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PART B: CHECKLIST ON DOSSIER REQUIREMENTS FOR MIV-2 (NOTIFICATION) VARIATION

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C1 Change of Drug Product Name	
C	1. There is no change to the drug product (formulation, release and shelf-life specifications, manufacturing source and process) except for the drug 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 drafts of the package insert and labelling incorporating the proposed variation. 2. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 3. An official letter from the product owner or product registrant authorising the change of the drug product name and committing to inform users of the relevant changes (where applicable). 4. A declaration from the product registrant that there are no other changes to the product/label except for the drug product name change.

C2 <u>Change of Content of Product Labelling</u> a) Addition or amendment of warnings, precautions, contraindications, drug interactions, overdose and/or adverse events that results in strengthening of safety information or restriction of use. b) Addition or amendment of information on “Instructions for Use” for drug products with special delivery system/device (e.g., transdermal patches, inhalers, prefilled syringes etc.). c) Tightening of product’s target population. d) Deletion of indication. e) Alignment of a generic drug product labelling with that of the Singapore Reference Product. f) Minor change of content of product labelling that does not have any impact on the product’s safety, efficacy and quality.	
C	1. The change is not listed in MIV-2 D12.
D	1. Approved product labelling. 2. Proposed product labelling: a pristine and annotated version highlighting the changes made. 3. Relevant document/reference of justification to support the changes (where applicable).

C3	**Addition or Replacement of Company or Party Responsible for Batch Release**
C	1. Only applicable for the change of batch releaser. 2. The manufacturer of the drug product remains unchanged.
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. An official letter from the product owner authorising the company/manufacturer to be responsible for batch release (where applicable).

C4	**Change of Batch Size of Drug Substance** a) Change of batch size of sterile drug substance. b) Change of batch size of non-sterile drug substance by more than 10-fold.
C	1. For a change of batch size of non-sterile drug substance up to 10-fold compared to the approved batch size, refer to MIV-2 D13. 2. The change does not affect the reproducibility of the process. Any changes to the manufacturing process are only those necessitated by scale-up or downscaling, e.g., use of different-sized equipment. 3. Specifications of the drug substance remain unchanged.
D	1. A letter of declaration from the product registrant that the specifications of the drug substance have not changed and the reproducibility of the process has not been affected. 2. For a sterile drug substance, process validation report. 3. Amended relevant CTD Section S (where applicable). 4. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two batches of the drug substance for all tests in the approved specification from the approved and proposed batch sizes.

C5	**Minor Change of Manufacturing Process of Drug Substance**
C	1. No adverse change in the qualitative and/or quantitative impurity profile which would require further qualification in safety studies. Otherwise, refer to MIV-1 B3. 2. The synthetic route remains unchanged (for example, intermediates remain the same). Otherwise, refer to MIV-1 B3. 3. Manufacturing process of the drug substance does not use any materials of human/animal origin for which assessment is required for viral safety.

	4. Physicochemical characteristics and other relevant properties of the drug substance remain unchanged. 5. Specifications and stability performance of the drug substance remain unchanged; if there are changes made to the specification of the drug substance, MIV-1 B5, MIV-2 C6 or D15 is applicable.
D	1. Drug Master File (DMF), or relevant updated CTD S section(s) or equivalent document. 2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 3. For a sterile drug substance, process validation report (where applicable). 4. 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. 5. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance for all tests in the approved specification from the approved and proposed manufacturing processes.

C6 Change of Specification of Non-compendial Drug Substance	
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. Addition or replacement of a specification parameter and limit. 3. For widening of specification limits and deletion of significant test parameter and limits of the drug substance, refer to MIV-1 B5. For tightening of specification limit, or deletion of non-significant parameter, refer to MIV-2 D15. 4. For compendial drug substance, refer to MIV-2 D16. 5. The new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
D	1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed specification of the drug substance with changes highlighted. 3. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance for all tests in the approved and proposed specification. 4. Description of any new analytical method and a summary of the validation data.

