APPENDIX 14 GUIDELINE ON MINOR VARIATION APPLICATIONS FOR BIOLOGICAL THERAPEUTIC PRODUCTS

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INTRODUCTION

This document describes the requirements of a Minor Variation Application (MIV) submitted for an existing registered **biologic** drug product in Singapore. Product registrants should be familiar with the contents of this document, Chapters F and H of this guidance and the governing legislation prior to submitting an MIV to HSA.

The following points should be considered when submitting an MIV:

- If one MIV contains multiple changes that belong to both MIV-1 and MIV-2 categories, then the MIV should be categorised as an MIV-1; and,
- If a proposed MIV-2 does not meet its specified conditions, then the MIV shall be submitted as an MIV-1 with the relevant supporting documents.

MIV-1 changes should be grouped together as one application when these changes are consequential changes. A consequential change is regarded as a change that is unavoidable and is a direct result of another change, not simply a change that occurs at the same time. HSA reserves the right to split any MIV-1 with non-consequential changes into separate MIV applications.

In exceptional situations, the evaluation timeline for MIV-1 applications may be extended beyond that published, for example, for extensive grouping of changes. In such cases, the extended timeline will be communicated to the applicant.

HSA also reserves the right to re-categorise the MIV if deemed appropriate.

NOTE: Product registrants are encouraged to email the *MIV Filing and Submission Enquiry Form* in Appendix 12 if there are any issues regarding MIV filing, such as the absence of a relevant checklist for a particular change.

1 REGISTRATION PROCESS

An MIV is submitted via the "*Amendment to a Registration of Western Drug Product*" form in PRISM.

Product registrants should disclose **all** proposed changes in *Section 0 Registration Summary* under *Section 0.4 MIV Checklist Number (Primary Change)* and *Section 0.5 MIV Checklist Number (Secondary Change(s));* and in the *Table of Amendment Details*, which can be downloaded via the link indicated in *Section 0.7 Table of Summary of Changes*. Any undisclosed variation(s) embedded in the submitted data, or any follow-on changes not specifically requested by HSA, will **not** be considered for evaluation. Please refer to Section 2 of Appendix 17 for more information on submitting a minor variation application.

2 DOCUMENTARY REQUIREMENTS

The following documents listed in Table A must be submitted with each MIV submission:

Table A MIV Application Submission Requirements

	Softcopy
PRISM Application Form	PRISM
Table of Contents	PRISM
Cover Letter	**PRISM**
Checklist for MIV(s)	PRISM
Table of Summary of Changes	PRISM
MIV-specific Supporting Documents - Administrative (Module 1/Part 1) - Other supporting documents	 PRISM PRISM/CD[#]
Approved and Proposed Product Labelling (annotated and pristine copies), where applicable	PRISM

 # All supporting documents may be submitted via PRISM or CD-ROM – do not combine PRISM attachments with a CD submission

The checklists for MIV-1 and MIV-2 (Notification and Do-and-Tell) for biologic drug products are located in Part A, B and C of this Appendix. These checklists serve as guides when submitting the required documents relevant to each proposed MIV. When submitting the Checklist, the following should be included:

- A copy of the relevant checklist(s) to each proposed MIV(s) – justifications should be provided below the respective document description if there is any omission of documentation; and
- A *Table of Summary of Changes* which concisely describes the proposed MIV(s). The following information must be stated in the Table:
  - Section(s) of the original dossier affected by the change(s);
  - Approved and proposed condition(s);
  - Reason(s) for the change(s); and
  - Registration status and date of the proposed change(s) in other countries/agencies that had approved the variation(s), especially the country of origin and HSA's reference agencies.

For an MIV application with multiple related or unrelated variations, all of the supporting documents for each individual variation should be submitted. If the required documents have not been submitted, justifications must be provided.

For MIV applications with labelling changes, annotations should be made on the proposed labelling materials based on the actual text to be added, and on approved labelling materials. Approved text which is proposed for deletion should be struck through, whereas new proposed text should be underlined or highlighted. Approved text that is not intended to be deleted should not be annotated. However, the translocation of approved text from one section to another can be allowed in its entirety.

