# Table of Contents

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

**B1 Addition or Replacement of Manufacturer/Site of Drug Substance, Drug Product, Process Intermediate and/or Primary Packager ..... 2**

**B2 Change in Manufacturing Process ..... 3**

**B3 Change of Specification of Drug Substance, Drug Product, Process Intermediate and/or In-process Control Tests ..... 4**

**B4 Qualitative or Quantitative Change of Excipient of Drug Substance and/or Drug Product ..... 4**

**B5 Change in Primary Packaging Material for Sterile Drug Substance or Drug Product ..... 6**

**B6 Change or Addition of Pack Size/Fill Volume ..... 7**

**B7 Inclusion or Replacement of Solvent/Diluent for Drug Product ..... 7**

**B8 Change of Shelf-life of Drug Substance, Drug Product or Process Intermediate ..... 8**

**B9 Change of Storage Condition of Drug Substance, Drug Product or Process Intermediate ..... 8**

**B10 Addition or Replacement of Site Responsible for Quality Control Testing Laboratory ..... 9**

**B11 Replacement of Master Cell/Seed Bank ..... 9**

**B12 Change of Test Procedure ..... 10**

**B13 Variation of Strain(s) for Seasonal Influenza Vaccine ..... 11**

**B14 Change of Reference Standard ..... 12**

**B15 Change of Content of Product Labelling ..... 12**

**B16 Implementation of a New Design Space or Extension of an Approved Design Space for Drug Substance or Drug Product ..... 13**

**B17 Addition or Replacement of New Plasma Master File (PMF) to Registered Human Plasma-derived Product ..... 13**

**B18 Change of Specification of Non-compendial Excipient ..... 14**

**B19 Variation of Strain(s) for SARS-CoV-2 Vaccine ..... 14**

| **B1** | **Addition or Replacement of Manufacturer/Site of Drug Substance, Drug Product, Process Intermediate 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.<br>2. If there are changes to the drug substance or drug product specification, MIV-1 B3, MIV-2 C5 or D14 is also applicable.<br>3. Not applicable to changes relating to the manufacturer responsible for batch release (refer MIV-2 C3). |
| D | 1. Amended relevant CTD Sections.<br>2. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>3. Evidence of GMP compliance for the proposed site as per Section 15.1(i) or 18.1(i) of the *Guidance on Therapeutic Product Registration in Singapore.*<br>4. Batch numbering system (where applicable).<br>5. In the case of a contract manufacturer, a letter of appointment for the proposed site to manufacture the drug substance or drug product and stating the types of activity to be performed (where applicable).<br>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.<br>7. Approved release and/or shelf life specifications of the drug substance, drug product or process intermediates.<br>8. For the change of manufacturing site for drug substance or drug substance intermediate: 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.<br>9. For the change of manufacturing site for drug product or drug product intermediate: 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.<br>10. Stability studies as per the relevant guidelines on the stability study of the drug substance or drug product.<br>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.<br>2. The change may cause a significant impact on the quality, safety and efficacy of the drug product.<br>3. The change does not adversely affect the reproducibility of the process.<br>4. Manufacturing site remains unchanged. If there is a change in manufacturing site, MIV-1 B1 is also applicable.<br>5. Specification of the drug substance or drug product remains unchanged. If there is a change in the specification, MIV-1 B3, MIV-2 C5 or D14 is also applicable.<br>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).<br>2. Description of the new manufacturing process and technical justifications for the change.<br>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.<br>4. Approved release and/or shelf life specifications of the drug substance, drug product or process intermediates.<br>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.<br>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.<br>7. Stability studies as per the relevant guidelines on the stability study of the drug substance or drug product.<br>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**<br>a) Widening of specification limits.<br>b) Deletion of specification parameters which may have a significant effect on the overall quality of the drug product. |
| C | 1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting.<br>2. Test procedures remain unchanged, or changes in the test procedure are minor.<br>3. For addition of new specification parameter, refer to MIV-2 C5. For tightening of the specification limit and deletion of non-significant specification parameter, refer to MIV-2 D14. |
| D | **Specification limits are widened**<br>1. Justification for change substantiated with scientific data.<br>2. Revised specification of the drug substance, drug product, process intermediate or in-process control test.<br>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.<br>4. Test results of two production batches of the drug substance, drug product, process intermediates or in-process control, for all tests in the revised specification.<br>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.<br>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.<br>**Deletion of test parameter and limits**<br>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.<br>2. Replacement of an excipient with a comparable excipient of the same functional characteristic. |

