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| **C1** | **Change of Drug Product Name** |
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| 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.<br>2. No confusion with another drug product either when spoken or written.<br>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.<br>2. Updated Certificate of Pharmaceutical Product (CPP) (where applicable).<br>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).<br>4. A declaration from the product registrant that there are no other changes to the product/label except for the drug product name change. |

| **C2** | **Change of Content of Product Labelling**<br>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.<br>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.).<br>c) Tightening of product’s target population.<br>d) Deletion of indication.<br>e) Minor change of content of product labelling that does not have any impact on the product’s safety, efficacy and quality. |
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| C | 1. The change is not listed in MIV-2 D13. |
| D | 1. Approved product labelling.<br>2. Proposed product labelling: a pristine and annotated version highlighting the changes made.<br>3. Relevant document/reference or justification to support the changes (where applicable). |

| C3 | Addition or Replacement of Company or Party Responsible for Batch Release |
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| C | 1. Only applicable for the change of batch releaser.<br>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).<br>2. Evidence of GMP compliance of the proposed site as per Section 15.1(i) or 18.1(i) of the *Guidance on Therapeutic Product Registration in Singapore*.<br>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 |
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| 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.<br>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.<br>3. No adverse change in the qualitative and/or quantitative impurity profile or in physico-chemical characteristics and other relevant properties.<br>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.<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. |
| D | 1. Comparative tabulated format of the approved and proposed 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, and a letter of declaration from the product registrant stating that the specifications of the drug substance or drug product have not changed.<br>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.<br>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 |

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| | 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** |
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| 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 addition or replacement of a specification parameter and limit.<br>3. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance or otherwise refer to MIV-1 B3.<br>4. For widening of specification limits and deletion of test parameter and limits, refer to MIV-1 B3. For tightening of specification limit, or deletion of non-significant parameter, refer to MIV-2 D14. |
| D | 1. Technical justification for the change.<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 proposed specification of the drug substance, drug product, process intermediate or in-process control test, with changes highlighted.<br>4. 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.<br>5. Description of any new analytical method and summary of the validation data (where applicable).<br>6. Justification of the new specification parameter and the limits.<br>7. 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. |

| **C6** | **Change of Colouring/Flavouring Agent of Drug Product** |
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| C | 1. Same functional characteristic, no change in dissolution profile for solid oral dosage forms.<br>2. The proposed colouring/flavouring agents must not have been rejected for pharmaceutical use.<br>3. The release and shelf-life specifications of the drug product remain unchanged except for the change in colour/flavour. |

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| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Revised CTD P1.<br>3. A declaration from product registrant that the change does not interfere with the drug product release and shelf-life specifications test method.<br>4. Comparative tabulated format of the approved and proposed drug product formulation and batch manufacturing formula, including the qualitative and quantitative information of colouring/flavouring agents.<br>5. 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>6. Revised release and shelf-life specifications of the drug product.<br>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. |

| **C7** | **Deletion of Solvent/Diluent for Drug Product** |
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| 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).<br>2. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent.<br>3. Amended relevant CTD Section P (where applicable). |

| **C8** | **Change of Specification of Non-compendial Excipient** |
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| C | 1. Addition or replacement of a specification parameter and limit of the excipient. For widening of specification limits or deletion of significant test parameter and limits of the excipient, refer to MIV-1 B18. Release and shelf life specifications of drug product remain unchanged. |

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| | 2. Notification is not required for a change in the supplier for the excipient with the same specification.<br>3. 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. Description of new method and summary of analytical validation (where applicable). 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 at least one batch of the excipient for all tests in the proposed specification. |

