# APPENDIX 13 GUIDELINE ON MINOR VARIATION APPLICATIONS FOR CHEMICAL THERAPEUTIC PRODUCTS

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## INTRODUCTION

This document describes the requirements of a Minor Variation Application (MIV) submitted for an existing registered **chemical** 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**<br>- Administrative (Module 1/Part 1)<br>- Other supporting documents | <br>PRISM<br>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 chemical drug products are located in Parts 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
- The *Table of Summary of Changes* should 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.

**NOTE**: For unstable drug substances or critical dosage forms, whenever stability data is required, a minimum of three batches (at least two pilot scale or larger) must be submitted.

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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## REVISION HISTORY

Guidance Version (Publish Date)

TPB-GN-014-001 (uploaded 15 January 2019)

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

| **B1** | **Addition or Replacement of Alternative Manufacturer/Site of Drug Substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]** |
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| C | 1. Specification of drug substance remains unchanged. If there are changes to the drug substance specification, MIV-1 B5 or MIV-2 C7 is also applicable.<br>2. For a change and/or addition of an alternative manufacturer/site of drug substance where a CEP is available, refer to MIV-1 B2. |
| D | 1. Complete CTD section S.1 - S.7, or both the open and closed parts of the Drug Master File (closed part to be provided directly by the drug substance manufacturer) with the Letter of Access.<br>2. Comparative tabulated format of the approved and proposed drug substance manufacture information (where applicable).<br>3. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites.<br>4. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance from the proposed manufacturing site in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| **B2** | **Addition or Replacement of Alternative Manufacturer/site of Drug Substance (where CEP is available)** |
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| C | 1. Specification of drug substance remains unchanged. If there are changes to the drug substance specification, MIV-1 B6 or MIV-2 C11 is also applicable.<br>2. For a change and/or addition of alternative manufacturer/site of drug substance where a CEP is not available, refer to MIV-1 B1. |
| D | 1. A copy of the duly authorised, valid CEP, including all annexes as issued by the European Directorate for the Quality of Medicines (EDQM).<br>2. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites.<br>3. If the re-test period is not stated in the CEP, long term and accelerated stability data up to the proposed re-test period on two pilot batches of the drug substance manufactured from the proposed manufacturing site.<br>4. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance from the proposed manufacturing site in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). |

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| | 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** | **Major Change of Manufacturing Process of Drug Substance (where CEP is not available)** |
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| C | 1. Synthetic route is different (for example, new intermediates are formed), which may have a potential to change important quality characteristics of the drug substance, e.g., qualitative and/or quantitative impurity profile, which may have significant impact on the quality, safety and efficacy of the drug product.<br>2. Specification of drug substance remains unchanged. If there are changes to the drug substance specification, MIV-1 B5 or MIV-2 C7 is also applicable.<br>3. For a major change of manufacturing process of the drug substance where a CEP is available, refer to MIV-1 B4. |
| D | 1. Relevant CTD section S.1 - S.7, or both the open and closed parts of the Drug Master File (closed part to be provided directly by the drug substance manufacturer) with the Letter of Access.<br>2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available).<br>3. For a sterile drug substance, process validation report (where applicable).<br>4. A letter of declaration from the product registrant stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities, or that there is no increase in the levels of impurities which require further safety studies. If there is any change in the qualitative and/or quantitative impurity profile, provide scientific justification and/or qualification data from safety studies.<br>5. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing processes.<br>6. Batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the currently approved and proposed processes.<br>7. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance using the proposed manufacturing process in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| **B4** | **Major Change of Manufacturing Process of Drug Substance (where CEP is available)** |
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| C | 1. Synthetic route is different (for example, new intermediates are formed), which may have a potential to change important quality characteristics of the drug substance, |

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| | e.g., qualitative and/or quantitative impurity profile, which may have significant impact on the quality, safety and efficacy of the drug product.<br>2. Specification of drug substance remains unchanged If there are changes to the drug substance specification, MIV-1 B6 or MIV-2 C11 is also applicable.<br>3. For a major change of the manufacturing process of a drug substance where a CEP is not available, refer to MIV-1 B3. |
| D | 1. A copy of the duly authorised, valid CEP, including all annexes as issued by the EDQM.<br>2. Additional data to address any relevant parameter(s) not addressed in the CEP, such as physicochemical characteristics (e.g. particle size, polymorphism etc.), where applicable.<br>3. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing processes.<br>4. If the re-test period is not stated in the CEP, long term and accelerated stability data up to the proposed re-test period on two pilot batches of the drug substance manufactured with the proposed manufacturing process.<br>5. A commitment letter to conduct relevant stability studies of the drug product manufactured with the drug substance using the proposed manufacturing process in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| **B5** | **Change of Specification of Drug Substance (where CEP is not available)**<br>a) Specification limits are widened.<br>b) Deletion of specification parameter which may have a significant effect on the overall quality of the drug substance and/or drug product. |
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| C | 1. Test procedures remain unchanged, or changes in the test procedure are minor.<br>2. For tightening of specification limits, addition of new specification parameter, deletion of a non-significant specification parameter (e.g., e.g. deletion of an obsolete parameter), refer to MIV-2 C7.<br>3. For change of specification of drug substance where a CEP is available, refer to MIV-1 B6.<br>4. For change of specification due to update of the compendium for compendial drug substance, refer to MIV-2 C47.<br>5. 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**<br>1. Proposed specification of drug substance. |

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| | 2. Comparative tabulated format of the currently approved and proposed specification of drug substance with changes highlighted.<br>3. Justification for change substantiated with scientific data to be provided.<br>4. Certificate of analysis or batch analysis data of the drug substance for all tests in the proposed specification for two pilot or production scale batches.<br>5. If the change is also applicable to the drug substance specification as controlled by the drug product manufacturer, data covering S4.1 to S4.5 from the drug product manufacturer should be submitted (where applicable).<br>6. For change of drug substance specification that involved stability-indicating parameters,<br>a) Results of at least six months of real time stability studies of at least two production batches of the drug substance.<br>b) A commitment letter to continue the stability studies to the approved retest period or shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.<br>c) A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.<br>**Deletion of test parameter and limits**<br>All the above documents except D6. |

| **B6** | **Change of Specification of Drug Substance (where CEP is available)**<br>a) Specification limits are widened.<br>b) Deletion of specification parameter which may have a significant effect on the overall quality of the drug substance and/or drug product. |
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| C | 1. Test procedures remain unchanged, or changes in the test procedure are minor.<br>2. For change of specification of drug substance where a CEP is not available, refer to MIV-1 B5.<br>3. For tightening of specification limits, addition of new specification parameter, deletion of a non-significant specification parameter (e.g., e.g. deletion of an obsolete parameter), refer to MIV-2 C11.<br>4. For a change in specification due to update of the compendium for compendial drug substance, refer to MIV-2 C47.<br>5. 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. |

