APPENDIX 10 GUIDELINE ON MINOR VARIATION (MIV) APPLICATION FOR CLASS 2 CELL, TISSUE OR GENE THERAPY PRODUCTS

Table of Contents

INTRODUCTION

This document describes the requirements of Minor Variation (MIV) Application submitted for an existing registered Class 2 Cell, Tissue or Gene Therapy Product in Singapore. Product registrants should be familiar with the contents of this document, and the governing legislation prior to submitting a MIV application to HSA.

The following points should be considered when submitting a MIV application:

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

MIV-1 changes should be grouped together and submitted as one application if the changes are consequential. A consequential change is an unavoidable and direct result of another change, e.g. a change of specifications is consequential to a change of manufacturing process. Grouping of non-consequential MIV-1 changes under one application is not allowed. HSA reserves the right to split any MIV-1 with non-consequential changes into separate MIV applications. HSA also reserves the right to re-categorise the application if deemed appropriate.

For each registered CTGTP, applicants may submit up to a maximum of two concurrent MIV-1 and one MIV-2 application at any one time.

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.

Product registrants are encouraged to email the Variation Application Filing and Submission Enquiry Form in Appendix 11 if there are any issues regarding MIV filing, such as the absence of a relevant checklist for a particular change.

SUBMISSION PROCESS

A MIV is submitted using the form, "Application for MIV-1 of Class 2 CTGTP" or

"Application for MIV-2 of Class 2 CTGTP".

Product registrants should disclose all proposed changes in *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.

DOCUMENTARY REQUIREMENTS

The following documents listed in Table 1 must be submitted with each MIV submission. The documents can be submitted to HSA_CTT_Enquiry@hsa.gov.sg or in a CD/DVD to Advanced Therapy Products Branch, Medicinal Products Pre-Market Cluster, Health Products Regulation Group, Health Sciences Authority at 11 Biopolis Way, #11-01, Singapore 138667.

Table 1: MIV Application Submission Requirements

• Application form
• Table of contents
• Cover letter
• Variation checklist (s)
• Table of summary of changes
• Variation specific supporting documents
• Current approved and proposed product labelling (annotated and pristine copies), if applicable

The *variation checklists* for MIV-1 and MIV-2 are located in Part A and B of this Appendix. These checklists serve as guides when submitting the required documents relevant to each proposed MIV. When submitting the variation checklist, a copy of the relevant checklist(s) to each proposed MIV(s) should be included. Justifications should be provided below the respective document description if there is any omission of documentation.

The *Table of Summary of Changes* which concisely describes the proposed MIV(s) should be submitted and should include the following information:

- 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 approval of the proposed change(s) in other countries/agencies

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

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

This document reflects the current thinking of HSA on the minimum data necessary for assessment. Product registrants are responsible for ensuring that all necessary validations were conducted to demonstrate that the change does not adversely affect the quality, safety or efficacy of the CTGTP concerned. HSA reserves the right to request for additional information if deemed appropriate.

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

A1	**Change and/or addition of alternative manufacturer/site of active substance, critical starting materials, CTGTP and/or process intermediates**
•	If there are changes to the manufacturing process, MIV-1 A2 or MIV-2 B4 is also applicable.
•	If there are changes to the active substance, critical starting materials or CTGTP specification, MIV-1 A3 or MIV-2 B5 is also applicable.
•	Not applicable to changes relating to the manufacturer responsible for batch release (refer MIV-2 B3).
1.	Amended relevant CTD Sections.
2.	Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
3.	Proof that the proposed site is appropriately authorised, such as a valid Good Manufacturing Practice (GMP) certificate. (Note: a GMP Conformity Assessment is required if the proposed manufacturing site is not currently registered with HSA).
4.	Batch numbering system (where applicable).
5.	In the case of a contract manufacturer, a letter of appointment for the proposed site to manufacture the CTGTP and stating the types of activity to be performed (where applicable).
6.	Validation scheme and/or report of the manufacturing process at the proposed site(s).
7.	Approved release and/or shelf life specifications of the active substance, critical starting materials, CTGTP or process intermediates.
8.	<u>For the change of manufacturing site for active substance or critical starting materials:</u> comparability study of the approved and proposed active substance or critical starting materials with respect to physico-chemical characterisation, biological activity and impurity profile, including certificate of analysis or comparative batch analysis data of at least two production batches, unless otherwise justified, from the approved and proposed sites.
9.	<u>For the change of manufacturing site for CTGTP:</u> comparability study including certificate of analysis or batch analysis data (in a comparative tabulated format) of the CTGTP from at least two production batches, unless otherwise justified, from the approved and proposed site.
10.	Stability studies as per the relevant guidelines on the stability study of the active substance, critical starting materials or CTGTP.
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.