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| **C9** | **Change in Primary Packaging Material for Non-sterile Drug Substance or Drug Product**<br>a) Change in qualitative and quantitative composition.<br>b) Change in same packaging / type of container.<br>c) Inclusion of new primary packaging material. |
| C | 1. The variation should not be submitted as a result of unexpected events that may lead to product defects. Variation is only to be submitted after concerns have been addressed and CAPAs concurred. Refer to the *Product Defect Reporting and Recall Procedures* on the HSA website for product defect reporting.<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. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties. If a less protective packaging material is proposed, refer to MIV-1 B5.<br>4. For a change in the primary packaging material for a sterile drug substance or drug product, refer to MIV-1 B5.<br>5. For change of specification parameters or limits, or test procedure of primary packaging material, refer to MIV-2 D16.<br>6. Release and shelf life specifications of the drug substance or drug product remain unchanged. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Justification for the change in packaging material and appropriate scientific studies on the new packaging.<br>3. Comparative tabulated format of the approved and proposed specifications of the primary packaging material (where applicable).<br>4. Revised CTD Sections P3 and/or P7 (where applicable). |

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| | 5. Declaration of compliance to the appropriate international standards or pharmacopoeia.<br>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).<br>7. Stability data 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. |

| **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).<br>2. Evidence of GMP compliance of the proposed site as per Section 15.1(i) or 18.1(i) of the *Guidance on Therapeutic Product Registration in Singapore.*<br>3. Official letter from the product owner authorising the new manufacturer or packager to perform secondary packaging (where applicable).<br>4. For local secondary packager, an official letter from the product registrant authorising the local secondary packager to perform secondary packaging (where applicable). |

| **C11 Replacement or Change of Working Cell/Seed Bank** | |
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| 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.<br>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.<br>3. A declaration that the release and shelf life specifications of the drug product have not been changed.<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 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 Minor Change of Test Procedure** | |
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| 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.<br>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.<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 methodology.<br>3. Appropriate verification/validation data.<br>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. |

| **C13 Minor Change of Reference Standard** | |
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| C | 1. For change of reference standard prepared and qualified by an approved preparation and 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 a change of the approved qualification protocol and the old reference standard material is not available anymore, refer to MIV-1 B14.<br>3. Notification is not required for the following changes:<br>a) Introduction of a new reference standard which is qualified in accordance with the approved qualification protocol, and when the old reference standard material is available for direct comparison with the new material.<br>b) Extension of the reference standard shelf-life or retest period if the reference standard is within the limits/conditions as detailed in the approved qualification protocol. |
| D | 1. Amended relevant CTD Sections.<br>2. A declaration that there is no change to the preparation and calibration/qualification protocols, if applicable.<br>3. Certificate of analysis of the proposed reference standard.<br>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. |

| **C14 Change in Supplier of Animal-derived Material** | |
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| C | 1. For animal-derived material of mammalian or avian origin used as a raw material in the drug substance manufacturing or as an excipient in the drug product, or as an adjuvant.<br>2. Notification is not required for a change in the supplier of a raw material or an excipient which is not of mammalian or avian origin if the specification of the raw material or excipient remains unchanged.<br>3. There is no change in the animal species from which the animal-derived material is obtained from.<br>4. 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*.<br>** Not required for animal derived products from milk and certain milk derivatives such as lactose.*<br>2. Declaration on the nature of the animal tissue and/or fluid used.<br>3. Certificate of analysis for the animal-derived material used, stating the name and address of the supplier.<br>4. Relevant information to demonstrate that the manufacturing process is capable of inactivating adventitious agents, where applicable.<br>5. For materials 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. |

| **C15 Change in Species of Animal-derived Material** | |
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| C | 1. For a change in species of animal-derived material used<br>a) at any stage in the manufacture of the drug substance and/or drug product (e.g., from pig to cow);<br>b) as excipient or active substance (e.g., bovine gelatine to porcine gelatine) of the drug product; or<br>c) as an adjuvant.<br>2. This variation includes all species of animals. |
| D | 1. Information on all countries which the animal was sourced from*****. |

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| | ** Not required for animal derived products from milk and certain milk derivatives such as lactose.*<br>2. Declaration on the nature of the animal tissue and/or fluid used.<br>3. Certificate of analysis for the animal-derived material used, stating the name and address of the supplier for mammalian and avian materials.<br>4. Identification of new adventitious agents, where applicable.<br>5. Relevant information to demonstrate that the manufacturing process is capable of inactivating new adventitious agents, where applicable.<br>6. For materials 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. |