

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

<b>B1</b>	<b>Change and/or Addition of Alternative Manufacturer/Site of Drug Substance, Drug Product, Process Intermediates and/or Primary Packager</b>
C	<ol style="list-style-type: none"> <li>1. If there are changes to the manufacturing process, including change in batch size, MIV-1 B2 or MIV-2 C4 is also applicable.</li> <li>2. If there are changes to the drug substance or drug product specification, MIV-1 B3 or MIV-2 C5 is also applicable.</li> <li>3. Not applicable to changes relating to the manufacturer responsible for batch release (refer MIV-2 C3).</li> </ol>
D	<ol style="list-style-type: none"> <li>1. Amended relevant CTD Sections.</li> <li>2. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).</li> <li>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. <i>(Note: a GMP Conformity Assessment is required if the proposed drug product manufacturing site is not currently registered with HSA).</i></li> <li>4. Batch numbering system (where applicable).</li> <li>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).</li> <li>6. Validation scheme and/or report of the manufacturing process as per <i>ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration</i> at the proposed site(s).</li> <li>7. Approved release and/or shelf life specifications of the drug substance, drug product or process intermediates.</li> <li>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.</li> <li>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.</li> <li>10. Stability studies as per the relevant guidelines on the stability study of the drug substance or drug product.</li> <li>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.</li> </ol>

<b>B2 Change in Manufacturing Process</b>	
<b>C</b>	<ol style="list-style-type: none"> <li>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.</li> <li>2. The change may cause a significant impact on the quality, safety and efficacy of the drug product.</li> <li>3. The change does not adversely affect the reproducibility of the process.</li> <li>4. Manufacturing site remains unchanged. If there is a change in manufacturing site, MIV-1 B1 is also applicable.</li> <li>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.</li> <li>6. For any change not covered by MIV-2 C4.</li> </ol>
<b>D</b>	<ol style="list-style-type: none"> <li>1. Comparative tabulated format of the approved and new processes with changes highlighted (where available).</li> <li>2. Description of the new manufacturing process and technical justifications for the change.</li> <li>3. Validation scheme and/or report of the proposed manufacturing process as per <i>ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration</i> should be provided upon submission.</li> <li>4. A copy of the approved release and shelf-life specifications.</li> <li>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.</li> <li>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.</li> <li>7. Stability studies as per the relevant guidelines on the stability study of the drug substance or drug product.</li> <li>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.</li> </ol>

	<p><b>B3 Change of Specification of Drug Substance, Drug Product, Process Intermediate and/or In-process Control Tests</b></p> <p>a) Widening of specification limits.</p> <p>b) Deletion of specification parameters which may have a significant effect on the overall quality of the drug product..</p>
<p>C</p>	<p>1. Test procedures remain unchanged, or changes in the test procedure are minor.</p> <p>2. For tightening of the specification limit, addition of new specification parameter, deletion of a non-significant specification parameter, refer to MIV-2 C5.</p> <p>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 <i>Product Defect Reporting and Recall Procedures</i> on the HSA website for product defect reporting.</p>
<p>D</p>	<p><b>Specification limits are widened</b></p> <p>1. Justification for change substantiated with scientific data.</p> <p>2. Revised specification of the drug substance, drug product, process intermediate or in-process control test.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p><b>Deletion of test parameter and limits</b></p> <p>All the above documents except D5 &amp; D6.</p>

	<p><b>B4 Qualitative or Quantitative Change of Excipient of Drug Substance and/or Drug Product</b></p>
<p>C</p>	<p>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.</p> <p>2. Replacement of an excipient with a comparable excipient of the same functional characteristic.</p> <p>3. HSA reserves the right to re-categorise the application to NDA, if deemed appropriate.</p>