A2 Change in manufacturing process
• For changes to the manufacturing process, at any stage during the manufacture of an active substance, critical starting materials, CTGTP and/or process intermediates. • The change may cause a significant impact on the quality, safety and efficacy of the CTGTP. • The change does not adversely affect the reproducibility of the process. • Manufacturing site remains unchanged. If there is a change in manufacturing site, MIV-1 A1 is also applicable. • Specification of the active substance, critical starting materials or CTGTP remains unchanged. If there is a change in the specification, MIV-1 A3 or MIV-2 B5 is also applicable. • For any change not covered by MIV-2 B4.
1. Comparative tabulated format of the approved and new processes with changes highlighted (where available). 2. Description of the new manufacturing process and justifications for the change. 3. Validation scheme and/or report of the proposed manufacturing process should be provided upon submission. 4. A copy of the approved release and shelf-life specifications. 5. <u>For the change of manufacturing process for active substance or critical starting materials:</u> comparability of the approved and proposed active substance or critical starting material with respect to physico-chemical characterisation, biological activity and impurity profile, including certificate of analysis or comparative batch analysis data of at least two production batches, unless otherwise justified, of the active substance from the approved and proposed processes. 6. <u>For the change of manufacturing process for CTGTP:</u> comparability study including certificate of analysis or batch analysis data (in a comparative tabulated format) of CTGTP of at least two production batches, unless otherwise justified, manufactured according to the approved and proposed processes. 7. Stability studies as per the relevant guidelines on the stability study of the active substance, critical starting materials or CTGTP. 8. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

A3 Change of specification of active substance, critical starting materials CTGTP, process intermediates and/or in-process control tests a) Widening of specification limits. b) Deletion of specification parameters which may have a significant effect on the overall quality of the CTGP.
• Test procedures remain unchanged, or changes in the test procedure are minor.

- For tightening of the specification limit, addition of new specification parameter, deletion of a non-significant specification parameter, refer to MIV-2 B5.
- 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.

a) Widening of specification limits

1. Justification for change substantiated with scientific data.
2. Revised specification of the active substance, critical starting materials, CTGTP, process intermediates or in-process control test.
3. Comparative tabulated format of the approved and revised specification of the active substance, critical starting materials, CTGTP, process intermediates or in-process control test, with changes highlighted.
4. Test results of two production batches, unless otherwise justified, of the active substance, critical starting materials, CTGTP, process intermediates or in-process control, from all tests in the revised specification.
5. For change of specification that involve stability-indicating parameters, stability studies as per the relevant guidelines on the stability study of the active substance, critical starting materials or CTGTP.
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.

b) Deletion of specification parameters

All the above documents except 5 & 6.

A4 Qualitative or quantitative change of excipient of active substance and/or CTGTP

- Change will need to comply with the active substance or CTGTP specifications, i.e., the release and shelf-life specifications of the active substance/CTGTP should remain unchanged, excluding product description.
- Replacement of an excipient with a comparable excipient of the same functional characteristic.
- HSA reserves the right to re-categorise the application to NDA, if deemed appropriate.