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| D | 1. A copy of the duly authorised, valid CEP, including all annexes as issued by the EDQM.<br>2. Proposed specification of the drug substance.<br>3. Comparative tabulated format of the currently approved and proposed specification of drug substance with changes highlighted.<br>4. Justification for change substantiated with scientific data to be provided.<br>5. Certificate of analysis or batch analysis data of the drug substance for all tests in the proposed specification for two pilot or production scale batches from the drug substance manufacturer*, demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP.<br>** If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should of be submitted.*<br>6. For change of drug substance specification that involved any stability-indicating parameters, and if the re-test period is not stated on the CEP,<br>(a) Results of at least six months of real time stability studies of at least two production batches of the drug substance.<br>(b) A commitment letter to continue the stability studies to the approved retest period or shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.<br>(c) A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.<br>**Deletion of test parameter and limits**<br>All the above documents except D6. |

| **B7** | **Addition or Replacement of Manufacturing Site of Drug Product** |
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| C | 1. Site change consists of changes in location of the site of manufacture only and does not include any scale-up changes, change in manufacturing process, or changes in components or composition.<br>2. If there are changes to the manufacturing process, MIV-1 B12 or MIV-2 C19 is also applicable.<br>3. If there are changes to the batch size, MIV-1 B10, MIV-1 B11, or MIV-2 C12 is also applicable.<br>4. If there are changes to the drug product specification, MIV-1 B9 or MIV-2 C23 is also applicable.<br>5. Not applicable to changes relating to the manufacturer responsible for batch release (refer to MIV-2 C3) or primary packager (refer to MIV-1 B8 or MIV-2 C28). |

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| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. 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: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA*).<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 the drug product and stating the types of activity to be performed (where applicable).<br>5. Drug product formula or batch manufacturing formula.<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(s).<br>7. Holding time studies of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).<br>8. Approved release and shelf-life specifications of the drug product.<br>9. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) from the approved and proposed manufacturing sites.<br>10. Stability studies as per *ASEAN Guideline on Stability Study of 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.<br>12. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured by the approved and proposed manufacturing site as per US FDA SUPAC IR or MR guidelines.<br>13. For modified release oral solid dosage form, justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). |

| **B8** | **Addition or Replacement of Alternative Site for Primary Packaging for Sterile Drug Substance or Drug Product** |
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| C | 1. No other changes except for the addition or replacement of an alternative site for primary packaging (direct contact with drug product) of sterile drug product.<br>2. The primary packaging material must be the same approved primary packaging material with the same specifications.<br>3. For non-sterile drug product, refer to MIV-2 C28. |

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| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Proof that the proposed site is appropriately authorised for the packaging activity of the pharmaceutical form concerned, such as a valid GMP Certificate and/or a CPP which covers GMP certification (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA).<br>3. In case of a contract primary packager, a letter of appointment for the proposed site to package the drug product and stating the types of activity to be performed by the packager (where applicable).<br>4. Validation scheme and/or report of the primary packaging processes, e.g., manufacturing and sterilization process, container closure system integrity, as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration*.<br>5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable).<br>6. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) from the approved and proposed sites. |

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| **B9** | **Change of Release and/or Shelf-Life Specifications of Drug Product**<br>a) Specification limits are widened.<br>b) Deletion of specification parameter 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 procedures are minor (MIV-2 C26 is also applicable if there is change in test methods).<br>2. For tightening of specification limits, addition of new specification parameter, deletion of a non-significant specification parameter (e.g., deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material), refer to MIV-2 C23.<br>3. For a change in specification due to update of the compendium for compendial drug product, refer to MIV-2 C47.<br>4. 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**<br>1. Proposed specification of drug product.<br>2. Comparative tabulated format of the currently approved and proposed specification of drug product with changes highlighted.<br>3. Certificate of analysis or batch analysis data of the drug product for all tests in the proposed specification for at least two batches (preferably production scale).<br>4. Justification for change substantiated with scientific data. |

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| | 5. For change of drug product specification that involved stability-indicating parameters, stability studies as per *ASEAN Guideline on Stability Study of 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. |

| **B10** | **Change of Batch Size of Sterile Drug Product** |
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| C | 1. The change does not affect consistency of production.<br>2. The drug product formulation remains unchanged.<br>3. Release and shelf-life specifications of the drug product remain unchanged. |
| D | 1. Comparative tabulated format of approved and proposed batch manufacturing formula.<br>2. 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 batch size.<br>3. Release and shelf-life specifications of the drug product.<br>4. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed batch sizes.<br>5. Stability studies as per *ASEAN Guideline on Stability Study of 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. |

| **B11** | **Change of Batch Size of Non-sterile Drug Product** |
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| C | 1. This is applicable to change of batch size of more than 10-fold the size of the approved batch size. For change of batch size up within 10-fold of the size of approved batch size, refer to MIV-2 C12.<br>2. The change does not affect consistency of production.<br>3. The drug product formulation remains unchanged.<br>4. Release and shelf-life specifications of the drug product remain unchanged. |

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| D | 1. Comparative tabulated format of approved and proposed batch manufacturing formula.<br>2. 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 batch size.<br>3. Release and shelf-life specifications of the drug product.<br>4. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed batch sizes.<br>5. Stability studies as per *ASEAN Guideline on Stability Study of 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>7. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured using the approved and proposed batch sizes as per US FDA SUPAC IR or MR guidelines. |

| **B12 Major Change in Manufacturing Process for Drug Product** | |
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| C | 1. The change may cause significant impact on the quality, safety and efficacy of the drug product.<br>2. For a minor change of the manufacturing process, refer to MIV-2 C19.<br>3. Manufacturing site remains the same. If there is a change in manufacturing site, MIV-1 B7 is also applicable.<br>4. Specification of the drug product remains unchanged. If there is a change in the specification, MIV-1 B9 or MIV-2 C23 is also applicable. |
| D | 1. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available).<br>2. Description of the proposed manufacturing process and technical justification 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*.<br>4. Release and shelf-life specifications of the drug product.<br>5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed processes.<br>6. Stability data as per *ASEAN Guideline on Stability Study of 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 |