This document reflects the current thinking of HSA on the minimum data necessary for assessment. Product registrants are responsible for ensuring that all necessary validations were conducted to demonstrate that the change does not adversely affect the quality, safety

or efficacy of the drug product concerned. HSA reserves the right to request for additional information if deemed appropriate.

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

B1	**Change and/or Addition of Alternative Manufacturer/Site of Drug Substance, Drug Product, Process Intermediates and/or Primary Packager**
C	1. If there are changes to the manufacturing process, including change in batch size, MIV-1 B2 or MIV-2 C4 is also applicable. 2. If there are changes to the drug substance or drug product specification, MIV-1 B3 or MIV-2 C5 is also applicable. 3. Not applicable to changes relating to the manufacturer responsible for batch release (refer MIV-2 C3).
D	1. Amended relevant CTD Sections. 2. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 3. Proof that the proposed site is appropriately authorised for the pharmaceutical form concerned, such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. *(Note: a GMP Conformity Assessment is required if the proposed drug product manufacturing site is not currently registered with HSA)*. 4. Batch numbering system (where applicable). 5. In the 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). 6. Validation scheme and/or report of the manufacturing process as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* at the proposed site(s). 7. Approved release and/or shelf life specifications of the drug substance, drug product or process intermediates. 8. <u>For the change of manufacturing site for drug substance or drug substance intermediate</u>: comparability study of the approved and proposed drug substance or any intermediate of the drug substance with respect to physico-chemical characterisation, biological activity and impurity profile, including certificate of analysis or comparative batch analysis data of at least two production batches, of the drug substance from the approved and proposed sites. 9. <u>For the change of manufacturing site for drug product or drug product intermediate</u>: certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product from at least two production batches from the approved and proposed site. 10. Stability studies as per the relevant guidelines on the stability study of the drug substance or 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.

B2	**Change in Manufacturing Process**
C	1. For changes to the manufacturing process, including change in batch size, at any stage during the manufacture of a drug substance, drug product, and/or process intermediates. 2. The change may cause a significant impact on the quality, safety and efficacy of the drug product. 3. The change does not adversely affect the reproducibility of the process. 4. Manufacturing site remains unchanged. If there is a change in manufacturing site, MIV-1 B1 is also applicable. 5. Specification of the drug substance or drug product remains unchanged. If there is a change in the specification, MIV-1 B3 or MIV-2 C5 is also applicable. 6. For any change not covered by MIV-2 C4.
D	1. Comparative tabulated format of the approved and new processes with changes highlighted (where available). 2. Description of the new manufacturing process and technical justifications 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* should be provided upon submission. 4. A copy of the approved release and shelf-life specifications. 5. <u>For the change of manufacturing process for drug substance or drug substance intermediate</u>: Comparability of the approved and proposed drug substance or any intermediate of the drug substance with respect to physico-chemical characterisation, biological activity and impurity profile, including certificate of analysis or comparative batch analysis data of at least two production batches of the drug substance from the approved and proposed processes. 6. <u>For the change of manufacturing process for drug product or drug product intermediate</u>: certificate of analysis or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches manufactured according to the approved and proposed processes. 7. Stability studies as per the relevant guidelines on the stability study of the drug substance or drug product. 8. 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.

B3	**Change of Specification of Drug Substance, Drug Product, Process Intermediate and/or In-process Control Tests** a) Widening of specification limits. b) Deletion of specification parameters which may have a significant effect on the overall quality of the drug product..
C	1. Test procedures remain unchanged, or changes in the test procedure are minor. 2. For tightening of the specification limit, addition of new specification parameter, deletion of a non-significant specification parameter, refer to MIV-2 C5. 3. 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.
D	**Specification limits are widened** 1. Justification for change substantiated with scientific data. 2. Revised specification of the drug substance, drug product, process intermediate or in-process control test. 3. Comparative tabulated format of the approved and revised specification of the drug substance, drug product, process intermediate or in-process control test, with changes highlighted. 4. Test results of two production batches of the drug substance, drug product, process intermediates or in-process control, from all tests in the revised specification. 5. For change of specification that involved stability-indicating parameters, stability studies as per the relevant guidelines on the stability study of the drug substance or 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.