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. Justification for the change must be given by appropriate development of product.
3. Comparative tabulated format of the approved and revised CTGTP formulation with calculated changes highlighted (state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable).
4. Revised CTD Section P3.1 to P3.4 (where applicable), including revised batch manufacturing formula.

5. Validation scheme and/or report of the manufacturing process appropriate to the proposed change in the product formula should be provided upon submission.
6. Information demonstrating comparability in terms of physico-chemical characterisation and impurity profile of the proposed excipient with the approved excipient (if applicable).
7. Specification of the proposed excipient(s).
8. For proposed excipients derived from TSE-relevant animals (i.e. cattle, sheep, goat, deer, elk, non-human primates):
   a) A valid CEP for the TSE risk evaluation;
   b) If CEP is not available,
      i. Description of the tissue/organ/fluid-collection procedures and measures in place to avoid cross-contamination.
      ii. Details of the risk factors associated with the route of administration and maximum therapeutic dosage of the CTGTP.
      iii. Relevant information demonstrating that the manufacturing process is capable of inactivating TSE agents.
9. Active substance or CTGTP release and shelf-life specifications.
10. Certification of analysis or batch analysis data (in a comparative tabulated format) of the active substance or CTGTP on at least two production batches, unless otherwise justified, according to the approved and proposed product formula.
11. Stability data as per relevant guidelines on the stability study of the active substance or CTGTP.
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.

A5 Change in primary packaging material for active substance or CTGTP

a) Change in qualitative and quantitative composition.
b) Change in type of container.
c) Inclusion of a new primary packaging material.

- For any change of the container closure system that is in immediate contact with the active substance, CTGTP, process intermediates, and/or diluent used for reconstitution.
- No submission is required if there is a change of the supplier for the same type of primary packaging material with the same specification.
- Release and shelf-life specifications of the CTGTP remain unchanged.

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. Justification for the change in packaging material.
3. Comparative tabulated format of the specification of the approved and proposed primary packaging material.
4. Revised CTD Sections (where applicable).

5. Information on the construction materials and design features of the proposed container closure system.
6. Declaration of compliance to the appropriate international standards or pharmacopoeia.
7. Appropriate scientific data on the new packaging (e.g. container closure integrity test).
8. Relevant studies to demonstrate that no interaction between the content and the packaging material occurs, e.g. no migration of components of the proposed material into the content and no loss of components of the CTGTP into the pack (where applicable).
9. Validation report of the manufacturing and sterilisation process appropriate to the proposed change in the primary packaging material should be provided upon submission.
10. Stability data as per the relevant guidelines on the stability study of the active substance or CTGTP.
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.

A6 Change or addition of pack size/fill volume
• The type and material of the primary packaging material remain unchanged. • The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. • Release and shelf-life specifications of the CTGTP remain unchanged, except pack size/fill volume specification.
1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Revised CTD Sections P3 and/or P7 (where applicable). 4. Validation data of the manufacturing process, sterilisation and container closure system (where applicable). 5. Stability data as per the relevant guidelines on the stability study of the CTGTP. 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.

A7 Inclusion or replacement of solvent/diluent for CTGTP
• The proposed change does not result in any change in the dosage form, regimen, indication or route of administration of the CTGTP. • For deletion of the solvent/diluent, refer to MIV-2 B6.

1. Revised drafts of the package insert and labelling incorporating the proposed variation.
2. Proof that the proposed manufacturing site of the solvent/diluent is appropriately authorised, such as a valid Good Manufacturing Practice (GMP) certificate. (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA).
3. Batch numbering system (where applicable).
4. In case of a contract manufacturer, a letter of appointment for the proposed site to manufacture and/or package the solvent/diluent and stating the types of activity to be performed (where applicable).
5. A declaration from the product registrant that the release and shelf-life specifications of CTGTP are not affected.
6. Complete CTD P sections (3.2.P.1 to 3.2.P.8) for the solvent/diluent, including reconstitution stability data, and section S may be required (where applicable).

A8 Change of shelf-life of active substance or CTGTP

a) As a package for sale; and/or
b) After first opening; and/or
c) After dilution/reconstitution.