C7	Change of Test Procedure of Non-compendial Drug Substance
C	1. Replacement or addition of a new test procedure. The new test does not concern a novel non-standard technique or a standard technique used in a novel way. 2. Results of method validation show that the new test procedure is at least equivalent to the former procedure. There have been no changes of the total impurity limits, and no new unqualified impurities are detected
D	1. Description of the test procedure, and a summary of validation data (where applicable). 2. Specification of the drug substance. 3. Comparative analytical results between the approved and proposed test (where applicable).

C8	Change of Shelf-life or Re-test Period of Drug Substance
C	1. The stability studies must show compliance with the specification. 2. There is no change in the storage condition.
D	1. Specification of the drug substance. 2. Stability data of the drug substance should be provided on at least three pilot or production scale batches at the proposed shelf-life or retest period.

C9	Change of Storage Conditions of Drug Substance
C	1. The stability studies must show compliance with the specification. 2. There is no change in the shelf-life or retest period.
D	1. Specification of the drug substance. 2. Stability data of the drug substance should be provided on at least three pilot or production scale batches at the proposed storage condition.

C10	Change of Batch Size of Non-sterile Drug Product
C	1. The change does not affect reproducibility and/or consistency of the product. 2. Release and shelf-life specifications of the drug product remain unchanged. 3. This is applicable to a change of batch size up to 10-fold compared to the approved batch size of the non-sterile drug product. For a change of batch size more than 10-fold compared to the approved batch size for non-sterile drug product, refer to MIV-1 B11.

	4. For a change of batch size for sterile drug products, refer to MIV-1 B10.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Revised CTD Section P3 (where applicable). 3. Validation scheme and report of the manufacturing process as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* of the proposed batch size appropriate to the proposed batch size. 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 batch sizes. 6. 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.

C11 Reduction or Removal of Overage	
C	1. Changes of approved manufacturing overages of the drug substance only. 2. Release and shelf-life specifications of the drug product remain unchanged.
D	1. Justification for the change. 2. Revised CTD section P1 and P3.2. 3. Comparative tabulated format of approved and proposed batch manufacturing formula. 4. Certificates 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 formula. 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.

C12 Qualitative and/or Quantitative Change of Excipient a) For immediate release oral solid dosage forms only (as per Level 1, Part III Components and Composition, SUPAC guideline). b) For other non-critical non-solid dosage forms, e.g., oral liquid, external preparation.	
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. 2. Replacement of an excipient with a comparable excipient of the same functional characteristic (where applicable). 3. The dissolution profile of the proposed drug product is comparable to that of the approved drug product. 4. For qualitative or quantitative changes of excipient for immediate release (Level 2 and 3 change as per US FDA SUPAC IR Guideline) and modified release oral solid dosage forms, and other critical dosage forms, refer to MIV-1 B13. 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 drug product formula (where applicable). 6. Specification of the proposed excipient(s). 7. A declaration that the proposed excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 8. 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.

	9. Release and shelf-life specifications of drug product. 10. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product on at least two batches (preferably production scale) manufactured according to the approved and proposed drug product formula. 11. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.* 12. 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. 13. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed oral solid dosage forms formulation as per US FDA SUPAC IR guideline.

C13 Quantitative Change in Coating Weight of Tablets or Weight and/or Size of Capsule Shell for Immediate Release Oral Solid Dosage Form	
C	1. The dissolution profile of the proposed 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 modified release oral solid dosage forms, refer to MIV-1 B14.
D	1. Revised drafts 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 P1. 4. Revised 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 solid dosage forms formulation as per US FDA SUPAC IR guidelines.

C14 Change of Colouring/Flavouring Agent of Drug Product	
C	1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring/flavouring agents must not have been rejected for pharmaceutical use. 3. The release and shelf-life specifications of the drug product remain unchanged except for the change in colour/flavour.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Revised CTD P1. 3. A declaration from the product registrant that the change does not interfere with the drug product release and shelf-life specifications test method. 4. Comparative tabulated format of the approved and proposed drug product formulation and batch manufacturing formula, including the qualitative and quantitative information of colouring/flavouring agents. 5. For proposed excipients 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. 6. Proposed release and shelf-life specifications of the drug product (where applicable). 7. 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.

C15 Deletion 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 addition of a solvent/diluent, refer to MIV-1 B17.
D	1. Revised drafts of the package insert and labelling 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 CTD P Sections (where applicable).

