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PART A: CHECKLIST ON DOSSIER REQUIREMENTS FOR MIV-1 VARIATION

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B1	**Addition or Replacement of Manufacturer/Site of Drug Substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. Specification of drug substance remains unchanged. If there are changes to the drug substance specification, MIV-1 B5, MIV-2 C6 or D15 is also applicable. 2. For a change and/or addition of manufacturer/site of drug substance where a CEP is available, refer to MIV-1 B2. 3. For application supported by a DMF, the electronic format of the DMF from the DMF holder must be received by HSA prior to the submission of the MIV-1 application.
D	1. Complete CTD section S.1 - S.7, or both the open and closed parts of the Drug Master File (closed part to be provided directly by the drug substance manufacturer) with the Letter of Access. 2. For application support by a DMF, to specify the assigned DMF number in the introduction letter or Table Summary of Changes and include a copy of the email acknowledgement from HSA on the receipt of the Letter of Access. 3. Evidence of GMP compliance for the proposed site as per Section 15.1(i) or 18.1(i) of the *Guidance on Therapeutic Product Registration in Singapore*. 4. Comparative tabulated format of the approved and proposed drug substance manufacture information (where applicable). 5. If there is any change made to the drug substance specification as controlled by the drug product manufacturer, data covering S4.1 to S4.5 from the drug product manufacturer should be submitted (where applicable). 6. Certificate of analysis 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. 7. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance from the proposed manufacturing site in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B2	**Addition or Replacement of Manufacturer/site of Drug Substance (where CEP is available)**
C	1. Specification of drug substance remains unchanged. If there are changes to the drug substance specification, MIV-1 B6, MIV-2 C6 or D16 is also applicable. 2. For a change and/or addition of manufacturer/site of drug substance where a CEP is not available, refer to MIV-1 B1.

D	1. A copy of the valid CEP, including all annexes, as issued by the European Directorate for the Quality of Medicines (EDQM), and a copy of the Letter of Access from the CEP holder to authorise the applicant to refer to the CEP in support of their application. 2. Revised CTD S2.1. 3. If there is any change made to the drug substance specification controlled by the drug product manufacturer, data covering S4.1 to S4.5 from the drug product manufacturer should be submitted (where applicable). 4. Certificate of analysis 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. 5. CTD S6 from the proposed drug substance manufacturer if the container closure system is not stated on the CEP. 6. 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 three pilot or production batches of the drug substance manufactured from the proposed manufacturing site. 7. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance from the proposed manufacturing site in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B3	**Major Change of Manufacturing Process of Drug Substance (where CEP is not available)**
C	1. Synthetic route is different (for example, new intermediates are formed), which may have a potential to change important quality characteristics of the drug substance, e.g., qualitative and/or quantitative impurity profile, which may have significant impact on the quality, safety and efficacy of the drug product. 2. Specification of drug substance remains unchanged. If there are changes to the drug substance specification, MIV-1 B5, MIV-2 C6 or D15 is also applicable. 3. For a major change of manufacturing process of the drug substance where a CEP is available, refer to MIV-1 B4. 4. For application supported by a DMF, the electronic format of the DMF from the DMF holder must be received by HSA prior to the submission of the MIV-1 application.
D	1. Relevant CTD section S.1 - S.7, or both the open and closed parts of the Drug Master File (closed part to be provided directly by the drug substance manufacturer) with the Letter of Access. 2. For application support by a DMF, to specify the assigned DMF number in the introduction letter or Table Summary of Changes and include a copy of the email acknowledgement from HSA on the receipt of the Letter of Access. 3. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available).

	4. For a sterile drug substance, process validation report (where applicable). 5. A letter of declaration from the product registrant 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. If there is any change in the qualitative and/or quantitative impurity profile, provide scientific justification and/or qualification data from safety studies. 6. If there is any change made to the drug substance specification as controlled by the drug product manufacturer, data covering S4.1 to S4.5 from the drug product manufacturer should be submitted (where applicable). 7. Certificate of analysis 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 processes. 8. Batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the currently approved and proposed processes. 9. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance using the proposed manufacturing process in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B4	**Major Change of Manufacturing Process of Drug Substance (where CEP is available)**
C	1. Synthetic route is different (for example, new intermediates are formed), which may have a potential to change important quality characteristics of the drug substance, e.g., qualitative and/or quantitative impurity profile, which may have significant impact on the quality, safety and efficacy of the drug product. 2. Specification of drug substance remains unchanged If there are changes to the drug substance specification, MIV-1 B6, MIV-2 D16 is also applicable. 3. For a major change of the manufacturing process of a drug substance where a CEP is not available, refer to MIV-1 B3.
D	1. A copy of the valid CEP, including all annexes as issued by the EDQM, and a copy of the Letter of Access from the CEP holder to authorise the applicant to refer to the CEP in support of their application. 2. Additional data to address any relevant parameter(s) not addressed in the CEP, such as physicochemical characteristics (e.g., particle size, polymorphism etc.), where applicable. 3. Certificate of analysis 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 processes.