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| | 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>8. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured using the approved and proposed manufacturing processes as per US FDA SUPAC IR or MR guidelines.<br>9. Justification for not submitting a new bioequivalence study according to the *ASEAN Guideline for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable). |

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| **B13 Qualitative or Quantitative Change of Excipient**<br>a) For immediate release oral solid dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline).<br>b) For modified release oral solid dosage forms.<br>c) For other critical dosage forms such as sterile preparations. | |
| C | 1. Change will need to comply with the drug product specifications, i.e., release and shelf-life specifications of the drug product remain the same, excluding product description.<br>2. Replacement of an excipient with a comparable excipient of the same functional characteristics.<br>3. The dissolution profile of the proposed drug product is comparable to that of the approved drug product.<br>4. For minor qualitative or quantitative changes of excipient for immediate release oral solid dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline) or other non-critical dosage forms, refer to MIV-2 C14.<br>5. HSA reserves the right to re-categorise the application to NDA or GDA, if deemed appropriate. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Justification for the change must be given by appropriate development of pharmaceutics.<br>3. Comparative tabulated format of the approved and proposed drug product formulation with calculated changes highlighted (state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable).<br>4. Revised CTD Section P1, 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.<br>6. Specification of the proposed excipient(s).<br>7. For materials derived from TSE-relevant animals (i.e. cattle, sheep, goat, deer, elk, non-human primates): |

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| | 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>8. Release and shelf-life specifications of the drug product.<br>9. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed drug product formula.<br>10. Stability data as per *ASEAN Guideline on Stability Study of 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.<br>12. For oral solid dosage form, comparative dissolution profile data of at least one representative pilot/production batch of the drug product manufactured using the approved and proposed formulation as per US FDA SUPAC IR or MR guidelines.<br>13. Justification for not submitting a new bioequivalence study according to the *ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable). |

| **B14** | **Quantitative Change in Coating Weight of Tablets, or Weight and/or Size of Capsule Shell for Modified Release Oral Solid Dosage Form** |
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| C | 1. The dissolution profile of the proposed drug product is comparable to that of the approved drug product.<br>2. The release and shelf-life specifications of the drug product remain unchanged except for the weight and/or size (where applicable).<br>3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral solid dosage forms, refer to MIV-2 C15. |
| D | 1. Revised draft of the product label incorporating the proposed change (where applicable).<br>2. Comparative tabulated format of the approved and proposed drug product and batch manufacturing formula.<br>3. Release and shelf-life specifications of the drug product.<br>4. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.*<br>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 |

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| | 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>6. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed formulation as per US FDA SUPAC MR guidelines.<br>7. Justification for not submitting a new bioequivalence study according to the *ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable). |

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| **B15** | **Change in Primary Packaging Material for Sterile Drug Substance or Drug Product**<br>a) Change in qualitative and quantitative composition.<br>b) Change of type of container.<br>c) Inclusion of new primary packaging material. |
| C | 1. No submission is required if there is a change in the supplier for the same type of primary packaging material with the same specification.<br>2. Release and shelf-life specifications of the drug product remain unchanged.<br>3. For a change in the primary packaging material for a non-sterile drug product, refer to MIV-2 C27. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Justification for the change in primary packaging material.<br>3. Comparative tabulated format of the specifications of the approved and proposed primary packaging material.<br>4. Revised CTD Sections P3 and/or P7 (where applicable).<br>5. Declaration of compliance to the appropriate international standards or pharmacopoeia.<br>6. Appropriate scientific data on the proposed packaging (comparative data on permeability, e.g. moisture, $O_2$, $CO_2$).<br>7. 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>8. Validation scheme and/or report of the manufacturing and sterilization process, container closure system integrity, as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* appropriate to the proposed change in primary packaging material.<br>9. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.*<br>10. 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 |

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| | 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. |

| **B16** | **Change or Addition of Pack Size/Fill Volume and/or Change of Shape or Dimension of Primary Packaging Material for Sterile Drug Product** |
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| 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 pack size/fill volume specification.<br>4. For change or addition of pack size/fill volume and/or change of shape or dimension of primary packaging material for a non-sterile drug product, refer to MIV-2 C30. |
| 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 and/or P7 (where applicable).<br>4. Validation scheme and/or report of the manufacturing and sterilization process, container closure system integrity, as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* appropriate to the proposed change in primary packaging material.<br>5. Stability data as per *ASEAN Guideline on Stability Study of 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** | **Inclusion or Replacement 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.<br>2. For deletion of the solvent/diluent, refer to MIV-2 C17.<br>3. For change of shelf-life and/or storage condition of the drug product as a package for sale, and/or after first opening, and/or after dilution/reconstitution, refer to MIV-1 B18 and/or B19. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation.<br>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 |

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| | Product (CPP) which covers GMP certification (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA.)<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).<br>5. A declaration from the product registrant that the release and shelf-life specifications of the 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). |

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| **B18** | **Change of Shelf-life of Drug Product**<br>a) As a package for sale; and/or<br>b) After first opening; and/or<br>c) After dilution/reconstitution. |
| C | 1. For (a) & (b), the studies must show conformance to the approved shelf-life specification.<br>2. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product.<br>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).<br>2. Justification for the change of shelf-life of the drug product (where applicable).<br>3. Results of appropriate real time stability studies covering the duration of the proposed shelf-life of at least two pilot/production scale batches of the 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 *ASEAN Guidelines on Stability Study of Drug Product*. |

| **B19 Change of Storage Conditions of Drug Product**<br>a) As a package for sale; and/or<br>b) After first opening; and/or<br>c) After dilution/reconstitution. | |
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| C | 1. For (a) & (b), the studies must show conformance to the approved shelf-life specification.<br>2. For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted drug product.<br>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).<br>2. Justification for the change of storage condition of the drug product (where applicable).<br>3. Results of appropriate real time stability studies covering the duration of the approved shelf-life (at the proposed storage condition) of at least two pilot/production scale batches of the drug product and 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 *ASEAN Guidelines on Stability Study of Drug Product*. |

| **B20 Addition or Change of Functional Score/Break Line of Tablet** | |
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| C | 1. New markings do not cause confusion with other registered drug products.<br>2. Release and shelf-life specifications of the drug product remain unchanged except for appearance.<br>3. Score/break-line is meant for functional but not cosmetic purpose. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Justification for the change (e.g., change in dosing regimen).<br>3. Detailed drawing or written description of the approved and proposed imprint/bossing/markings.<br>4. Release and shelf-life specifications of the drug product with the new product description.<br>5. Data on test of content uniformity of the subdivided parts of the tablets at release as conformed to compendial requirement should be submitted. |