| | |
|---|---|
| | 3. The Health Sciences Authority 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).<br>2. Justification for the change must be given by appropriate development of pharmaceutics.<br>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).<br>4. Revised CTD Section P3.1 to P3.4 (where applicable), including revised batch manufacturing formula.<br>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.<br>6. Information demonstrating comparability in terms of physico-chemical characterisation and impurity profile of the proposed excipient with the approved excipient (if applicable).<br>7. Specification of the proposed excipient(s).<br>8. For proposed excipients derived from TSE-relevant animals (i.e., cattle, sheep, goat, deer, elk, non-human primates):<br>a) A valid TSE Risk evaluation CEP; or<br>b) If CEP is not available,<br>i. Description of the tissue/organ/fluid-collection procedures and measures in place to avoid cross-contamination.<br>ii. Details of the risk factors associated with the route of administration and maximum therapeutic dosage of the drug product.<br>iii. Relevant information demonstrating that the manufacturing process is capable of inactivating TSE agents.<br>9. Approved release and/or shelf life specifications of the drug substance or drug product.<br>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.<br>11. Stability data as per relevant guidelines on the stability study of the drug substance or drug product.<br>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**<br>a) Change in qualitative and quantitative composition.<br>b) Change in type of container.<br>c) Inclusion of a new primary packaging material.<br>d) Also applicable for non-sterile drug substance or product that does not fall under MIV-2 C9. |
| 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.<br>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.<br>3. Release and shelf-life specifications of the drug product remain unchanged.<br>4. For change in the primary packaging material for non-sterile drug substance or drug product, refer to MIV-2 C9.<br>5. For change of specification parameters or limits, or test procedure of primary packaging material, refer to MIV-2 D16. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Justification for the change in packaging material.<br>3. Comparative tabulated format of the specification of the approved and proposed primary packaging material.<br>4. Revised CTD Sections (where applicable).<br>5. Information on the construction materials and design features of the proposed container closure system.<br>6. Declaration of compliance to the appropriate international standards or pharmacopoeia.<br>7. Appropriate scientific data on the new packaging (comparative data on permeability, e.g., moisture, $O_2$, $CO_2$, container closure integrity test).<br>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).<br>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.<br>10. Stability data as per the relevant guidelines on the stability study of the drug substance or drug product.<br>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.<br>2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert.<br>3. Release and shelf-life specifications of the drug product remain unchanged, except for the pack size/fill volume. For change or addition of pack size involving the number of blister strips or containers in a pack, refer to MIV-2 D15. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert.<br>3. Revised CTD Sections P3, P5.1 and/or P7 (where applicable).<br>4. Validation data of the manufacturing process, sterilisation and container closure system (where applicable).<br>5. Stability data as per the relevant guidelines on the stability study of the drug substance or drug product.<br>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.<br>2. For deletion of the solvent/diluent, refer to MIV-2 C7.<br>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.<br>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*.<br>3. Batch numbering system (where applicable).<br>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.<br>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**<br>a) As a package for sale; and/or<br>b) After first opening; and/or<br>c) After dilution/reconstitution. |
| C | 1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting.<br>2. For (a) & (b), the studies must show conformance to the approved shelf-life specification.<br>3. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Justification for the change of shelf-life (where applicable).<br>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<br>a. as a package for sale; and/or<br>b. after first opening; and/or<br>c. after the dilution/reconstitution<br>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**<br>a) As a package for sale; and/or<br>b) After first opening; and/or<br>c) After dilution/reconstitution. |
| C | 1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting. |