	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 three pilot batches of the drug substance manufactured with the proposed manufacturing process. 5. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance using the proposed manufacturing process in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B5	**Change of Specification of Drug Substance (where CEP is not available)** a) Specification limits are widened. b) Deletion of specification parameter which may have a significant effect on the overall quality of the drug substance and/or drug product.
C	1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting. 2. Test procedures remain unchanged, or changes in the test procedure are minor, refer to MIV-2 C7. 3. For addition of new specification parameter, refer to MIV-2 C6. For tightening of specification limits or deletion of a non-significant specification parameter (e.g., deletion of an obsolete parameter), refer to MIV-2 D15. 4. For change of specification of drug substance where a CEP is available, refer to MIV-1 B6. 5. For change of specification due to update of the compendium for compendial drug substance, refer to MIV-2 D16.
D	**Specification limits are widened** 1. Proposed specification of drug substance. 2. Comparative tabulated format of the currently approved and proposed specification of drug substance with changes highlighted. 3. Justification for change substantiated with scientific data to be provided. 4. Certificate of analysis or batch analysis data of the drug substance for all tests in the proposed specification for two pilot or production scale batches. 5. If the change is also applicable to the drug substance specification as controlled by the drug product manufacturer, data covering S4.1 to S4.5 from the drug product manufacturer should be submitted (where applicable). 6. For change of drug substance specification that involved stability-indicating parameters, a) Results of at least six months of real time stability studies of at least three production batches of the drug substance.

	b) A commitment letter to continue the stability studies to the approved retest period or shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. c) A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. **Deletion of test parameter and limits** All the above documents except D6.

B6 Change of Specification of Drug Substance (where CEP is available) a) Specification limits are widened. b) Deletion of specification parameter which may have a significant effect on the overall quality of the drug substance and/or drug product.	
C	1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting. 2. Test procedures remain unchanged, or changes in the test procedure are minor. 3. For change of specification of drug substance where a CEP is not available, refer to MIV-1 B5. 4. For addition of new specification parameter, refer to MIV-2 C6. For tightening of specification limits or deletion of a non-significant specification parameter (e.g., deletion of an obsolete parameter), refer to MIV-2 D15. 5. For a change in specification due to update of the compendium for compendial drug substance, refer to MIV-2 D16.
D	1. A copy of the valid CEP, including all annexes as issued by the EDQM, and a copy of the Letter of Access from the CEP holder to authorise the applicant to refer to the CEP in support of their application. 2. Proposed specification of the drug substance. 3. Comparative tabulated format of the currently approved and proposed specification of drug substance with changes highlighted. 4. Justification for change substantiated with scientific data to be provided. 5. Certificate of analysis or batch analysis data of the drug substance for all tests in the proposed specification for two pilot or production scale batches from the drug substance manufacturer*, demonstrating compliance with the Ph. Eur. monograph and including additional test/limits listed on the CEP.

	** 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 of be submitted.* 6. For change of drug substance specification that involved any stability-indicating parameters, and if the re-test period is not stated on the CEP, (a) Results of at least six months of real time stability studies of at least three production batches of the drug substance. (b) A commitment letter to continue the stability studies to the approved retest period or shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. (c) A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. **Deletion of test parameter and limits** All the above documents except D6.