D	<ol style="list-style-type: none"><li>1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).</li><li>2. Justification for the change must be given by appropriate development of pharmaceuticals.</li><li>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).</li><li>4. Revised CTD Section P3.1 to P3.4 (where applicable), including revised batch manufacturing formula.</li><li>5. Validation scheme and/or report of the manufacturing process as per <i>ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration</i> appropriate to the proposed change in the drug product formula should be provided upon submission.</li><li>6. Information demonstrating comparability in terms of physico-chemical characterisation and impurity profile of the proposed excipient with the approved excipient (if applicable).</li><li>7. Specification of the proposed excipient(s).</li><li>8. For proposed excipients derived from TSE-relevant animals (i.e. cattle, sheep, goat, deer, elk, non-human primates):<ol style="list-style-type: none"><li>a) A valid TSE Risk evaluation CEP; or</li><li>b) If CEP is not available,<ol style="list-style-type: none"><li>i. Description of the tissue/organ/fluid-collection procedures and measures in place to avoid cross-contamination.</li><li>ii. Details of the risk factors associated with the route of administration and maximum therapeutic dosage of the drug product.</li><li>iii. Relevant information demonstrating that the manufacturing process is capable of inactivating TSE agents.</li></ol></li></ol></li><li>9. Drug substance or drug product release and shelf-life specifications.</li><li>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.</li><li>11. Stability data as per relevant guidelines on the stability study of the drug substance or drug product.</li><li>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.</li></ol>
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	<p><b>B5 Change in Primary Packaging Material for Sterile Drug Substance or Drug Product</b></p> <p>a) Change in qualitative and quantitative composition.</p> <p>b) Change in type of container.</p> <p>c) Inclusion of a new primary packaging material.</p>
<p>C</p>	<ol style="list-style-type: none"> <li>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.</li> <li>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.</li> <li>3. Release and shelf-life specifications of the drug product remain unchanged.</li> <li>4. For a minor change in the primary packaging material, refer to MIV-2 C9.</li> </ol>
<p>D</p>	<ol style="list-style-type: none"> <li>1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).</li> <li>2. Justification for the change in packaging material.</li> <li>3. Comparative tabulated format of the specification of the approved and proposed primary packaging material.</li> <li>4. Revised CTD Sections (where applicable).</li> <li>5. Information on the construction materials and design features of the proposed container closure system.</li> <li>6. Declaration of compliance to the appropriate international standards or pharmacopoeia.</li> <li>7. Appropriate scientific data on the new packaging (comparative data on permeability, e.g. moisture, O<sub>2</sub>, CO<sub>2</sub>, container closure integrity test).</li> <li>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).</li> <li>9. Validation report of the manufacturing and sterilisation process as per <i>ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration</i> appropriate to the proposed change in the primary packaging material should be provided upon submission.</li> <li>10. Stability data as per the relevant guidelines on the stability study of the drug substance or drug product.</li> <li>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.</li> </ol>

<b>B6 Change or Addition of Pack Size/Fill Volume</b>	
<b>C</b>	<ol style="list-style-type: none"> <li>1. The type and material of the primary packaging material remain unchanged.</li> <li>2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert.</li> <li>3. Release and shelf-life specifications of the drug product remain unchanged, except pack size/fill volume specification.</li> <li>5. For any change that only concerns the number of units or containers in a pack, refer to MIV-2 C11.</li> </ol>
<b>D</b>	<ol style="list-style-type: none"> <li>1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).</li> <li>2. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert.</li> <li>3. Revised CTD Sections P3 and/or P7 (where applicable).</li> <li>4. Validation data of the manufacturing process, sterilisation and container closure system (where applicable).</li> <li>5. Stability data as per the relevant guidelines on the stability study of the drug substance or drug product.</li> <li>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.</li> </ol>

<b>B7 Inclusion or Replacement of Solvent/Diluent for Drug Product</b>	
<b>C</b>	<ol style="list-style-type: none"> <li>1. The proposed change does not result in any change in the dosage form, regimen, indication or method of administration of the drug product.</li> <li>2. For deletion of the solvent/diluent, refer to MIV-2 C7.</li> <li>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.</li> </ol>
<b>D</b>	<ol style="list-style-type: none"> <li>1. Revised drafts of the package insert and labelling incorporating the proposed variation.</li> <li>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).</li> <li>3. Batch numbering system (where applicable).</li> </ol>