B4	**Qualitative or Quantitative Change of Excipient of Drug Substance and/or Drug Product**
C	1. Change will need to comply with the drug substance or drug product specifications, i.e., the release and shelf-life specifications of the drug substance/drug product remain unchanged, excluding product description. 2. Replacement of an excipient with a comparable excipient of the same functional characteristic. 3. HSA reserves the right to re-categorise the application to NDA, 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 revised 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 P3.1 to P3.4 (where applicable), including revised batch manufacturing formula. 5. Validation scheme and/or report of the manufacturing process as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* appropriate to the proposed change in the drug product formula should be provided upon submission. 6. Information demonstrating comparability in terms of physico-chemical characterisation and impurity profile of the proposed excipient with the approved excipient (if applicable). 7. Specification of the proposed excipient(s). 8. 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. 9. Drug substance or drug product release and shelf-life specifications. 10. Certification of analysis or batch analysis data (in a comparative tabulated format) of the drug substance or drug product on at least two production batches according to the approved and proposed drug product formula. 11. Stability data as per relevant guidelines on the stability study of the drug substance or 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.

B5	**Change in Primary Packaging Material for Sterile Drug Substance or Drug Product** a) Change in qualitative and quantitative composition. b) Change in type of container. c) Inclusion of a new primary packaging material.
C	1. For any change of the container closure system that is in immediate contact with the drug substance, drug product, process intermediates, and/or diluent used for reconstitution. 2. No submission is required if there is a change of the supplier for the same type of primary packaging material with the same specification. 3. Release and shelf-life specifications of the drug product remain unchanged. 4. For a minor change in the primary packaging material, refer to MIV-2 C9.
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 specification of the approved and proposed primary packaging material. 4. Revised CTD Sections (where applicable). 5. Information on the construction materials and design features of the proposed container closure system. 6. Declaration of compliance to the appropriate international standards or pharmacopoeia. 7. Appropriate scientific data on the new packaging (comparative data on permeability, e.g. moisture, O_2, CO_2, container closure integrity test). 8. 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). 9. Validation report of the manufacturing and sterilisation process as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* appropriate to the proposed change in the primary packaging material should be provided upon submission. 10. Stability data as per the relevant guidelines on the stability study of the drug substance or 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.

B6	**Change or Addition of Pack Size/Fill Volume**
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. 5. For any change that only concerns the number of units or containers in a pack, refer to MIV-2 C11.
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 and/or P7 (where applicable). 4. Validation data of the manufacturing process, sterilisation and container closure system (where applicable). 5. Stability data as per the relevant guidelines on the stability study of the drug substance or 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.

B7	**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 C7. 3. For change of shelf-life and/or storage condition of the drug product as a package of sale, and/or after first opening, and/or after dilution/reconstitution, refer to MIV-1 B8 and/or B9.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation. 2. Proof that the proposed manufacturing site of the solvent/diluent is appropriately authorised for the pharmaceutical form concerned, such as a valid Good Manufacturing Practice (GMP) certificate and/or a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA). 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 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).

B8	**Change of Shelf-life of Drug Substance, Drug Product or Process Intermediate** a) As a package for sale; and/or b) After first opening; and/or c) After dilution/reconstitution.
C	1. For (a) & (b), the studies must show conformance to the approved shelf-life specification. 2. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product. 3. 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.
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 long term stability studies covering the duration of the proposed shelf-life of at least two production batches of the drug substance or 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 relevant guidelines on the stability study of the drug substance or drug product.

B9	**Change of Storage Condition of Drug Substance, Drug Product or Process Intermediate** a) As a package for sale; and/or b) After first opening; and/or c) After dilution/reconstitution.
C	1. For (a) & (b), the studies must show conformance to the approved shelf-life specification.

	2. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product. 3. 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.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long term stability studies covering the duration of the approved shelf-life (at the proposed storage condition) of at least two production batches of the drug substance or 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 relevant guidelines on the stability study of the drug substance or drug product.