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| | 6. Certificates of analysis or batch analysis of two pilot/ production scale batches. |

| **B21 Change of Sterility Testing to Parametric Release** | |
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| C | 1. Consult HSA prior to submission.<br>2. Only a manufacturing site located in a PIC/S participating country with parametric release being approved by the local authority is eligible to apply. |
| D | 1. A complete and detailed description of the current terminal sterilization cycle including type/design/process parameters, drug product and container closure system to be sterilised.<br>2. Identification of the critical process parameters (process/cycle parameters and appropriate sterilisation load monitors essential for drug product release), including the minimum and maximum limits.<br>3. Risk assessment: A discussion of risk to the sterility of the drug product relative to the following: (a) prior knowledge from developmental and registration batches, (b) consistency of performance of steriliser and historical batch analysis data, (c) the production loading pattern (d) container closure system (including secondary packaging), (e) any potential contamination risks from the environment, and (f) reprocessing plan.<br>4. Process validation of sterilizer: Validation of sterilization process includes the validation of cycle parameters and its microbiological effectiveness through use of biological indicators, container closure system integrity, production load patterns, cycle process parameters and acceptance criteria, heat distribution study for three consecutive runs, heat penetration studies for three consecutive runs for each loading pattern and container size, effectiveness of the load monitor used for each routine run, bioburden, sterility assurance level of $10^{-6}$ or better should be demonstrated, re-processing (where applicable).<br>5. Control Strategy: (a) tabulation of all validated critical process parameter and loading pattern, (b) describes the process and requirement for releasing/rejection of a batch, (c) bioburden monitoring and control program, (d) segregation of sterile from non-sterile drug product, (e) routine maintenance/re-validation program for steriliser, etc.<br>6. Approval letter or recent documentary evidence of approval status (i.e. GMP) for parametric release issued by a local authority (PIC/s). The manufacturing site and drug product name must be clearly stated. (Note: GMP Conformity Assessment is required if proposed site is not currently registered with HSA for parametric release).<br>7. Release and shelf life specifications of the drug product. Revision of the certificates of analysis that parametric release is now the method used to provide assurance of the requirement of sterility.<br>8. Stability data (includes sterility test) as per *ASEAN Guideline on Stability Study of Drug Product*.<br>9. A commitment letter to complete the on-going stability studies (including sterility test) 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. |

| **B22** | **Implementation of a New Design Space or Extension of an Approved Design Space for Drug Substance or Drug Product** |
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| 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 B5 or MIV-1 B9. |
| 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 studies 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 *ASEAN Guideline on Stability Study of 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. |

| **B23** | **Change of Content of Product Labelling** |
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| C | 1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), outer carton label, inner label and/or blister label.<br>2. 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 clean 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).<br>4. Justification for the changes proposed and supporting clinical documents where applicable. |

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

| **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 the drug product name and committing to inform users of the relevant changes (where applicable).<br>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** | **<u>Change of Product Labelling</u>**<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 drug 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) Alignment of a generic drug product labelling with that of the Singapore Reference Product.<br>f) Administrative/editorial changes that have no impact on safety, efficacy and quality. |
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| C | 1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), carton label, inner label and/or blister label.<br>2. The change is not an MIV-1 and does not contain promotional information. |
| D | 1. Approved product labelling.<br>2. Proposed product labelling, and a clean and annotated version highlighting the changes made.<br>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.<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. 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).<br>3. An official letter from the product owner authorising the company/manufacturer to be responsible for batch release (where applicable). |

| C4 | Change of Batch Size of Drug Substance (where CEP is not available) |
|---|---|
| C | 1. The change does not affect the reproducibility of the process.<br>2. Specifications of the drug substance remain unchanged. |
| D | 1. A letter of declaration from the product registrant that the specifications of the drug substance have not changed and the reproducibility of the process has not been affected.<br>2. Amended relevant CTD Section S (where applicable).<br>3. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two batches of the drug substance for all tests in the approved specification from the approved and proposed batch sizes. |

| C5 | Change of In-process Controls Applied during Manufacture of Drug Substance (where CEP is not available) |
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| C | 1. In-process limits are tightened or new tests are added.<br>2. The change is not a consequence of any commitment from previous assessments to review the specification limits.<br>3. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity or change in total impurity limits.<br>4. Any new test method that does not concern a novel non-standard technique or a standard technique used in a novel way. |
| D | 1. A description of the analytical method and summary of validation data must be provided for all new analytical methods (where applicable).<br>2. Comparative tabulated format of the approved and proposed in-process controls and the relevant changes. |

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| | 3. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance for all tests in the approved and proposed specification (where applicable). |

| **C6** | **Minor Change of Manufacturing Process of Drug Substance (where CEP is not available)** |
|---|---|
| C | 1. No adverse change in the qualitative and/or quantitative impurity profile which would require further qualification in safety studies. Otherwise, refer to MIV-1 B3.<br>2. The synthetic route remains unchanged (for example, intermediates remain the same). Otherwise, refer to MIV-1 B3.<br>3. Manufacturing process of the drug substance does not use any materials of human/animal origin for which assessment is required for viral safety.<br>4. Physicochemical characteristics and other relevant properties of the drug substance remain unchanged.<br>5. Specifications and stability performance of the drug substance remain unchanged; if there is changes made to the specification of the drug substance, MIV-1 B5 or MIV-2 C7 is applicable. |
| D | 1. Drug Master File (DMF), or relevant updated CTD S section(s) or equivalent document.<br>2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available).<br>3. For a sterile drug substance, process validation report (where applicable).<br>4. A letter of declaration from the product registrant stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies.<br>5. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance for all tests in the approved specification from the approved and proposed manufacturing processes. |

| **C7** | **Change of Specification of Non-compendial Drug Substance**<br>a) Specification limits are tightened.<br>b) Addition of new test parameter and limits.<br>c) Deletion of non-significant parameter (e.g., obsolete parameter). |
|---|---|
| C | 1. This is only applicable for drug substances which are non-compendial or without a CEP.<br>2. For widening of specification limits and deletion of significant test parameter and limits of the drug substance, refer to MIV-1 B5.<br>3. Test procedures remain the same or changes in the test procedure are minor. |