C16 Change of In-process Controls Applied during Manufacture of Drug Product	
C	1. Addition or replacement of new in-process control (IPC). The new test method that does not concern a novel non-standard technique or a standard technique used in a novel way. 2. For widening of specification limits of IPC or deletion of test parameters and limits of IPC, refer to MIV-1 B24. For tightening of specification limits 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. 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 or comparative batch analysis data of the drug product of at least two production batches.

C17 Minor Change of Manufacturing Process for Drug Product	
C	1. The manufacturing site remains unchanged. If there is a change in manufacturing site, MIV-1 B7 is also applicable. 2. For major change in the manufacturing process for the drug product, refer to MIV-1 B12, or refer to MIV-2 D21 for minor change as per SUPAC Guideline Level 1. 3. The overall manufacturing principle remains unchanged. 4. Applicable to a change in the hold time of an intermediate or bulk product if the approved drug product shelf life remains unchanged. Otherwise, MIV-1 B18 is also applicable. 5. The change does not cause negative impact on the quality, safety and efficacy of the drug product. 6. The dissolution profile of the proposed drug product is comparable to that of the currently approved drug product.

	7. Release and shelf-life specifications of the drug product remain 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. 2. Description of the proposed manufacturing process and technical justification for the change. 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*. 4. Approved 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 on at least two batches (preferably production scale) manufactured to both the approved and the proposed processes. 6. 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. 7. For oral solid dosage forms, comparative dissolution profile data of at least one representative production batch of the drug product between the currently approved and proposed oral solid dosage forms formulation as per US FDA SUPAC IR or MR guidelines.

C18 Change of Specification of Non-compendial Excipient	
C	1. Addition or replacement of a specification parameter and limit of the excipient. For widening of specification limits and deletion of significant test parameter and limits of the excipient, refer to MIV-1 B25. 2. Notification is not required for a change in the supplier for the excipient with the same specification. 3. Applicable to non-compendial excipients. For compendial excipients, refer to MIV-2 D25. 4. Release and shelf-life specifications of the drug product remain unchanged.
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. Description of new method and summary of analytical validation (where applicable). 4. Comparative tabulated format of the approved and proposed specification of the excipient with changes highlighted. 5. Certificate of analysis or batch analysis data of at least two batches the excipient including all tests in the proposed specification.

C19 Change of Test Procedure for Excipient	
C	1. For replacement or addition of a test procedure for excipients. 2. For minor change of a test procedure for excipient, refer to MIV-2 D24.
D	1. Description of the analytical methodology with a comparative tabulation of the changes. 2. Results of appropriate method validation to show proposed test procedure to be at least equivalent to the approved procedure. 3. For quantitative test change, comparative analytical validation results showing that the approved and proposed tests are equivalent.

C20 Change in Source of Empty Hard Capsule	
C	1. Replacement of a TSE-risk material by a different TSE-risk material, or from vegetable-sourced or synthetic capsule to TSE-risk material capsule. 2. For change of TSE-risk material to vegetable-sourced or synthetic empty hard capsule, please refer to MIV-2 D26. 3. Not applicable to a change from a hard capsule to a soft gel. 4. The formulation and manufacturing process of the drug product remain unchanged. 5. The specifications of excipients and specifications of the release and shelf-life of drug product remain unchanged.
D	1. Technical specifications and composition of the empty hard capsule of the proposed source. 2. Certificates of analysis of the empty hard capsule of the proposed source. 3. For empty hard capsule 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. 4. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product using the hard capsule between the two sources (where applicable) as per US FDA SUPAC IR or MR guidelines.

	5. 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.

C21 Change of Release and/or Shelf-life Specifications of 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. Addition or replacement of a specification parameter and limits where the change does not concern any impurities (including genotoxic) or dissolution 3. For widening of specification limits and/or deletion of test parameter and limits of the drug product, refer to MIV-1 B9. For tightening of specification limits, or deletion of non-significant parameter, 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	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 or batch analysis data of the drug product on at least two batches (preferably production scale) for all tests in the proposed specification. 4. Description of any new method and summary of analytical validation data for the non-compendial method (where applicable). 5. Justification of the new specification parameter and the limits. 6. For stability indicating parameter, 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.