B10	**Addition or Replacement of Site Responsible for Quality Control Testing Laboratory**
C	1. For addition or replacement of the approved laboratories for release and/or stability test of a biological/ immunological/ immunochemical test method, or a method using a biological reagent (does not include standard pharmacopoeia microbiological methods).
D	1. Approved release and shelf life specification. 2. Analytical procedures to be carried out at the proposed site. 3. Validation of analytical procedures performed at the proposed site. 4. Certification of analysis or batch analysis data (in a comparative tabular format) of at least two production batches tested at the approved and proposed sites.

B11	**Replacement of Master Cell/Seed Bank**
C	1. For the generation of a new master cell/seed bank derived from the original or pre-approved master cell/seed bank or working cell/seed bank by sub-cloning. 2. This does not relate to any change in the host cell line. 3. HSA reserves the right to re-categorise the application to NDA, if deemed appropriate.

D	1. Source, history and passage number of the new master cell/seed with documentation of all raw material of human or animal origin used for the entire culture history. 2. Result of all identity testing, including cytogenetic characteristics that could be used to identify the cells. 3. Results of all available adventitious agent testing on the donor and the new master cells. 4. Growth and expression characteristic if the cell substrate is used to produce a recombinant protein. This includes evaluating the copy number and stability of introduced nucleic acids and the quantity and quality of express protein up to a passage level beyond the anticipated production cycle time. 5. Validated cell stability under the freezing and storage conditions using cell recovery or viability data. 6. For viral master seed, document all manipulation of the viral phenotype, such as attenuation of virulence or genetic re-assortment or recombinant. This includes the determination of the nucleic acid sequences and sourcing of the biological starting material. 7. Sterility tests, mycoplasmas and adventitious viruses test data if appropriate. 8. Comparability of approved and proposed drug substance with respect to physico-chemical characterisation, biological activity and impurity profile. 9. Batch analysis data (in a comparative tabular format) of at least three production batches of drug substance derived from the approved and proposed cell/seed banks. 10. Stability data as per the relevant guidelines on the stability study of the drug substance. 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.

B12 Change of Test Procedure	
C	1. For substantial change or replacement of a biological/ immunological/ immunochemical test method, or a method using a biological reagent (does not include standard pharmacopoeia microbiological methods). 2. For any change not covered by MIV-2 C13. 3. The specification of the drug substance, drug product, excipient and/or in-process test remain unchanged. If there are changes made to the specification, submit MIV-1 B3 or MIV-2 C5 at the same time.
D	1. Justification for the proposed change. 2. Description of the proposed analytical procedure. 3. Validation of the analytical procedure.

	4. Comparative test results between the approved and proposed test procedure, or certificate of analysis or comparative batch analysis, of two production batches of the drug substance, drug product, excipient, or in process control test.

B13	**Seasonal Variation of Influenza Strains for Vaccine**
C	1. For a change of **only** influenza strains for the formulation of an influenza vaccine according to WHO Recommendations for Influenza Vaccine Composition may be expedited. *(Note: additional changes other than strain changes will require additional supporting documents, which may delay the evaluation timeline).* 2. If there is no change of influenza strains for the formulation of an influenza vaccine according to WHO Recommendations for Influenza Vaccine Composition, documentation listed in (B) is to be submitted.
D	**A) Variation involved change of the virus strain** 1. Approved product label (outer carton, inner label and package insert) with the proposed change(s) clearly highlighted, underscored, or otherwise indicated. 2. Proposed product label (outer carton, inner label and package insert) with all change(s) incorporated, which include, but not limited to: a. Strain type. b. Year/Year. c. Southern hemisphere or northern hemisphere. 3. Quality Overall Summary. 4. Identification of working seed stock as per the pharmacopoeial requirements. 5. Validation study reports and/or summaries of the critical manufacturing process for drug substances (new strain), e.g. inactivation, splitting efficiency. 6. Release and/or shelf life specification for the drug substances. 7. Validation study reports and summaries of the test method for the new strain. 8. Batch analyses data for drug substances. 9. Composition of the vaccine. 10. Actual formula(e) of the vaccine used for clinical trial studies for the change of influenza strains and commercial purpose (in a table). 11. Release and/or shelf life specification for the vaccine. 12. Comparative batch analyses data (in a table) of the vaccines manufactured using the approved and proposed strains. 13. Stability study result of at least 6 months of the vaccine from the preceding year or season. 14. 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. **B) Variation submission for no change of virus strains**