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| | 4. 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**<br>1. Technical justification for the change.<br>2. Comparative tabulated format of the approved and proposed specification of the drug substance with changes highlighted.<br>3. Certificate of analysis or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance for all tests in the approved and proposed specification.<br>**Addition of new test parameter and limits**<br>In addition to the above documents,<br>4. Description of any new analytical method and a summary of the validation data.<br>**Deletion of non-significant parameter**<br>In addition to documents (1) and (2),<br>5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete. |

| **C8** | **Change of Test Procedure of Non-compendial Drug Substance** |
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| C | 1. Results of method validation show that the new test procedure is at least equivalent to the former procedure.<br>2. Refer to MIV-2 C11 if this change resulted in a revision of a CEP. |
| D | 1. Description of the analytical methodology, and a summary of validation data (where applicable).<br>2. Specification of the drug substance.<br>3. Comparative analytical results between the approved and proposed test (where applicable). |

| **C9** | **Change of Shelf-life or Re-test Period of Drug Substance** |
|---|---|
| C | 1. The stability studies must show compliance with the specification.<br>2. There is no change in the storage condition.<br>3. Refer to MIV-2 C11 if this change resulted in a revision of a CEP. |
| D | 1. Specification of the drug substance.<br>2. Stability data of the drug substance should be provided on at least two pilot or production scale batches at the proposed shelf-life or retest period. |

| C10 Change of Storage Conditions of Drug Substance | |
|---|---|
| C | 1. The stability studies must show compliance with the specification.<br>2. There is no change in the shelf-life or retest period.<br>3. Refer to MIV-2 C11 if this change resulted in a revision of a CEP. |
| D | 1. Specification of the drug substance.<br>2. Stability data of the drug substance should be provided on at least two pilot or production scale batches at the proposed storage condition. |

| C11 Revision of CEP of Drug Substance | |
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| C | 1. Includes minor change of manufacturing process, change of batch size, in-process controls, specification (tightening or addition of test parameters), test procedure, shelf life/re-test period, and/or storage condition that are covered by a valid CEP.<br>2. Refer to MIV-1 B4 if this change is due to a major change of the manufacturing process of the drug substance.<br>3. Refer to MIV-1 B6 if this change is due to a widening of the specification limits or deletion of test parameters. |
| D | 1. A copy of the duly authorised, valid CEP, including all annexes as issued by the EDQM.<br>2. Specification of the drug substance (where applicable).<br>3. Results of batch analysis from the drug substance manufacturer* demonstrating compliance with the Ph. Eur. monograph and including additional test/limits listed on the CEP (where applicable).<br>* *If the drug substance manufacturer is CEP-certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc.), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.*<br>4. Additional data to address any relevant parameter(s) not addressed in the CEP, such as stability data (S7) if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc.), where applicable.<br>5. If this change is due to a drug substance specification change, a commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.be provided only if outside of the specification (with proposed action). |

| C12 | Change of Batch Size of Non-sterile Drug Product |
|---|---|
| C | 1. The change does not affect the consistency of production.<br>2. Release and shelf-life specifications of the drug product remain unchanged.<br>3. This is applicable to a change of batch size up to 10-fold compared to the approved batch size.<br>4. For a change of batch size for sterile drug products, refer to MIV-1 B10 and for a change of batch size more than 10-fold compared to the approved batch size for non-sterile drug products, refer to MIV-1 B11. |
| D | 1. Comparative tabulated format of approved and proposed batch manufacturing formula.<br>2. Revised CTD Section P3 (where applicable).<br>3. Validation scheme and/or report of the manufacturing process as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration* of the proposed batch size appropriate to the proposed batch size.<br>4. Release and shelf-life specifications of the drug product.<br>5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed batch sizes.<br>6. A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| C13 | Reduction or Removal of Overage |
|---|---|
| C | 1. Changes of approved manufacturing overages of the drug substance only.<br>2. Release and shelf-life specifications of the drug product remain unchanged. |
| D | 1. Justification for the change.<br>2. Comparative tabulated format of approved and proposed batch manufacturing formula.<br>3. Certificates of analysis or batch analysis data (in a comparative tabulated format) of the drug product of at least two batches (preferably production scale) manufactured according to the approved and proposed formula.<br>4. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.*<br>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. |

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| **C14 Qualitative and/or Quantitative Change of Excipient**<br>a) For immediate release oral solid dosage forms only (as per Level 1, Part III Components and Composition, SUPAC guideline).<br>b) For other non-critical non-solid dosage forms, e.g. oral liquid, external preparation. | |
| C | 1. Change will need to comply with the drug product specifications, i.e., release and shelf-life specifications of the drug product remain the same, excluding product description.<br>2. Replacement of an excipient with a comparable excipient of the same functional characteristic (where applicable).<br>3. The dissolution profile of the proposed drug product is comparable to that of the approved drug product.<br>4. For qualitative or quantitative changes of excipient for immediate release (Level 2 and 3 change as per US FDA SUPAC IR Guideline) and modified release oral solid dosage forms, and other critical dosage forms, refer to MIV-1 B13. |
| 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 proposed drug product formulation with calculated changes highlighted (state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable).<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 drug product formula (where applicable).<br>6. Specification of the proposed excipient(s).<br>7. A declaration that the proposed excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable).<br>8. 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. |