| | |
|---|---|
| | 2. For (a) & (b), the studies must show conformance to the approved shelf-life specification.<br>3. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Technical justification for the proposed change.<br>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<br>a. as a package for sale; and/or<br>b. after first opening; and/or<br>c. after the dilution/reconstitution<br>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).<br>2. For addition or replacement of the approved laboratories for release and/or stability test that is of compendial method, refer to MIV-2 D12. |
| D | 1. Approved release and/or shelf life specifications of the drug substance or drug product.<br>2. Analytical procedures to be carried out at the proposed site.<br>3. Validation of analytical procedures performed at the proposed site.<br>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.<br>2. This does not relate to any change in the host cell line.<br>3. The Health Sciences Authority 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.<br>2. Result of all identity testing, including cytogenetic characteristics that could be used to identify the cells.<br>3. Results of all available adventitious agent testing on the donor and the new master cells.<br>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.<br>5. Validated cell stability under the freezing and storage conditions using cell recovery or viability data.<br>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.<br>7. Sterility tests, mycoplasmas and adventitious viruses test data if appropriate.<br>8. Comparability of approved and proposed drug substance with respect to physico-chemical characterisation, biological activity and impurity profile.<br>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.<br>10. Stability data as per the relevant guidelines on the stability study of the drug substance.<br>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).<br>2. For any change not covered by MIV-2 C12.<br>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, MIV-2 C5 or D14 at the same time. |
| D | 1. Justification for the proposed change.<br>2. Description of the proposed analytical procedure.<br>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 Variation of Strain(s) for Seasonal Influenza Vaccine** | |
|---|---|
| C | 1. For update of seasonal influenza vaccine according to WHO Recommendations for Influenza Vaccine Composition.<br>a) If there is a change in the influenza strain(s), documentation listed in (A) should be submitted.<br>b) If there is no change in the influenza strains, documentation listed in (B) should be submitted.<br>2. Non-consequential changes should not be submitted together with MIV-1 B13. (Note: additional changes other than strain changes will require additional supporting documents, which may delay the evaluation timeline). |
| D | **A) Variation involving change of the virus strain(s)**<br>1. Approved product labels (outer carton, inner label and package insert) with the proposed change(s) clearly highlighted, underscored, or otherwise indicated.<br>2. Proposed product labels (outer carton, inner label and package insert) with all change(s) incorporated, which include, but not limited to:<br>a. Strain type.<br>b. Year/Year.<br>c. Southern hemisphere or northern hemisphere.<br>3. Identification of working seed stock as per the pharmacopoeial requirements.<br>4. Validation study reports and/or summaries of the critical manufacturing process for drug substance(s), e.g., inactivation, splitting efficiency.<br>5. Release and/or shelf life specification for the drug substance(s).<br>6. Validation study reports of single radial diffusion (SRD) test for the proposed strain(s).<br>7. Batch analyses data for drug substance(s).<br>8. Composition of the vaccine.<br>9. Release and/or shelf life specification for the vaccine.<br>10. Comparative batch analyses data (tabulated) of the vaccines manufactured using the approved and proposed strains.<br>11. Stability study result of at least 6 months of the vaccine from the preceding year or season.<br>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 any out-of-specification result (with proposed action). Submission of the stability studies report is not required but the data shall be provided to the Health Sciences Authority upon request.<br>**B) Variation submission for no change of virus strains** |