	1. Approved product label (outer carton, inner label and package insert) with the proposed change(s) clearly highlighted, underscored, or otherwise indicated. 2. Proposed product label (outer carton, inner label and package insert) with all change(s) incorporated, which include, but not limited to: a. Strain type. b. Year/Year. c. Southern hemisphere or northern hemisphere. 3. Quality Overall Summary. 4. Stability study result of at least 6 months of the vaccine from the preceding year or season. 5. 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. 6. Composition of the vaccine.

B14 Change of Reference Standard	
C	1. For change of in-house/non-compendial reference standard not covered by an approved calibration/qualification protocol. If there is no change of the approved protocol, refer to MIV-2 C14. 2. To change from a compendial to non-compendial/in house reference standard.
D	1. The preparation protocol for the new reference standard. 2. The calibration/qualification protocol for the reference standard. 3. Amended relevant CTD Sections. 4. Summary report on the calibration/qualification of the new lot(s) of reference standard, e.g. characterisation, information regarding the manufacturing process used to establish the reference standard, certificate of analysis, expiry date, storage condition, stability and re-qualification, should be provided. 5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug substance or drug product on at least two production batches using the approved and proposed reference standard.

B15 Change of Content of Product Labelling	
C	1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister labels. 2. 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 clean and annotated version highlighting the changes made. 3. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4. Justifications for the changes proposed and supporting clinical documents where applicable.

B16	**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 B3.
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 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 relevant guidelines on the stability study of the drug substance or 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	**Addition or Replacement of New Plasma Master File (PMF) to Registered Human Plasma-derived Product**
C	1. The change does not cause a negative impact on the quality, safety and efficacy of the drug product.

D	1. New or latest version of the PMF. 2. Latest EMA annual recertification letter and recertification assessment report, if available. 3. Letter of Access issued by the PMF holder to the product owner. 4. An expert statement outlining all changes introduced to the PMF with evaluation of the potential impact on the drug product, including specific risk assessments. 5. Amended relevant CTD Sections. 6. Certificate of analysis or comparative batch analysis data of the drug product of at least three production batches manufactured using the previous and new PMF. 7. Stability data as per the relevant guidelines on the stability study of the drug substance or drug product. 8. 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.

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

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 drug product name and committing to inform users of the relevant changes (where applicable). 4. A declaration from the product registrant that there is no other changes to the product/label except for the drug product name change.

C2	Change of Product Labelling
	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 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) Administrative/editorial changes that have no impact on safety, efficacy and quality.
C	1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister label. 2. The change is not an MIV-1 and does not contain promotional information.
D	1. Approved product labelling. 2. Proposed product labelling, and a clean and annotated version highlighting the changes made. 3. Relevant document/reference 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. Proof that the proposed site is appropriately authorised (accredited by the authority) to be responsible for batch release, such as a valid GMP certificate or CPP which covers the GMP certification, where applicable. 3. An official letter from the product owner authorising the company/manufacturer to be responsible for batch release (where applicable).

C4 Minor Change of Manufacturing Process	
C	1. For any minor change of the approved manufacturing process at any stage during manufacture of the drug substance, drug product and/or process intermediates. 2. Relates to a non-critical change in the process that does not require an assessment of comparability, such as change in harvesting and/or pooling procedures without a change in the method of manufacturing, recovery, storage conditions or production scale; duplication of a fermentation train; addition of identical or similar/comparable bioreactors. 3. No adverse change in the qualitative and/or quantitative impurity profile or in physico-chemical characteristics and other relevant properties. 4. Proposed manufacturing process of the drug substance and/or drug product does not use any new materials of human/animal origin for which assessment is required for viral safety. 5. Specification of the drug substance or drug product remains unchanged. If there is a change in the specification, MIV-1 B3 or MIV-2 C5 is also applicable.
D	1. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 2. Description of the new manufacturing process and technical justifications 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* should be provided upon submission. 4. A copy of the approved release and shelf-life specifications, and a letter of declaration from the product registrant stating that the specifications of the drug substance or drug product have not changed. 5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug substance or drug product of at least two batches manufactured according to the approved and proposed processes, where appropriate. 6. A commitment letter to complete the relevant on-going stability studies of the drug substance or drug product in accordance with the relevant guideline. 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.

