in the manufacturing process for drug product

C	1.The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 2.The same currently approved manufacturing site. If there is a change in manufacturing site, MaV-5 is also applicable. 3.For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA21.
D	1.Description of the new manufacturing process and technical justification for the change. 2.Comparative dissolution profile data between the products manufactured with the currently approved and proposed manufacturing process for oral solid dosage forms as per compendium and validated dissolution test method. 3.Validation scheme and/or report of the proposed manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration should be provided upon submission. 4.Copy of currently approved release and shelf-life specifications. Or, alternatively, copy of proposed release and shelf-life specifications that supports that the new process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 5.Certificate of analysis and comparative batch analysis data of drug product for a minimum of one production batch manufactured according to currently registered and proposed processes. 6.Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 7.Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

Qualitative or Quantitative Change of Expicient

MaV-11: Qualitative or quantitative change of excipient

- a) For immediate release oral dosage forms.
  - (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline).
- b) For modified release oral dosage forms.
- c) For other critical dosage forms such as sterile preparations.

MaV-12: Quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form.

MiV-PA16, MiV-PA17, MiV-PA18 (will be presented by Mr Chai):

Example MiV-PA16

- Qualitative and/or quantitative change of excipient.
- a) For immediate release oral dosage forms.
  - (as per Level 1, Part III Components and Composition, SUPAC guideline).
- b) For other non-critical dosage forms eg. oral liquid, external preparation.

MaV-11: Qualitative or quantitative change of excipient

a. **For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)**
b. **For modified release oral dosage forms**
c. **For other critical dosage forms such as sterile preparations.**

C	1. Change will need to comply with the finished product specifications for example release and shelf-life specifications of the drug product remain the same, excluding product description. 2. Replacement of an excipient with a comparable excipient of the same functional characteristics. 3. The dissolution profile of the proposed product is comparable to that of the current approved product. 4. Process validation scheme and/or report is available or validation of the manufacturing process has been successfully carried out according to protocol with at least three batches of the proposed new product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data For Drug Registration. 5. For other qualitative or quantitative changes of excipient for immediate release oral dosage forms and other non-critical dosage forms, please refer to MiV-PA16. 6. For Quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form, please refer to MaV-12.

MaV-11: Qualitative or quantitative change of excipient

D	1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Justification for the change must be given by appropriate development of pharmaceutics. 3. Comparative tabulated format of the current and revised product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). **Please refer Table 1** 4. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation (where applicable). 5. Revised batch manufacturing formula. **To declare all of the excipients used including the coating materials.** 6. Validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula should be provided upon submission. 7. Revised ACTD Section P3.1 to P3.4 (where applicable). 8. Specifications of the proposed excipient. To revise Part P4 (where applicable) 9. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free cert issued from relevant veterinary authority of the issuing country (where applicable). 10. Drug product release and shelf-life specifications. 11. Certificate of analysis and batch analysis data (in a comparative tabulated format) of drug product on at least two production (or one production batch and two pilot batches) according to currently approved and proposed product formula. 12. Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action). 13. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

Table 1 : Product Formula

(comparison table old and new formula)

No.	Ingredient	Type/Function	Quantity Unit Per Tablet (registered)	Quantity Unit Per Tablet (Proposed)	% difference / proposed quantity	Additive effect
1.	Folic Acid	Active Ingredient	5mg	5mg	nil	
2.	Lactose Monohydrate	Excipient: Bulking agent	70mg	80mg	**80 – 70 = 10mg** **10mg/105 mg x100% = 9.52%**	**9.52%**
3.	Corn Starch	Excipient: Disintegrant	30mg	28.5mg	**28.5-30mg= 1.5mg** **1.5mg/105mg x 100% = - 1.43%**	**1.43%**
4.	Magnesium Stearate	Excipient: Lubricant	None	2mg	**2mg/105mgx100% = 1.90%**	**1.90%**
			Total weight = 105mg	Total weight =115.5mg		**Total = 12.85%** **Therefore, Level 3**

MaV-12 : Quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form

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

MaV-13: Change in primary packaging material for sterile product

a) Qualitative and quantitative composition and/or
b) Type of container and/or
c) Inclusion of primary packaging material

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

MaV-14: Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product	
C	1.The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2.The packaging material remains the same. 3.Release and shelf-life specifications of the drug product are not affected, except pack size/fill volume specification. 4.Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile drug product, please refer to MiV-PA31.
D	1.Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2.Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3.Validation data of the manufacturing process, sterilization and container closure system (where applicable). 4.Stability data as per ASEAN Guideline On Stability Study Of Drug Product and report if any results fall outside shelf-life specifications (with proposed action).