B7	**Addition or Replacement of Manufacturing Site of Drug Product**
C	1. Site change consists of changes in location of the site of manufacturing only and does not include any scale-up changes, change in manufacturing process, or changes in components or composition. 2. If there are changes to the manufacturing process, MIV-1 B12 or MIV-2 C17 is also applicable. 3. If there are changes to the batch size, MIV-1 B10, MIV-1 B11, or MIV-2 C10 is also applicable. 4. If there are changes to the drug product specification, MIV-1 B9, MIV-2 C21 or D22 is also applicable. 5. Not applicable to changes relating to the manufacturer responsible for batch release (refer to MIV-2 C3) or primary packager (refer to MIV-1 B8, MIV-2 C26).
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Evidence of GMP compliance for the proposed site as per Section 15.1(i) or 18.1(i) of the *Guidance on Therapeutic Product Registration in Singapore*. 3. Batch numbering system (where applicable). 4. In case of a contract manufacturer, a letter of appointment for the proposed site to manufacture the drug product and stating the types of activity to be performed (where applicable). 5. Drug product formula or batch manufacturing formula.

	6. Validation scheme and report of the manufacturing process as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* at the proposed site(s). 7. Holding time studies of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 8. Approved release and shelf-life specifications of the drug product. 9. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) from the approved and proposed manufacturing sites. 10. Stability studies as per *ASEAN Guideline on Stability Study of Drug Product*. 11. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. 12. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured by the approved and proposed manufacturing site as per US FDA SUPAC IR or MR guidelines. 13. For modified release oral solid dosage form, justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

B8	**Addition or Replacement of Manufacturing Site for Primary Packaging for Sterile Drug Product**
C	1. No other changes except for the addition or replacement of a manufacturing site for primary packaging (direct contact with drug product). 2. The primary packaging material must be the same approved primary packaging material with the same specifications. 3. For non-sterile drug product, refer to MIV-2 C26
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Evidence of GMP compliance of the proposed site as per Section 15.1(i) or 18.1(i) of the *Guidance on Therapeutic Product Registration in Singapore*. 3. In case of a contract primary packager, a letter of appointment for the proposed site to package the drug product and stating the types of activity to be performed by the packager (where applicable). 4. Validation scheme and report of the primary packaging processes, e.g., manufacturing and sterilization process, container closure system integrity, as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration*. 5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable).

	6. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) from the approved and proposed sites.

B9 Change of Release and/or Shelf-Life Specifications of Drug Product a) Specification limits are widened. b) Deletion of specification parameter which may have a significant effect on the overall quality of the drug product.	
C	1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting. 2. Test procedures remain unchanged, or changes in the test procedures are minor (MIV-2 C24 is also applicable if there is change in test methods). 3. For addition of new specification parameter, refer to MIV-2 C21. For tightening of specification limits or deletion of a non-significant specification parameter (e.g., deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material), refer to MIV-2 D22. 4. For a change in specification due to update of the compendium for compendial drug product, refer to MIV-2 D23.
D	**Specification limits are widened** 1. Proposed specification of drug product. 2. Comparative tabulated format of the currently approved and proposed specification of drug product with changes highlighted. 3. Certificate of analysis or batch analysis data of the drug product for all tests in the proposed specification for at least two batches (preferably production scale). 4. Justification for change substantiated with scientific data. 5. For change of drug product specification that involved stability-indicating parameters, stability studies as per *ASEAN Guideline on Stability Study of Drug* Product. 6. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. **Deletion of test parameter and limits** All the above documents except D5 & D6.

B10 Change of Batch Size of Sterile Drug Product	
C	1. The change does not affect reproducibility and/or consistency of the product.

	2. The drug product formulation remains unchanged. 3. Release and shelf-life specifications of the drug product remain unchanged.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Validation scheme and 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. 3. Release and shelf-life specifications of the drug product. 4. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed batch sizes. 5. Stability studies as per *ASEAN Guideline on Stability Study of Drug Product.* 6. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B11 Change of Batch Size of Non-sterile Drug Product	
C	1. This is applicable to change of batch size of more than 10-fold the size of the approved batch size. For change of batch size up within 10-fold of the size of approved batch size, refer to MIV-2 C10. 2. The change does not affect consistency of production. 3. The drug product formulation remains unchanged. 4. Release and shelf-life specifications of the drug product remain unchanged.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Validation scheme and 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. 3. Release and shelf-life specifications of the drug product. 4. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed batch sizes. 5. Stability studies as per *ASEAN Guideline on Stability Study of Drug Product.* 6. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

	7. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured using the approved and proposed batch sizes as per US FDA SUPAC IR or MR guidelines.