C5	**Change of Specification of Drug Substance, Drug Product, Process Intermediate and/or In-process Control Tests** a) Specification limits are tightened. b) Addition of new test parameter and limits. c) Deletion of non-significant parameter (e.g., obsolete parameter).
C	1. Test procedures remain unchanged. If there are changes to the test procedures, MIV-1 B12 or MIV-2 C13 is also applicable. 2. For widening of specification limits and deletion of test parameter and limits, refer to MIV-1 B3. 3. 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.
D	**Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed specification with changes highlighted. 3. Test results of two production scale batches of the drug substance, drug product, process intermediates or in-process controls, for all tests in the revised specification. **Addition of new test parameter and limits** In addition to the above documents, 4. Description of any new analytical method and summary of the validation data (where applicable). 5. Justification of the new specification parameter and the limits. 6. For stability indicating parameter, stability data as per the relevant guidelines on the stability study of the drug substance or drug product. 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 non-significant parameter** In addition to documents (1) and (2), 7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.

C6	Change of Colouring/Flavouring Agent of Drug Product
C	1. Same functional characteristic, 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. A declaration from product registrant that the change does not interfere with the drug product release and shelf-life specifications test method. 3. 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. 4. 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. 5. Revised release and shelf-life specifications of the 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.

C7	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.
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 Section P (where applicable).

C8	**Change of Specification of Non-compendial Excipient**
C	1. Release and shelf life specifications of drug product remain unchanged. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 3. Applicable to non compendial excipients. For compendial excipients, refer to MIV-2 C24.
D	1. A declaration from the product registrant that the change does not impact the quality and safety of the drug product. 2. Description of new method and summary of analytical validation (applicable for addition or replacement of new parameter). 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 for all tests in the proposed specification.

C9	**Minor Change in Primary Packaging Material for Non-sterile Drug Substance or Drug Product** a) Change in qualitative and quantitative composition. b) Change in type of container. c) Inclusion of new primary packaging material.
C	1. No submission is required if there is a change of the supplier for the same type of primary packaging material with the same specification. 2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties. 3. Release and shelf life specifications of the drug substance or drug product remain unchanged. 4. For a change in the primary packaging material for a sterile drug substance or drug product, refer to MIV-1 B5.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 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. 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.

C10 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. Proof that the proposed site is appropriately authorised (accredited by the authority) for the packaging activity concerned, such as a valid GMP certificate and/or CPP which covers the GMP certification (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA). 3. Official letter from the product owner authorising the new manufacturer or packager to perform secondary packaging (where applicable).

C11 Change of Pack Sizes for Drug Product	
C	1. For change that only concerns the number of units (e.g., tablets, ampoules, etc.) or containers in a pack; otherwise, refer to MIV-1 B6. 2. The type and material of the primary packaging material remain unchanged. 3. The remaining product presentation(s) must be adequate for the dosing regimen and duration of use as per the approved product labelling.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A letter of declaration from the product registrant stating that there are no other changes except for the change of pack sizes for a drug product. 3. A commitment letter to conduct relevant stability studies of the 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.

C12 Replacement or Change of Working Cell/Seed Bank	
C	1. Establishing a new working cell/seed bank derived from a previously approved master cell/seed bank according to approved protocols.
D	1. Comparative summary characterisation and testing of the approved and proposed working cell/seed banks. 2. Certificate of analysis or batch analysis data (in a comparative tabulated format) of at least three batches of drug substance derived from the approved and proposed cell/seed banks. 3. A declaration that the release and shelf life specifications of the drug product have not been changed. 4. Acommitment 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.