- For (a) & (b), the studies must show conformance to the approved shelf-life specification.
- For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted CTGTP.
- 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.

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. Justification for the change of shelf-life (where applicable).
3. Results of appropriate long term stability studies covering the duration of the proposed shelf-life of at least two production batches, unless otherwise justified, of the active substance or CTGTP in the authorised packaging material
   a) as a package for sale; and/or
   b) after first opening; and/or
   c) after the dilution/reconstitution

   in accordance with the relevant guidelines on the stability study of the active substance or CTGTP.

A9 Change of storage condition of active substance or CTGTP

a) As a package for sale; and/or
b) After first opening; and/or
c) After dilution/reconstitution.

- For (a) & (b), the studies must show conformance to the approved shelf-life

specification.

- For (c), the studies must show conformance to the approved shelf-life specification for the reconstituted CTGTP.
- 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.

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. Justification for the change of storage condition.
3. Results of appropriate long term stability studies covering the duration of the approved shelf-life (at the proposed storage condition) of at least two production batches, unless otherwise justified, of the active substance or CTGTP in the authorised packaging material
   a) as a package for sale; and/or
   b) after first opening; and/or
   c) after the dilution/reconstitution

   in accordance with the relevant guidelines on the stability study of the active substance or CTGTP.
4. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

A10 Addition or replacement of site responsible for quality control testing laboratory

- For addition or replacement of the approved laboratories for release and/or stability test of a biological/ immunological/ immunochemical test method, or a method using a biological reagent (does not include standard pharmacopoeia microbiological methods).

1. Proof that the proposed site is appropriately authorised, such as valid and relevant accreditation certificates or licences (e.g. GMP, CAP, ISO 13485, ISO/IEC 17025).
2. Approved release and shelf life specification.
3. Analytical procedures to be carried out at the proposed site.
4. Validation of analytical procedures performed at the proposed site.
5. Certification of analysis or batch analysis data (in a comparative tabular format) of at least two production batches, unless otherwise justified, tested at the approved and proposed sites.

A11 Replacement of master cell/seed bank

- For the generation of a new master cell/seed bank derived from the original or pre- approved master cell/seed bank or working cell/seed bank by sub-cloning.
- This does not relate to any change in the host cell line.

- HSA reserves the right to re-categorise the application to NDA, if deemed appropriate.

1. Source, history and passage number of the new master cell/seed with documentation of all raw material of human or animal origin used for the entire culture history.
2. Result of all identity testing, including cytogenetic characteristics that could be used to identify the cells.
3. Results of all available adventitious agent testing on the donor and the new master cells.
4. Validated cell stability under the freezing and storage conditions using cell recovery or viability data.
5. For viral master seed, document all manipulations of the viral seed bank. This includes the determination of the nucleic acid sequences of the recombinant constructs and sourcing of the biological starting material.
6. Sterility tests, mycoplasmas and adventitious viruses test data if appropriate.
7. Comparability of approved and proposed active substance with respect to physico- chemical characterisation, biological activity and impurity profile.
8. Batch analysis data (in a comparative tabular format) of at least three production batches, unless otherwise justified, of active substance derived from the approved and proposed cell/seed banks.
9. Stability data as per the relevant guidelines on the stability study of the active substance.
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 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.

A12 Change of test procedure

- For substantial change or replacement of a biological/ immunological/ immunochemical test method, or a method using a biological reagent (does not include standard pharmacopoeia microbiological methods).
- For any change not covered by MIV-2 B10.
- The specification of the active substance, critical starting materials, CTGTP, excipient and/or in-process test remain unchanged. If there are changes made to the specification, submit MIV-1 A3 or MIV-2 B5 at the same time.

1. Justification for the proposed change.
2. Description and validation of the proposed analytical procedure.
3. Comparative test results between the approved and proposed test procedure, or certificate of analysis or comparative batch analysis, of two production batches, unless otherwise justified, of the active substance, critical starting materials, CTGTP, excipient, or in process control test.