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

| **C15** | **Quantitative Change in Coating Weight of Tablets or Weight and/or Size of Capsule Shell for Immediate Release Oral Solid Dosage Form** |
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| C | 1. The dissolution profile of the proposed drug product is comparable to that of the approved drug product.<br>2. The release and shelf-life specifications of the drug product remain unchanged except for the weight and/or size (where applicable).<br>3. For quantitative change in coating weight of tablets or weight and/or size of capsule shell for modified release oral solid dosage forms, refer to MIV-1 B14. |
| D | 1. Revised drafts of the product label incorporating the proposed change (where applicable).<br>2. Comparative tabulated format of the approved and proposed drug product and batch manufacturing formula.<br>3. Revised release and shelf-life specifications of the drug product.<br>4. Stability data as per *ASEAN Guideline on Stability Study of Drug Product.*<br>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.<br>6. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation as per US FDA SUPAC IR guidelines. |

| **C16** | **Change of Colouring/Flavouring Agent of Drug Product** |
|---|---|
| C | 1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. |

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| | 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. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. A declaration from the product registrant that the change does not interfere with the drug product release and shelf-life specifications test method.<br>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.<br>4. 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>5. Proposed release and shelf-life specifications of the drug product (where applicable).<br>6. A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| **C17 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).<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 P Sections (where applicable). |

| C18 Change of In-process Controls Applied during Manufacture of Drug Product | |
|---|---|
| C | 1. Release and shelf-life specifications of the drug product remain unchanged.<br>2. The change is not a consequence of any commitment from previous assessments to review the specification limits.<br>3. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity or change in total impurity limits.<br>4. Any new test method that does not concern a novel non-standard technique or a standard technique used in a novel way. |
| D | 1. Comparative tabulated format of currently approved and proposed in-process controls.<br>2. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable).<br>3. Proposed in-process specifications together with justification and relevant process validation data.<br>4. Certificate of analysis or comparative batch analysis data of the drug product of at least two production/pilot batches. |

| C19 Minor Change of Manufacturing Process for Drug Product | |
|---|---|
| C | 1. The manufacturing site remains unchanged. If there is a change in manufacturing site, MIV-1 B7 is also applicable.<br>2. For major change in the manufacturing process for the drug product, refer to MIV-1 B12.<br>3. The overall manufacturing principle remains unchanged.<br>4. The change does not cause negative impact on the quality, safety and efficacy of the drug product.<br>5. The dissolution profile of the proposed drug product is comparable to that of the currently approved drug product.<br>6. Release and shelf-life specifications of the drug product remain unchanged. If there is a change in the specification, MIV-1 B9 or MIV-2 C23 is also applicable. |
| D | 1. Comparative tabulated format of the approved and proposed processes with changes highlighted.<br>2. Description of the proposed manufacturing process and technical justification 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*.<br>4. Approved release and shelf-life specifications of the drug product. |

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| | 5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the drug product on at least two batches (preferably production scale) manufactured to both the approved and the proposed processes.<br>6. A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.<br>7. For oral solid dosage forms, comparative dissolution profile data of at least one representative production batch of the drug product between the currently approved and proposed oral solid dosage forms formulation as per US FDA SUPAC IR or MR guidelines. |

| **C20 Change of Specification of Non-compendial Excipient** | |
|---|---|
| C | 1. Release and shelf-life specifications of the drug product remain unchanged.<br>2. Applicable to non-compendial excipients. For compendial excipients, refer to MIV-2 C47. |
| D | 1. A declaration from the product registrant that the change does not impact the quality and safety of the drug product.<br>2. Description of new method and summary of analytical validation (applicable for addition or replacement of new parameter).<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. |

| **C21 Change of Test Procedure for Excipient** | |
|---|---|
| C | 1. The specification of the excipient remains unchanged. |
| D | 1. Description of the analytical methodology with a comparative tabulation of the changes.<br>2. Results of appropriate method validation to show proposed test procedure to be at least equivalent to the approved procedure.<br>3. For quantitative test change, comparative analytical validation results showing that the approved and proposed tests are equivalent. |

| **C22 Change in Source of Empty Hard Capsule** | |
|---|---|
| C | 1. From TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa.<br>2. The formulation and manufacturing process of the drug product remain unchanged.<br>3. Not applicable to a change from a hard capsule to a soft gel.<br>4. The specifications of excipients and specifications of the release and shelf-life of drug product remain unchanged. |
| D | 1. A letter of declaration from the manufacturer or the product registrant of the material that it is purely of vegetable, animal or synthetic origin.<br>2. Technical specifications and composition of the empty hard capsule of the proposed source.<br>3. Certificates of analysis of the empty hard capsule of the proposed source.<br>4. For empty hard capsule 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>5. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product using the hard capsule between the two sources (where applicable) as per US FDA SUPAC IR or MR guidelines.<br>6. A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| **C23 Change of Release and/or Shelf-life Specifications of Drug Product**<br>a) Specification limits are tightened.<br>b) Addition of new test parameter and limits.<br>c) Deletion of non-significant parameter (e.g., obsolete parameter such as odour and taste or identification test for a colouring or flavouring material). | |
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| C | 1. Test procedures remain unchanged, or changes in the test procedures are minor (MIV-2 C26 is also applicable if there is change in test methods). |

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|---|---|
| | 2. For widening of specification limits and/or deletion of test parameter and limits of the drug product, refer to MIV-1 B9.<br>3. For a change in specification due to update of the compendium for compendial drug product, refer to MIV-2 C47.<br>4. 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**<br>1. Technical justification for the change.<br>2. Comparative tabulated format of the approved and proposed release and shelf-life specifications of the drug product with changes highlighted.<br>3. Certificate of analysis or batch analysis data of the drug product on at least two batches (preferably production scale) for all tests in the proposed specification.<br>**Addition of new test parameter and limits**<br>In addition to the above documents,<br>4. Description of any new method and summary of analytical validation data for the non-compendial method (where applicable).<br>5. Justification of the new specification parameter and the limits.<br>6. For stability indicating parameter, stability data as per *ASEAN Guideline on Stability Study of 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.<br>**Deletion of non-significant parameter**<br>In addition to documents (1) and (2),<br>8. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete. |

| **C24** | **Change of Imprints, Embossing/Debossing or Other Markings on Tablets or Printing on Capsules including Addition or Change of Inks Used for Product Marking** |
|---|---|
| C | 1. New markings do not cause confusion with other registered drug products.<br>2. The proposed ink used must comply to relevant pharmaceutical legislation or be of food grade.<br>3. Release and shelf-life specifications of the drug product remain unchanged except for appearance.<br>4. Refer to MIV-1 B20 for addition or change of functional score/break-line. |