C13 Minor Change of Test Procedure	
C	1. Applicable to change of test procedure to comply with the updated general monograph in official pharmacopoeia, such as Ph. Eur., USP, BP and JP. This includes standard compendial microbiological methods. 2. For change of test procedure of the drug substance, drug product, excipient, and/or in-process control where the test method is a biological/ immunological/ immunochemical method, or a method using a biological reagent, refer to MIV-1 B12. 3. The specification of the drug substance, drug product, excipient and/or in-process test remain unchanged. If there are changes made to the specification, submit MIV-1 B3 or MIV-2 C5 at the same time.
D	1. Justification for the proposed change. 2. Description of the proposed analytical methodology. 3. Appropriate verification/validation data. 4. Comparative test results between the approved and proposed test procedure, or certificate of analysis or comparative batch analysis of two production batches of the drug substance, drug product, excipient, or in-process control.

C14 Minor Change of Reference Standard	
C	1. For change of in-house/non-compendial reference standard prepared and qualified by an approved preparation and calibration/qualification protocols. If there is a change of the approved protocol, refer to MIV-1 B14.

	2. For change of compendial reference standard, or change from a non-compendial/in house to a compendial reference standard.
D	1. Amended relevant CTD Sections. 2. A declaration that there is no change to the preparation and calibration/qualification protocols, if applicable. 3. Certificate of analysis of the proposed reference standard. 4. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug substance or drug product on at least two production batches using the approved and proposed reference standard.

C15 Change in Supplier of Animal-derived Material	
C	1. For animal-derived material of mammalian or avian origin used as an excipient or active ingredient in the drug product, or as an adjuvant. 2. There is no change in the animal species from which the animal-derived material is obtained from. 3. Animal derived material from other species (e.g. insects and fish) is exempted from this variation.
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.

C16 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 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.

PART C: CHECKLIST ON DOSSIER REQUIREMENTS FOR MIV-2 (DO-AND-TELL) VARIATION

Declaration of the product registrant for MIV-2 Do-and-Tell

I hereby declare that:

- All changes submitted are categorised as MIV-2 Do-and-Tell, and no other changes have been included in this application.
- The change(s) will not adversely affect the quality, efficacy and safety of the therapeutic product concerned.
- All information provided by me in this MIV-2 Do-and-Tell is true and accurate.

Name	Signature	Date
_____	_____	_____

C17 Change in Packaging Material Not in Contact with Drug Product	
C	1. For change of packaging material not in contact with drug product, such as colour of flip-off caps, colour code rings on ampoules, change of needle shield. 2. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the drug product.
D	1. Amendment of the relevant section(s) of the dossier (presented in the CTD format), including revised product labelling as appropriate.

C18 Change of Product Owner or Change in Name and/or Address (for example: postal code, street name) of Product Owner	
C	1. The prod28uct registrant remains unchanged. 2. The manufacturing site remains unchanged. 3. There are no other variation applications pending approval. All changes should be submitted and approved before the registration transfer takes place.
D	**For change of product owner:** 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A declaration on the transfer of ownership between the old product owner and new owner.

	3. An official letter from the new product owner declaring the change and authorising the local registrant to be responsible for the product registration. 4. If the new product owner is not the manufacturer of the drug product, an official letter by the new product owner authorising the manufacturer to manufacture the drug product on its behalf. **For change of name and/or address of product owner:** 5. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 6. An official letter from the product owner declaring the change and authorising the local registrant to be responsible for the product registration.

C19 Change in Ownership of Manufacturer	
C	1. The manufacturing site remains unchanged. 2. No other changes except for the change in ownership of manufacturer.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A letter of justification on the transfer of ownership, such as a valid GMP certificate. 3. An official letter stating the transfer of ownership from old manufacturer to the new manufacturer (where applicable). 4. In case of a contract manufacturer, an official letter from the product owner declaring the change and authorising the new manufacturer to manufacture the drug product(s) on its behalf.