| | |
|---|---|
| | 1. Approved product labels (outer carton, inner label and package insert) with the proposed change(s) clearly highlighted, underscored, or otherwise indicated.<br>2. Proposed product labels (outer carton, inner label and package insert) with all change(s) incorporated, which include, but not limited to:<br>a. Strain type.<br>b. Year/Year.<br>c. Southern hemisphere or northern hemisphere.<br>3. Stability study result of at least 6 months of the vaccine from the preceding year or season.<br>4. 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 any out-of-specification result (with proposed action). Submission of the stability studies report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| **B14 Change of Reference Standard** | |
|---|---|
| C | 1. For change of reference standard not covered by an approved calibration/qualification protocol, and the old reference standard material is not available anymore for direct comparison with the new material.<br>2. If there is no change to the approved qualification protocol, and/or old reference standard material is still available, refer to MIV-2 C13. |
| D | 1. The preparation protocol for the new reference standard.<br>2. The calibration/qualification protocol for the reference standard.<br>3. Amended relevant CTD Sections.<br>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.<br>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. The change is not an MIV-2 and not within the scope of MAV-1. |
| D | 1. Approved product labelling.<br>2. Proposed product labelling: a pristine and annotated version highlighting the changes made.<br>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.<br>2. For changes to proven acceptable ranges (i.e., loosening), refer to checklist MIV-1 B3. |
| D | 1. Amended relevant CTD Sections.<br>2. A comparative table of the approved and proposed design space, including the variables (material attributes and/or process parameters).<br>3. Justification for the proposed change.<br>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.<br>5. Stability data as per relevant guidelines on the stability study of the drug substance or drug product.<br>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.<br>2. Latest EMA annual recertification letter and recertification assessment report, if available.<br>3. Letter of Access issued by the PMF holder to the product owner.<br>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.<br>5. Amended relevant CTD Sections.<br>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.<br>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. |

| **B18 Change of Specification of Non-compendial Excipient** | |
|---|---|
| C | 1. For widening of specification limits or deletion of significant test parameter. For addition or replacement of a specification parameter and limit, refer to MIV-2 C8.<br>2. Applicable to non-compendial excipients. For compendial excipients, refer to MIV-2 D8. |
| D | 1. A declaration from the product registrant that the change does not impact the quality and safety of the drug product.<br>2. Revised specification of the excipient.<br>3. Comparative tabulated format of the approved and proposed specification of the excipient with changes highlighted.<br>4. Certificate of analysis or batch analysis data of the excipient including all tests in the proposed specification of at least two batches. |

| **B19 Variation of Strain(s) for SARS-CoV-2 Vaccine** | |
|---|---|
| C | 1. For replacement of strain, antigen or coding sequence, according to the official recommendations from relevant authorities (e.g., WHO) or established global forum, where the efficacy and safety of the modified vaccine can be inferred from the data of the approved vaccine.<br>2. Non-consequential changes should not be submitted together with MIV-1 B19. (Note: additional changes other than strain changes will require additional supporting documents, which may delay the evaluation timeline). |
| D | 1. Revised product labels (outer carton, inner label and package insert) incorporating the proposed variation.<br>2. Details of changes to the starting material, e.g., construction and synthesis of DNA template, virus seed.<br>3. Process validation reports and/or summaries of the critical manufacturing process for the drug substance(s) to demonstrate manufacturing consistency.<br>4. Release and/or shelf life specification for the drug substance(s). Any major change to the specifications would require adequate scientific and/or clinical justification.<br>5. Update and re-validation of analytical procedures and reference standards for the proposed strain(s).<br>6. Batch analyses data for drug substance(s).<br>7. Details of changes to the composition of the vaccine due to the proposed strain(s).<br>8. Release and/or shelf life specification for the vaccine. Any major change to the specifications would require adequate scientific and/or clinical justification. |

| | |
|---|---|
| | 9. Comparative batch analyses data (tabulated) of the vaccines manufactured using the approved and proposed strain(s).<br>10. Demonstration of the applicability of the approved shelf life of the drug substance(s) and finished product to the modified vaccine, e.g., with real-time stability data, accelerated and/or stress stability data, or predictive stability models.<br>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 any out-of-specification result (with proposed action). Submission of the stability studies report is not required but the data shall be provided to the Health Sciences Authority upon request.<br>12. Justification for not submitting new clinical data for the proposed strain(s).<br>13. Revised Risk Management Plan, if required. |