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| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Details and specifications of the proposed ink (where applicable).<br>3. Detailed drawing or written description of the approved and proposed imprint/bossing/markings.<br>4. Certificate of analysis of the ink/printing material (pharmaceutical grade and of food grade) (where applicable).<br>5. Release and shelf-life specifications of the drug product with the new drug product description (where applicable). |

| **C25** | **Change of Dimensions and/or Shape of Tablets, Capsules, Suppositories or Pessaries Without Change in Qualitative and Quantitative Composition and Mean Mass** |
|---|---|
| C | 1. If appropriate, the dissolution profile of the proposed drug product is comparable to that of the currently approved drug product.<br>2. Release and shelf-life specifications of the drug product remain unchanged except for dimension and/or shape. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Detailed drawing or written description of the current and proposed appearance, and revised relevant CTD sections (where applicable).<br>3. Data on test of content uniformity of the subdivided parts of tablets at release as conformed to compendial requirement should be submitted (only applicable for drug product with score/break-line).<br>4. Release and shelf-life specifications of the drug product.<br>5. Comparative dissolution profile data of one batch representative of pilot/production batch of the drug product of the approved and proposed dimensions as per US FDA SUPAC IR or MR guidelines (where applicable).<br>6. Justification for not submitting a new bioequivalence study according to the ASEAN *Guidelines for the Conduct of Bioavailability and Bioequivalence Studies* (where applicable) for dosage forms other than immediate release oral solid dosage forms, suppositories and pessaries. |

| **C26** | **Change in Test Procedure of Drug Product** |
|---|---|
| C | 1. Replacement or addition of a test procedure for the testing of drug product.<br>2. The specifications of drug product remain unchanged; if the specification is changed, MIV-1 B9 or MIV-2 C23 is also applicable.<br>3. Results of method verification/validation show the new test procedure to be at least equivalent to the former procedure. |

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| | 4. 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. Justification for the proposed change.<br>2. Comparative tabulated format of the approved and proposed specifications of the drug product.<br>3. Description of the analytical methodology.<br>4. Appropriate verification/validation data and comparative analytical results between the currently approved and proposed test (where applicable).<br>5. Certificate of analysis or batch analysis data of the drug product on at least two batches (preferably production scale) for all tests in the proposed specification. |

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| **C27** | **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 type of container.<br>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.<br>2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.<br>3. Release and shelf-life specifications of the drug substance or drug product remain unchanged.<br>4. For a change in the primary packaging material for a sterile drug substance or drug product, refer to MIV-1 B15. |
| 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 approved and proposed specifications of the primary packaging material (where applicable).<br>4. Revised CTD Sections P3 and/or P7 (where applicable).<br>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 *ASEAN Guideline on Stability Study of 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 |

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| | 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. |

| **C28** | **Addition or Replacement of Alternative Site for Primary Packaging for Non-Sterile Drug Product** |
|---|---|
| C | 1. No other changes except for the addition or replacement of an alternative site(s) for primary packaging (direct contact with drug product) for non-sterile drug product.<br>2. The primary packaging material must be the same approved primary packaging material with the same specifications.<br>3. For sterile drug product, refer to MIV-1 B8. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Proof that the proposed site is appropriately authorised for the packaging activity of the pharmaceutical form concerned, such as a valid GMP Certificate and/or a CPP which covers GMP certification (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA).<br>3. In case of a contract primary packager, a letter of appointment for the proposed site to package the drug product and stating the types of activity to be performed by the packager (where applicable).<br>4. Validation scheme and/or report of the primary packaging processes, e.g., manufacturing and sterilization process, container closure system integrity, as per *ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration.*<br>5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). |

| **C29** | **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. 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 a CPP which covers the GMP certification (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA).<br>3. Official letter from the product owner authorising the proposed manufacturer or packager to perform secondary packaging (where applicable). |

| C30 | Change or Addition of Pack Size/Fill Volume and/or Change of Shape or Dimension of Primary Packaging Material for Non-sterile Drug Product |
|---|---|
| C | 1. The type and material of the primary packaging material remain unchanged.<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 pack size/fill volume specification.<br>4. For change or addition of pack size/fill volume and/or change of shape or dimension of primary packaging material for a sterile drug product, refer to MIV-1 B16. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<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. A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| C31 | Change of Pack Sizes of the 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 B16 or MIV-2 C30.<br>2. The type and material of the primary packaging material remain unchanged.<br>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).<br>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.<br>3. A commitment letter to conduct relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request. |

| C32 | Addition or Replacement of Measuring Device for Oral Liquid Dosage Forms and Other Dosage Forms |
|---|---|
| C | 1. The size and the accuracy of the proposed measuring device must be compatible with the approved posology, where applicable.<br>2. The proposed device is compatible with the drug product. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Description of the device (including a drawing; where applicable).<br>3. The composition of the device material. The materials should comply with the pharmacopoeia, where applicable.<br>4. Justification that the size and accuracy of the device are adequate for the posology as approved in the product labelling. |

| C33 | 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.<br>2. There is no change in the animal species from which the animal-derived material is obtained from.<br>3. Animal-derived materials from other species (e.g. insects and fish) are exempted from this variation.<br>4. For change in source of empty hard capsule, refer to MIV-2 C22. |
| 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. |

| **C34 Change in Species of Animal-derived Material** | |
|---|---|
| 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 an 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*.<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 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. |

| **C35 Addition or Replacement of Drug Substance Intermediate Manufacturer** | |
|---|---|
| C | 1. No adverse change in the qualitative and/or quantitative impurity profile which would require further qualification in safety studies. Otherwise, refer to MIV-1 B3.<br>2. The synthetic route remains unchanged (for example, intermediates remain the same). Otherwise, refer to MIV-1 B3.<br>3. Specification of drug substance remains unchanged. If there are changes to the drug substance specification, MIV-1 B5 or MIV-2 C7 is also applicable. |
| D | 1. Justification for change. |