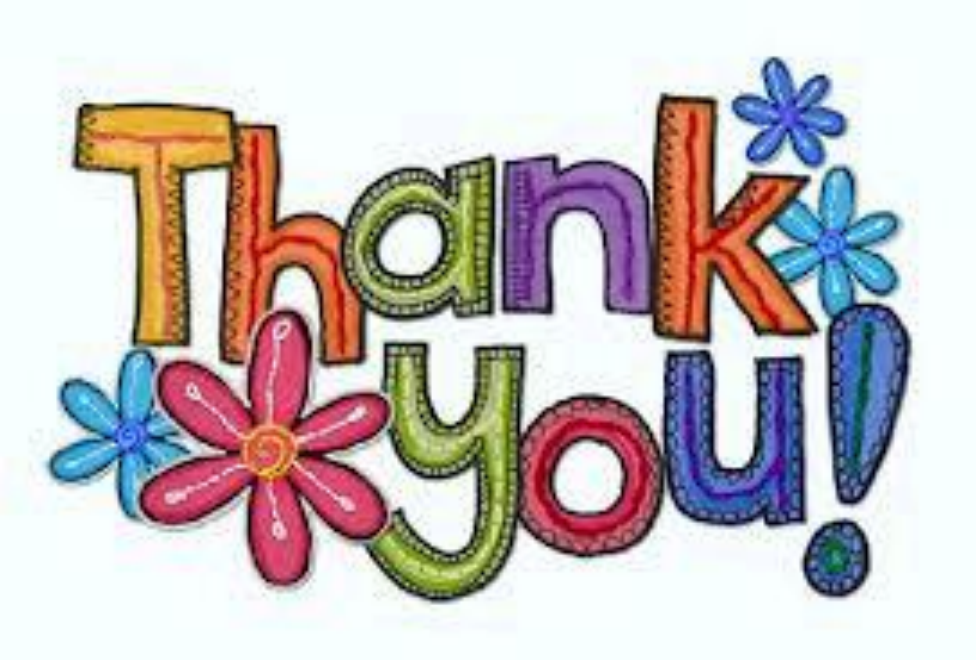
MaV-15: Inclusion or replacement of the solvent/diluent for the drug product	
C	1.The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product. 2.For deletion of the solvent/diluent, please refer to MiV-PA19. 3.For change of shelf-life and/or storage condition of the drug product after first opening and/or after dilution/reconstitution, please also refer to MaV-16/MiV-PA35 and/or MaV-17/MiV-PA36 (where applicable).
D	1.Revised drafts of the package insert and labeling incorporating the proposed variation. 2.Approved PI/SmPC from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 3.Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 4.A letter of authorization from product owner to authorize the manufacturing site to manufacture and package the solvent/diluent (where applicable). 5.A declaration from the product registration holder that the release and shelf-life specifications of drug product are not affected. 6.Revised section P for the solvent/diluent and reconstitution stability data (where applicable).

MaV-16: Extension of shelf-life of the drug product

a) As a package for sale and/or
b) After first opening and/or
c) After dilution/reconstitution

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

MaV-17: Change of storage conditions of the drug product (Lowering from the current approved storage condition) a) As a package for sale and/or b) After first opening and/or c) After dilution/reconstitution	
C	1.For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2.For (c) – The studies must show conformance to the currently approved shelf-life specification for the reconstituted product. 3.For change of storage condition (Increasing from the current approved storage condition), please refer to MiV-PA36.
D	1.Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2.Technical justification for the change. 3.Results of appropriate real time stability studies covering the duration of currently approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product.


Thank you!