	<ol style="list-style-type: none"> <li>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).</li> <li>5. A declaration from the product registrant that the release and shelf-life specifications of drug product are not affected.</li> <li>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).</li> </ol>
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<p><b>B8 Change of Shelf-life of Drug Substance, Drug Product or Process Intermediate</b></p> <ol style="list-style-type: none"> <li>a) As a package for sale; and/or</li> <li>b) After first opening; and/or</li> <li>c) After dilution/reconstitution.</li> </ol>	
C	<ol style="list-style-type: none"> <li>1. For (a) &amp; (b), the studies must show conformance to the approved shelf-life specification.</li> <li>2. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product.</li> <li>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 <i>Product Defect Reporting and Recall Procedures</i> on the HSA website for product defect reporting.</li> </ol>
D	<ol style="list-style-type: none"> <li>1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).</li> <li>2. Justification for the change of shelf-life of the drug product (where applicable).</li> <li>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                     <ol style="list-style-type: none"> <li>a. as a package for sale; and/or</li> <li>b. after first opening; and/or</li> <li>c. after the dilution/reconstitution</li> </ol>                     in accordance with the relevant guidelines on the stability study of the drug substance or drug product.                 </li> </ol>

<p><b>B9 Change of Storage Condition of Drug Substance, Drug Product or Process Intermediate</b></p> <ol style="list-style-type: none"> <li>a) As a package for sale; and/or</li> <li>b) After first opening; and/or</li> <li>c) After dilution/reconstitution.</li> </ol>	
C	<ol style="list-style-type: none"> <li>1. For (a) &amp; (b), the studies must show conformance to the approved shelf-life specification.</li> </ol>

	<p>2. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product.</p> <p>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 <i>Product Defect Reporting and Recall Procedures</i> on the HSA website for product defect reporting.</p>
D	<p>1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).</p> <p>2. Technical justification for the proposed change.</p> <p>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</p> <p style="margin-left: 20px;">a. as a package for sale; and/or</p> <p style="margin-left: 20px;">b. after first opening; and/or</p> <p style="margin-left: 20px;">c. after the dilution/reconstitution</p> <p>in accordance with the relevant guidelines on the stability study of the drug substance or drug product.</p>

<b>B10 Addition or Replacement of Site Responsible for Quality Control Testing Laboratory</b>	
C	<p>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).</p>
D	<p>1. Approved release and shelf life specification.</p> <p>2. Analytical procedures to be carried out at the proposed site.</p> <p>3. Validation of analytical procedures performed at the proposed site.</p> <p>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.</p>

<b>B11 Replacement of Master Cell/Seed Bank</b>	
C	<p>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.</p> <p>2. This does not relate to any change in the host cell line.</p> <p>3. HSA reserves the right to re-categorise the application to NDA, if deemed appropriate.</p>



D	<ol style="list-style-type: none"> <li>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.</li> <li>2. Result of all identity testing, including cytogenetic characteristics that could be used to identify the cells.</li> <li>3. Results of all available adventitious agent testing on the donor and the new master cells.</li> <li>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.</li> <li>5. Validated cell stability under the freezing and storage conditions using cell recovery or viability data.</li> <li>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.</li> <li>7. Sterility tests, mycoplasmas and adventitious viruses test data if appropriate.</li> <li>8. Comparability of approved and proposed drug substance with respect to physico-chemical characterisation, biological activity and impurity profile.</li> <li>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.</li> <li>10. Stability data as per the relevant guidelines on the stability study of the drug substance.</li> <li>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.</li> </ol>
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<b>B12 Change of Test Procedure</b>	
C	<ol style="list-style-type: none"> <li>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).</li> <li>2. For any change not covered by MIV-2 C13.</li> <li>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.</li> </ol>
D	<ol style="list-style-type: none"> <li>1. Justification for the proposed change.</li> <li>2. Description of the proposed analytical procedure.</li> <li>3. Validation of the analytical procedure.</li> </ol>