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| | 2. Revised relevant CTD, e.g., 3.2.S.2.<br>3. A letter of declaration from the product registrant stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies.<br>4. Certificate of analysis or batch analysis data for at least two pilot batches of the drug substance manufactured using the drug substance intermediate from the new drug substance intermediate site. |

| **C36 Submission of CEP for an Approved Drug Substance Manufacturer** | |
|---|---|
| C | 4. Submission of CEP for an approved drug substance manufacturer that is currently supported by Drug Master File (DMF) / ICH Common Technical Document (CTD) / ASEAN CTD (ACTD) dossier.<br>5. If there are other changes to the drug substance, the relevant MIV checklists will apply. |
| D | 1. A copy of the duly authorised, valid CEP, including all annexes as issued by the EDQM.<br>2. A letter of declaration from the product registrant that there are no other changes except for the change from DMF / ICH CTD / ACTD to CEP. |

| **C37 Change of Specification of Starting Material** | |
|---|---|
| C | 1. Only for the change of specification of starting material.<br>2. No submission is required if there is a change in the supplier for the starting material with the same specification.<br>3. Specification of the drug substance remains unchanged.<br>4. No adverse change in the qualitative and/or quantitative impurity profile which would require further qualification in safety studies. Otherwise, submit MIV-1 B3 or B4. |
| D | 1. Justification for the change.<br>2. A copy of the updated dossier 3.2.S.2.3 and/or 3.2.R.<br>3. Proposed specifications of the starting material and/or a copy of the Certificate of analysis.<br>4. A letter of declaration stating that the specification of the drug substance has not changed. |

## 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 |
|---|---|---|

| **C38** | **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.<br>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. |

| **C39** | **Addition or Replacement of Site Responsible for Quality Control (QC) Testing of Drug Product** |
|---|---|
| C | 1. The manufacturer and primary packager of the drug product remains unchanged.<br>2. Method transfer from the approved to the proposed site or test laboratory has been successfully completed. |
| D | 1. Declaration from the drug product manufacturer / product owner on the following:<br>a) The change does not affect the release and shelf life specifications of the drug product.<br>b) The tests used by the proposed QC testing site are equivalent to the registered methods. |

| | |
|---|---|
| | c) List of tests used by the proposed QC testing site with indication if the method suitability / transfer / validation has been completed for each test. |

| **C40** | **Change of Product Owner or Change in Name and/or Address (for example: postal code, street name) of Product Owner** |
|---|---|
| C | 1. The product registrant remains unchanged.<br>2. The manufacturing site remains unchanged.<br>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:**<br>1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. A declaration on the transfer of ownership between the old product owner and new owner.<br>3. An official letter from the new product owner declaring the change and authorising the local registrant to be responsible for the product registration.<br>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.<br>**For change of name and/or address of product owner:**<br>5. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>6. An official letter from the product owner declaring the change and authorising the local registrant to be responsible for the product registration. |

| **C41** | **Change in Ownership of Manufacturer** |
|---|---|
| C | 1. The manufacturing site remains unchanged.<br>2. No other changes except for the change in ownership of the manufacturer. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. A letter of justification on the transfer of ownership, such as a valid GMP certificate.<br>3. An official letter stating the transfer of ownership from the old manufacturer to the new manufacturer (where applicable).<br>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. |

| C42 | Change of Name or Address (for example: postal code, street name) of Manufacturer of Drug Product |
|---|---|
| C | 1. The manufacturing site remains unchanged.<br>2. No other changes except for the change of the name and/or address of a manufacturer of the drug product.<br>3. For a change in ownership of manufacturer, refer to MIV-2 C41. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>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.<br>3. An official letter from product owner authorising the manufacturer with the new name/address to manufacture the drug product. |

| C43 | 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.<br>2. The batch release site remains unchanged.<br>3. For a change in ownership of manufacturer, refer to MIV-2 C41. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>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 (where applicable).<br>3. An official letter from the product owner authorising the company/manufacturer with the new name/address that is responsible for batch release.<br>4. A declaration from the product registrant that the change does not involve a change of batch release site. |

| C44 | 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.<br>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.<br>2. An official document/evidence confirming the new name and/or address. |

| **C45** | **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 | 2. Reason for withdrawal/deletion. |

| **C46** | **Renewal of CEP** |
|---|---|
| C | 1. Only applicable if the renewal of a CEP does not involve any CMC changes.<br>2. Refer to MIV-2 C11 if there is minor change to the drug substance (where CEP is available) which includes change of batch size / in-process controls / manufacturing process / specification / test procedure / shelf life / storage condition. |
| D | 1. A copy of the duly authorised, valid CEP, including all annexes as issued by the EDQM. |

| **C47** | **Change of Release and Shelf-life specification to Comply with Latest Compendium for:**<br>a) Drug Product.<br>b) Drug Substance.<br>c) Excipient. |
|---|---|
| C | 1. Applicable to compendial specifications only.<br>2. Change is made to comply with an update of the relevant monograph of the compendium or from one recognised pharmacopoeia to another.<br>3. Pharmacopoeia recognised by HSA: United States Pharmacopeia, European Pharmacopoeia, British Pharmacopoeia and Japanese Pharmacopoeia. |
| D | 1. Proposed release and/or retest/shelf-life specifications.<br>2. Tabulation of the approved and proposed release and/or retest/shelf-life specifications of the drug product and/or drug substance and/or excipient with changes highlighted.<br>3. Certificate of analysis or batch analysis of the drug product and/or drug substance and/or excipient for all tests in the proposed specification of at least two batches.<br>4. For change of specification of excipients and drug substances, a declaration that the change has no impact on the manufacturing process and quality of the drug product. |

| **C48 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.<br>2. For addition of pack size for sterile and non-sterile drug products, refer to MIV-1 B16 and MIV-2 C30 respectively. For change in the outer carton pack size, refer to MIV-2 C31. |
| D | 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).<br>2. Reason for the deletion. |

| **C49 Change of Batch Numbering System** | |
|---|---|
| C | 1. The manufacturing site remains unchanged. |
| D | 1. Description of the revised batch numbering system.<br>2. An official letter stating the commencement date of the change. |

| **C50 Update of Product Labelling**<br>• Changes to non-English language text (e.g. Chinese).<br>• Rearrangement/re-formatting of text/images without any change in information.<br>• Addition/change of labelling intended for foreign markets (i.e. shared pack), e.g. other countries' registration or licence number/ poison labels/foreign language text in the package insert.<br>• 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.<br>2. The change is not an MIV-1 and does not contain promotional information. |
| D | 1. Current approved product labelling.<br>2. Proposed product labelling, and a clean and annotated version highlighting the changes made.<br>3. Relevant document/reference to support the changes (where applicable). |