C22 Change of Imprints, Embossing/Debossing or Other Markings on Tablets or Printing on Capsules including Addition or Change of Inks Used for Product Marking	
C	1. New markings do not cause confusion with other registered drug products.

	2. The proposed ink used must comply to relevant pharmaceutical legislation or be of food grade. 3. Release and shelf-life specifications of the drug product remain unchanged except for appearance. 4. Refer to MIV-1 B20 for addition or change of functional score/break-line.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Details and specifications of the proposed ink (where applicable). 3. Detailed drawing or written description of the approved and proposed imprint/bossing/markings. 4. Certificate of analysis of the ink/printing material (pharmaceutical grade and of food grade) (where applicable). 5. Release and shelf-life specifications of the drug product with the new drug product description (where applicable).

C23	**Change of Dimensions and/or Shape of Tablets, Capsules, Suppositories or Pessaries Without Change in Qualitative and Quantitative Composition and Mean Mass**
C	1. If appropriate, the dissolution profile of the proposed drug product is comparable to that of the currently approved drug product. 2. Release and shelf-life specifications of the drug product remain unchanged except for dimension and/or shape.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Detailed drawing or written description of the current and proposed appearance, and revised relevant CTD sections, i.e., Section P1 (where applicable). 3. Data on test of content uniformity of the subdivided parts of tablets at release as conformed to compendial requirement should be submitted (only applicable for drug product with score/break-line). 4. Release and shelf-life specifications of the drug product. 5. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product of the approved and proposed dimensions as per US FDA SUPAC IR or MR guidelines (where applicable). 6. Justification for not submitting a new bioequivalence study according to the ASEAN *Guidelines for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable) for dosage forms other than immediate release oral solid dosage forms, suppositories and pessaries.

C24 Change in Test Procedure of 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. Replacement or addition of a test procedure for the testing of drug product. 3. The specifications of drug product remain unchanged; if the specification is changed, MIV-1 B9, MIV-2 C21 or D22 is also applicable. 4. Results of method verification/validation show the new test procedure to be at least equivalent to the former procedure.
D	1. Justification for the proposed change. 2. Comparative tabulated format of the approved and proposed specifications of the drug product. 3. Description of the analytical methodology. 4. Appropriate verification/validation data and comparative analytical results between the currently approved and proposed test (where applicable). 5. Certificate of analysis or batch analysis data of the drug product on at least two batches (preferably production scale) for all tests in the proposed specification.

C25 Change in Primary Packaging Material for Non-sterile Drug Substance or Drug Product a) Change in qualitative and quantitative composition. b) Change in same packaging / type of container, i.e., from blister to blister. c) Inclusion of new primary packaging material.	
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. Notification is not required if there is a change of the supplier for the same type of primary packaging material with the same specification. 3. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties. If a less protective primary packaging material is proposed, refer to MIV-1 B15. 4. For a change in the primary packaging material for a sterile drug substance or drug product, refer to MIV-1 B15. 5. For a change of specification parameters or limits, or test procedure of primary packaging material, refer to MIV-2 D28. 6. Release and shelf-life specifications of the drug substance or drug product remain unchanged.

D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the change in packaging material. 3. Comparative tabulated format of the approved and proposed specifications of the primary packaging material (where applicable). 4. Revised CTD Sections P3 and/or P7 (where applicable). 5. Declaration of compliance to the appropriate international standards or pharmacopoeia. 6. For semi-solid and liquid dosage forms, relevant studies to demonstrate that no interaction between the content and the packaging material occurs (where applicable). 7. For drug substance: Results of at least three 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. 8. 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.

C26 Addition or Replacement of Manufacturing Site for Primary Packaging for Non-Sterile Drug Product	
C	1. No other changes except for the addition or replacement of an alternative site(s) for primary packaging (direct contact with drug product) for non-sterile drug product. 2. The primary packaging material must be the same approved primary packaging material with the same specifications. 3. For sterile drug product, refer to MIV-1 B8.
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. 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).