B12 Major Change in Manufacturing Process for Drug Product	
C	1. The change may cause significant impact on the quality, safety and efficacy of the drug product. 2. For a minor change of the manufacturing process, refer to MIV-2 C17. 3. Manufacturing site remains the same. If there is a change in manufacturing site, MIV-1 B7 is also applicable. 4. Specification of the drug product remains unchanged. If there is a change in the specification, MIV-1 B9, MIV-2 C21 or D22 is also applicable.
D	1. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 2. Description of the proposed manufacturing process and technical justification for the change. 3. Validation scheme and report of the proposed manufacturing process as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration*. 4. Release and shelf-life specifications of the drug product. 5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed processes. 6. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.* 7. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. 8. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured using the approved and proposed manufacturing processes as per US FDA SUPAC IR or MR guidelines. 9. Justification for not submitting a new bioequivalence study according to the *ASEAN Guideline for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable).

B13 Qualitative and/or Quantitative Change of Excipient a) For immediate release oral solid dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline). b) For modified release oral solid dosage forms. c) For other critical dosage forms such as sterile preparations. d) For non-critical dosage forms that do not fall under MIV-2 C12	
C	1. Change will need to comply with the drug product specifications, i.e., release and shelf-life specifications of the drug product remain the same, excluding product description. If there is a change in specification, refer to MIV-1 B9, MIV-2 C21 or D22. 2. Replacement of an excipient with a comparable excipient of the same functional characteristics. 3. The dissolution profile of the proposed drug product is comparable to that of the approved drug product. 4. For minor qualitative or quantitative changes of excipient for immediate release oral solid dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline) or other non-critical dosage forms, refer to MIV-2 C12. 5. HSA reserves the right to re-categorise the application to NDA or GDA, if deemed appropriate.
D	1. Revised drafts of the package insert and labelling 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 approved and proposed drug product formulation with calculated changes highlighted (state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 4. Revised CTD Section P1, P3.1 to P3.4 (where applicable), including revised batch manufacturing formula. 5. Validation scheme and 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 the drug product formula. 6. Specification of the proposed excipient(s). 7. For materials derived from TSE-relevant animals (i.e., cattle, sheep, goat, deer, elk, non-human primates): a. A valid TSE Risk evaluation CEP; or b. If CEP is not available, i. Description of the tissue/organ/fluid-collection procedures and measures in place to avoid cross-contamination. ii. Details of the risk factors associated with the route of administration and maximum therapeutic dosage of the drug product. iii. Relevant information demonstrating that the manufacturing process is capable of inactivating TSE agents.

	8. Release and shelf-life specifications of the drug product. 9. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed drug product formula. 10. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.* 11. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. 12. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured using the approved and proposed formulation as per US FDA SUPAC IR or MR guidelines. 13. Justification for not submitting a new bioequivalence study according to the *ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable).

B14 Quantitative Change in Coating Weight of Tablets, or Weight and/or Size of Capsule Shell for Modified Release Oral Solid Dosage Form	
C	1. The dissolution profile of the proposed drug product is comparable to that of the approved drug 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, refer to MIV-2 C13.
D	1. Revised draft of the product label incorporating the proposed change (where applicable). 2. Comparative tabulated format of the approved and proposed drug product and batch manufacturing formula. 3. Revised CTD Section P1. 4. Release and shelf-life specifications of the drug product. 5. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.* 6. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. 7. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed formulation as per US FDA SUPAC MR guidelines.

	8. Justification for not submitting a new bioequivalence study according to the *ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable).

B15	**Change in Primary Packaging Material for Sterile Drug Substance or Drug Product** a) Change in qualitative and quantitative composition. b) Change of type of container. c) Inclusion of new primary packaging material. d) Also applicable for non-sterile drug substance or product that does not fall under MIV-2 C25.
C	1. Notification is not required if there is a change in the supplier for the same type of primary packaging material with the same specification. 2. Release and shelf-life specifications of the drug product remain unchanged. 3. For change in the primary packaging material for a non-sterile drug substance or drug product, refer to MIV-2 C25. 4. For a change of specification parameters or limits, or test procedure of primary packaging material, refer to MIV-2 D28.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the change in primary packaging material. 3. Comparative tabulated format of the specifications of the approved and proposed primary packaging material. 4. Revised CTD Sections P3 and/or P7 (where applicable). 5. Declaration of compliance to the appropriate international standards or pharmacopoeia. 6. Appropriate scientific data on the proposed packaging (comparative data on permeability, e.g., moisture, O_2, CO_2). 7. Relevant studies to demonstrate 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 drug product into the pack (where applicable). 8. Validation scheme and report of the manufacturing and sterilization process, container closure system integrity, as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* appropriate to the proposed change in primary packaging material. 9. For drug substance: Results of at least six months of real time stability studies of at least three production batches of the drug substance, and a commitment letter to continue the stability studies to the approved retest period or shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report