	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.
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<b>B13 Seasonal Variation of Influenza Strains for Vaccine</b>	
<b>C</b>	<ol style="list-style-type: none"> <li>1. For a change of <b>only</b> influenza strains for the formulation of an influenza vaccine according to WHO Recommendations for Influenza Vaccine Composition may be expedited. <i>(Note: additional changes other than strain changes will require additional supporting documents, which may delay the evaluation timeline).</i></li> <li>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.</li> </ol>
<b>D</b>	<p><b>A) Variation involved change of the virus strain</b></p> <ol style="list-style-type: none"> <li>1. Approved product label (outer carton, inner label and package insert) with the proposed change(s) clearly highlighted, underscored, or otherwise indicated.</li> <li>2. Proposed product label (outer carton, inner label and package insert) with all change(s) incorporated, which include, but not limited to:                     <ol style="list-style-type: none"> <li>a. Strain type.</li> <li>b. Year/Year.</li> <li>c. Southern hemisphere or northern hemisphere.</li> </ol> </li> <li>3. Quality Overall Summary.</li> <li>4. Identification of working seed stock as per the pharmacopoeial requirements.</li> <li>5. Validation study reports and/or summaries of the critical manufacturing process for drug substances (new strain), e.g. inactivation, splitting efficiency.</li> <li>6. Release and/or shelf life specification for the drug substances.</li> <li>7. Validation study reports and summaries of the test method for the new strain.</li> <li>8. Batch analyses data for drug substances.</li> <li>9. Composition of the vaccine.</li> <li>10. Actual formula(e) of the vaccine used for clinical trial studies for the change of influenza strains and commercial purpose (in a table).</li> <li>11. Release and/or shelf life specification for the vaccine.</li> <li>12. Comparative batch analyses data (in a table) of the vaccines manufactured using the approved and proposed strains.</li> <li>13. Stability study result of at least 6 months of the vaccine from the preceding year or season.</li> <li>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.</li> </ol> <p><b>B) Variation submission for no change of virus strains</b></p>

	<ol style="list-style-type: none"> <li>1. Approved product label (outer carton, inner label and package insert) with the proposed change(s) clearly highlighted, underscored, or otherwise indicated.</li> <li>2. Proposed product label (outer carton, inner label and package insert) with all change(s) incorporated, which include, but not limited to:                     <ol style="list-style-type: none"> <li>a. Strain type.</li> <li>b. Year/Year.</li> <li>c. Southern hemisphere or northern hemisphere.</li> </ol> </li> <li>3. Quality Overall Summary.</li> <li>4. Stability study result of at least 6 months of the vaccine from the preceding year or season.</li> <li>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.</li> <li>6. Composition of the vaccine.</li> </ol>
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<b>B14 Change of Reference Standard</b>	
C	<ol style="list-style-type: none"> <li>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.</li> <li>2. To change from a compendial to non-compendial/in house reference standard.</li> </ol>
D	<ol style="list-style-type: none"> <li>1. The preparation protocol for the new reference standard.</li> <li>2. The calibration/qualification protocol for the reference standard.</li> <li>3. Amended relevant CTD Sections.</li> <li>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.</li> <li>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.</li> </ol>

<b>B15 Change of Content of Product Labelling</b>	
C	<ol style="list-style-type: none"> <li>1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister labels.</li> <li>2. The change is not an MIV-2 and not within the scope of MAV-1.</li> </ol>
D	<ol style="list-style-type: none"> <li>1. Approved product labelling.</li> </ol>

	<ol style="list-style-type: none"> <li>2. Proposed product labelling, a clean and annotated version highlighting the changes made.</li> <li>3. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable).</li> <li>4. Justifications for the changes proposed and supporting clinical documents where applicable.</li> </ol>
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<b>B16 Implementation of a New Design Space or Extension of an Approved Design Space for Drug Substance or Drug Product</b>	
C	<ol style="list-style-type: none"> <li>1. Applies to a design space with multidimensional combination and interaction of input variables and process parameters.</li> <li>2. For changes to proven acceptable ranges (i.e. loosening), refer to checklist MIV-1 B3.</li> </ol>
D	<ol style="list-style-type: none"> <li>1. Amended relevant CTD Sections.</li> <li>2. A comparative table of the approved and proposed design space, including the variables (material attributes and/or process parameters).</li> <li>3. Justification for the proposed change.</li> <li>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.</li> <li>5. Stability data as per relevant guidelines on the stability study of the drug substance or drug product.</li> <li>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.</li> </ol>

<b>B17 Addition or Replacement of New Plasma Master File (PMF) to Registered Human Plasma-derived Product</b>	
C	<ol style="list-style-type: none"> <li>1. The change does not cause a negative impact on the quality, safety and efficacy of the drug product.</li> </ol>

D	<ol style="list-style-type: none"><li>1. New or latest version of the PMF.</li><li>2. Latest EMA annual recertification letter and recertification assessment report, if available.</li><li>3. Letter of Access issued by the PMF holder to the product owner.</li><li>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.</li><li>5. Amended relevant CTD Sections.</li><li>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.</li><li>7. Stability data as per the relevant guidelines on the stability study of the drug substance or drug product.</li><li>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.</li></ol>
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## REVISION HISTORY

### Guidance Version (Publish Date)

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