C27 Addition or Replacement of Manufacturer for Secondary Packaging	
C	None.
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. Official letter from the product owner authorising the proposed manufacturer or packager to perform secondary packaging (where applicable) 4. For local secondary packager, an official letter from the product registrant authorising the local secondary packager to perform secondary packaging (where applicable).

C28 Change or Addition of Pack Size/Fill Volume and/or Change of Shape or Dimension of Primary Packaging Material for Non-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 pack size/fill volume specification. 4. For change or addition of pack size/fill volume and/or change of shape or dimension of primary packaging material for a sterile drug product, refer to MIV-1 B16.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Revised CTD Sections P3, P5.1 and/or P7 (where applicable). 3. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 4. 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.

C29 Addition or Replacement of Measuring Device for Oral Liquid Dosage Forms and Other Dosage Forms	
C	1. The size and the accuracy of the proposed measuring device must be compatible with the approved posology, where applicable. 2. The proposed device is compatible with the drug product.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Description of the device (including a drawing; where applicable). 3. The composition of the device material. The materials should comply with the pharmacopoeia, where applicable. 4. Justification that the size and accuracy of the device are adequate for the posology as approved in the product labelling.

C30 Change in Supplier of Animal-derived Material	
C	1. For animal-derived material of mammalian or avian origin used as a raw material in the drug substance manufacturing or as an excipient in the drug product. 2. Notification is not required for a change in the supplier of a raw material or an excipient which is not of mammalian or avian origin if the specification of the raw material or excipient remains unchanged. 3. There is no change in the animal species from which the animal-derived material is obtained from. 4. Animal-derived materials from other species (e.g., insects and fish) are exempted from this variation. 5. For change in gelatin source of empty hard capsule, refer to MIV-2 C20.
D	1. Information on all countries which the animal was sourced from*. ** Not required for animal derived products from milk and certain milk derivatives such as lactose.* 2. Declaration on the nature of the animal tissue and/or fluid used. 3. Certificate of analysis for the animal-derived material used, stating the name and address of the supplier. 4. Relevant information to demonstrate that the manufacturing process is capable of inactivating adventitious agents, where applicable. 5. 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.

C31 Change in Species of Animal-derived Material	
C	1. For a change in species of animal-derived material used a) at any stage in the manufacture of the drug substance and/or drug product (e.g., from pig to cow); b) as an excipient or active substance (e.g., bovine gelatine to porcine gelatine) of the drug product; or c) as an adjuvant. 2. This variation includes all species of animals.
D	1. Information on all countries which the animal was sourced from*. ** Not required for animal derived products from milk and certain milk derivatives such as lactose.* 2. Declaration on the nature of the animal tissue and/or fluid used. 3. Certificate of analysis for the animal-derived material used, stating the name and address of the supplier for mammalian and avian materials. 4. Identification of new adventitious agents, where applicable. 5. Relevant information to demonstrate that the manufacturing process is capable of inactivating new adventitious agents, where applicable. 6. 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.

C32 Addition or Replacement of Drug Substance Intermediate Manufacturer	
C	1. No adverse change in the qualitative and/or quantitative impurity profile which would require further qualification in safety studies. Otherwise, refer to MIV-1 B3.

	2. The synthetic route remains unchanged (for example, intermediates remain the same). Otherwise, refer to MIV-1 B3. 3. 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.
D	1. Justification for change. 2. Revised relevant CTD, e.g., 3.2.S.2. 3. 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. 4. Certificate of analysis or batch analysis data for at least two pilot batches of the drug substance manufactured using the drug substance intermediate from the new drug substance intermediate site.

C33 Change of Specification of Starting Material	
C	1. Only for the change of specification of starting material. 2. Notification is not required if there is a change in the supplier for the starting material with the same specification. 3. Refer to MIV-2 D25 for the change of specification of starting material to comply with latest compendium. 4. Specification of the drug substance remains unchanged. 5. No adverse change in the qualitative and/or quantitative impurity profile which would require further qualification in safety studies. Otherwise, submit MIV-1 B3 or B4.
D	1. Justification for the change. 2. A copy of the updated dossier 3.2.S.2.3 and/or 3.2.R. 3. Proposed specifications of the starting material and/or a copy of the Certificate of analysis. 4. A letter of declaration stating that the specification of the drug substance has not changed.