	is not required but the data shall be provided to the Health Sciences Authority upon request. 10. For drug product: Stability data as per *ASEAN Guideline on Stability Study of Drug Product, and* A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B16 Change or Addition of Pack Size/Fill Volume and/or Change of Shape or Dimension of Primary Packaging Material for Sterile Drug Product	
C	1. The type and material of the primary packaging material remain unchanged. 2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Release and shelf-life specifications of the drug product remain unchanged, except for the pack size/fill volume. 4. For change or addition of pack size/fill volume and/or change of shape or dimension of primary packaging material for a non-sterile drug product, refer to MIV-2 C28. For change or addition of pack size involving the number of blister strips or containers in a pack, refer to MIV-2 D27.
D	1. Revised drafts of the package insert and labelling 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. Revised CTD Sections P3, P5.1 and/or P7 (where applicable). 4. Validation scheme and report of the manufacturing and sterilization process, container closure system integrity, as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* appropriate to the proposed change in primary packaging material. 5. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.* 6. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B17 Inclusion or Replacement of Solvent/Diluent for Drug Product	
C	1. The proposed change does not result in any change in the dosage form, regimen, indication or method of administration of the drug product. 2. For deletion of the solvent/diluent, refer to MIV-2 C15.

	3. For change of shelf-life and/or storage condition of the drug product as a package for sale, and/or after first opening, and/or after dilution/reconstitution, refer to MIV-1 B18 and/or B19.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation. 2. Evidence of GMP compliance of the proposed site as per Section 15.1(i) or 18.1(i) of the *Guidance on Therapeutic Product Registration in Singapore*. 3. Batch numbering system (where applicable). 4. In case of a contract manufacturer, a letter of appointment for the proposed site to manufacture and/or package the solvent/diluent and stating the types of activity to be performed (where applicable). 5. A declaration from the product registrant that the release and shelf-life specifications of the drug product are not affected. 6. Complete CTD P sections (3.2.P.1 to 3.2.P.8) for the solvent/diluent, including reconstitution stability data, and section S may be required (where applicable).

B18 Change of Shelf-life of Drug Product a) As a package for sale; and/or b) After first opening; and/or c) After dilution/reconstitution.	
C	1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting. 2. For (a) & (b), the stability studies must show conformance to the approved shelf-life specification. 3. For (c), the stability studies must show conformance to the approved shelf-life specification for the reconstituted drug product.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the change of shelf-life of the drug product (where applicable). 3. Results of appropriate real time stability studies covering the duration of the proposed shelf-life of at least two pilot/production scale batches of the drug product in the authorised 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*.

B19 Change of Storage Conditions of Drug Product a) As a package for sale; and/or b) After first opening; and/or c) After dilution/reconstitution.	
C	1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting. 2. For (a) & (b), the stability studies must show conformance to the approved shelf-life specification. 3. For (c), the stability studies must show conformance to the approved shelf-life specification for the reconstituted drug product.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the change of storage condition of the drug product (where applicable). 3. Results of appropriate real time stability studies covering the duration of the approved shelf-life (at the proposed storage condition) of at least two pilot/production scale batches of the drug product and in the authorised 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*.

B20 Addition or Change of Functional Score/Break Line of Tablet	
C	1. New markings do not cause confusion with other registered drug products. 2. Release and shelf-life specifications of the drug product remain unchanged except for appearance. 3. Score/break-line is meant for functional but not cosmetic purpose. 4. The dissolution profile of the proposed drug product is comparable to that of the approved drug product.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the change (e.g., change in dosing regimen). 3. Detailed drawing or written description of the approved and proposed imprint/bossing/markings. 4. Revised CTD Section P1.

	5. Release and shelf-life specifications of the drug product with the new product description. 6. Data on test of content uniformity of the subdivided parts of the tablets at release as conformed to compendial requirement should be submitted. 7. Certificates of analysis or batch analysis of two pilot/ production scale batches.