C20 Change of Name or Address (for example: postal code, street name) of Manufacturer of Drug Product	
C	1. The manufacturing site remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug product. 3. Not applicable to the case involving a change in ownership of the manufacturer. For a change in ownership of manufacturer, refer MIV-2 C19.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A valid GMP certificate, a CPP which covers the GMP certification or an official document from a relevant authority confirming the new name and/or address. 3. An official letter from the product owner authorising the manufacturer with the new name/address to manufacture the drug product.

C21 Change of Name or Address (for example: postal code, street name) of Company or Manufacturer Responsible for Batch Release	
C	1. The manufacturer of the drug product remains unchanged. 2. The batch release site remains unchanged. 3. Not applicable to the case involving a change in ownership of the manufacturer. For a change in ownership of manufacturer, refer MIV-2 C19.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A valid GMP certificate, a CPP which covers the GMP certification or an official document from a relevant authority confirming the new name or address (where applicable). 3. An official letter from the product owner authorising the company/manufacturer with the new name/address that is responsible for batch release. 4. A declaration from the product registrant that the change does not involve a change of batch release site.

C22 Change of Name and/or Address (for example: postal code, street name) of Manufacturer of Drug Substance	
C	1. The manufacturing site of the drug substance remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug substance.
D	1. Updated information of the manufacturer of the drug substance. 2. An official document/evidence confirming the new name and/or address.

C23 Withdrawal/Deletion of Alternative Manufacturer(s) for Drug Substance and/or Drug Product and/or Packager and/or batch releaser	
C	1. An alternative manufacturer is registered.
D	1. Reason for withdrawal/deletion.

C24 Change of Specification of Excipient to Comply with Pharmacopoeia	
C	1. Applicable to compendial specifications only. 2. Change is made to comply with an update of the relevant monograph of the compendium or from one recognised pharmacopoeia to another. 3. Pharmacopoeia recognized by HSA: United States Pharmacopeia, European Pharmacopoeia, British Pharmacopoeia and Japanese Pharmacopoeia.

D	1. Specification of the excipient. 2. Tabulation of the approved and proposed specification of the excipient(s) with changes highlighted. 3. Certificate of analysis or batch analysis of the excipient(s) for all tests in the new specification of at least two batches. 4. A declaration that the change has no impact on the manufacturing process and quality of the drug product.

C25 Deletion of Pack Size for Drug Product	
C	1. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labelling. 2. For addition of pack size for sterile drug products, refer to MIV-1 B6. For a change in the outer carton pack size, refer to MIV-2 C11.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Reason for deletion.

C26 Change of Batch Numbering System	
C	1. The manufacturing site remains unchanged.
D	1. Description of the revised batch numbering system. 2. An official letter stating the commencement date of the change.

C27 Change of Name of Quality Control (QC) Testing Laboratory	
C	1. No other changes except for the change of the name and/or address of the approved laboratory(ies) for stability tests or any quality control tests.
D	1. Updated information of the testing laboratory. 2. An official letter from the product owner authorising the testing laboratory with the new name/address.

C28 Addition or Replacement of Site Responsible for Quality Control Testing Laboratory	
C	1. For addition or replacement of the approved laboratories for release and/or stability test that is of compendial method.

	2. For addition or replacement of the approved laboratories for release and/or stability tests not covered in MIV-1 B10.
D	1. Approved release and shelf life specification. 2. Analytical procedures to be carried out at the proposed site. 3. Certificate of analysis or batch analysis data (in a comparative tabular format) of at least two production batches tested at the approved and proposed site.

C29 Update of Product Labelling • Changes to non-English language text (e.g. Chinese). • Rearrangement/re-formatting of text/images without any change in information. • Addition/change of labelling intended for foreign markets (i.e. shared pack), e.g. other countries' registration/ licence no./ poison labels/foreign language text in package insert. • Addition/update/deletion of barcode / QR code for logistic purposes.	
C	1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not an MIV-1 and does not contain promotional information.
D	1. Current approved product labelling. 2. Proposed product labelling, a clean and annotated version highlighting the changes made. 3. Relevant document/reference to support the changes (where applicable).