B21 Change of Sterility Testing to Parametric Release	
C	1. Only a manufacturing site located in a PIC/S participating country with parametric release being approved by the local authority is eligible to apply.
D	1. A complete and detailed description of the current terminal sterilization cycle including type/design/process parameters, drug product and container closure system to be sterilised. 2. Identification of the critical process parameters (process/cycle parameters and appropriate sterilisation load monitors essential for drug product release), including the minimum and maximum limits. 3. Risk assessment: A discussion of risk to the sterility of the drug product relative to the following: (a) prior knowledge from developmental and registration batches, (b) consistency of performance of steriliser and historical batch analysis data, (c) the production loading pattern (d) container closure system (including secondary packaging), (e) any potential contamination risks from the environment, and (f) reprocessing plan. 4. Process validation of sterilizer: Validation of sterilization process includes the validation of cycle parameters and its microbiological effectiveness through use of biological indicators, container closure system integrity, production load patterns, cycle process parameters and acceptance criteria, heat distribution study for three consecutive runs, heat penetration studies for three consecutive runs for each loading pattern and container size, effectiveness of the load monitor used for each routine run, bioburden, sterility assurance level of 10^{-6} or better should be demonstrated, re-processing (where applicable). 5. Control Strategy: (a) tabulation of all validated critical process parameter and loading pattern, (b) describes the process and requirement for releasing/rejection of a batch, (c) bioburden monitoring and control program, (d) segregation of sterile from non-sterile drug product, (e) routine maintenance/re-validation program for steriliser, etc. 6. Approval letter and recent documentary evidence of approval status (i.e., GMP) for parametric release issued by a local authority (PIC/S). The manufacturing site and drug product name must be clearly stated. A GMP Conformity Assessment for parametric release of the specified drug product is required for overseas drug product manufacturers. 7. Release and shelf life specifications of the drug product. Revision of the certificates of analysis that parametric release is now the method used to provide assurance of the requirement of sterility. 8. Stability data (includes sterility test) as per *ASEAN Guideline on Stability Study of Drug Product*.

	9. A commitment letter to complete the on-going stability studies (including sterility test) to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B22 Implementation of a New Design Space or Extension of an Approved Design Space for Drug Substance or Drug Product	
C	1. Applies to a design space with multidimensional combination and interaction of input variables and process parameters. 2. For changes to proven acceptable ranges (i.e., loosening), refer to checklist MIV-1 B5 or MIV-1 B9.
D	1. Amended relevant CTD sections. 2. A comparative table of the approved and proposed design space, including the variables (material attributes and/or process parameters). 3. Justification for the proposed change. 4. Results from drug product, process and analytical development studies (e.g., interaction studies of the different parameters forming the design space, including risk assessment and multivariate studies, where appropriate) to support the proposed design space in production scale manufacturing. 5. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.* 6. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

B23 Change of Content of Product Labelling	
C	1. The change is not an MIV-2 and not within the scope of MAV-1.
D	1. Approved product labelling. 2. Proposed product labelling: a pristine 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. Justification for the changes proposed and supporting clinical documents where applicable.

B24 Change of In-process Controls Applied during Manufacture of Drug Product	
C	1. Widening of specification limits of in-process control (IPC) or deletion of test parameters and limits of IPC. 2. For addition or replacement of new IPC, refer to MIV-2 C16. For tightening of IPC or deletion of a non-significant IPC, refer to MIV-2 D20. 3. Release and shelf-life specifications of the drug product remain unchanged. 4. The change is not a consequence of any commitment from previous assessments to review the specification limits. 5. The change does not result from unexpected events arising during manufacture, e.g., new unqualified impurity or change in total impurity limits.
D	1. Comparative tabulated format of currently approved and proposed in-process controls. 2. Proposed in-process specifications together with justification and relevant process validation data. 3. Certificate of analysis or comparative batch analysis data of the drug product of at least two production batches.

B25 Change of Specification of Non-compendial Excipient	
C	1. For widening of specification limits and deletion of significant test parameter. For addition or replacement of a specification parameter and limit, refer to MIV-2 C18. 2. Applicable to non-compendial excipients. For compendial excipients, refer to MIV-2 D25.
D	1. A declaration from the product registrant that the change does not impact the quality and safety of the drug product. 2. Revised specification of the excipient. 3. Comparative tabulated format of the approved and proposed specification of the excipient with changes highlighted. 4. Certificate of analysis or batch analysis data of the excipient including all tests in the proposed specification of at least two batches.