A13 Change of reference standard

- For change of in-house/non-compendial reference standard not covered by an

approved calibration/qualification protocol. If there is no change of the approved protocol, refer to MIV-2 B11. • To change from a compendial to non-compendial/in house reference standard.
1. The preparation protocol for the new reference standard. 2. The calibration/qualification protocol for the reference standard. 3. Amended relevant CTD Sections. 4. Summary report on the calibration/qualification of the new lot(s) of reference standard, e.g. characterisation, information regarding the manufacturing process used to establish the reference standard, certificate of analysis, expiry date, storage condition, stability and re-qualification, should be provided. 5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the active substance or CTGTP on at least two production batches, unless otherwise justified, using the approved and proposed reference standard.

A14 Change of content of product labelling
• Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label and/or inner label. • The change is not a MIV-2 and not within the scope of MAV-1.
1. Current approved product labelling. 2. Proposed product labelling, a clean and annotated version highlighting the changes. 3. Approved PI/SmPC/PIL containing the proposed changes from a comparable oversea regulatory agency or the country of origin (as the case may be). 4. Justifications for the changes proposed and supporting clinical documents where applicable.

A15 Change and/or addition of alternative cell/tissue procurement site
• Human cell/tissue procurement site including apheresis site and tissue bank.
1. Amended relevant CTD Sections. 2. Proof that the proposed site is appropriately authorised, such as valid and relevant accreditation certificates or licences (e.g. AABB, AATB, JACIE, FACT, GTP). 3. Validation scheme and/or report of the manufacturing process at the proposed site. 4. Comparability study, including comparative batch analysis data of at least two production batches, unless otherwise justified, of CTGTP manufactured from the approved and proposed sites. 5. Stability studies as per the relevant guidelines on the stability of the human cell/tissue. 6. A commitment letter to complete the on-going stability studies. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be provided to the Health Sciences Authority upon request.

PART B: CHECKLIST ON DOSSIER REQUIREMENTS FOR MIV-2 APPLICATION

B1 Change of product name
• There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the product name change. • No confusion with another product either when spoken or written. • 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.
1. Revised drafts of the package insert and labelling incorporating the proposed variation. 2. An official letter from the product owner or product registrant authorising the change of product name and committing to inform users of the relevant changes (where applicable). 3. A declaration from the product registrant that there is no other changes to the product/label except for the product name change.

B2 Change of product labelling a) Addition or amendment of warnings, precautions, contraindications drug interactions, overdose and/or adverse events that results in strengthening of safety information or restriction of use. b) Addition or amendment of information on “Instructions for Use” for products with special delivery system/device. c) Tightening of product’s target population. d) Deletion of indication. e) Administrative/editorial changes that have no impact on safety, efficacy and quality. f) Rearrangement/re-formatting of text/images without any change in information. g) Addition/change of labelling intended for foreign markets (i.e. shared pack), e.g. other countries’ registration/ licence no./ in package insert. h) Addition/update/deletion of barcode / QR code for logistic purposes.
• Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label and/ or inner label. • The change is not a MIV-1 and does not contain promotional information.
1. Current approved product labelling. 2. Proposed product labelling, and a clean and annotated version highlighting the changes. 3. Approved PI/SmPC/PIL containing the proposed changes from a comparable oversea regulatory agency or the country of origin (as the case may be). 4. Relevant document/reference to support the changes (where applicable).

B3 Addition or replacement of company or party responsible for batch release
• Only applicable for the change of batch releaser. • The manufacturer of the CTGTP remains unchanged.
1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorised to be responsible for batch release, such as a valid GMP certificate, where applicable. 3. An official letter from the product owner authorising the company/manufacturer to be responsible for batch release.

B4 Minor change in manufacturing process
• For any minor change of the approved manufacturing process at any stage during manufacture of the active substance, critical starting materials, CTGTP and/or process intermediates. • Relates to a non-critical change in the process that does not require an assessment of comparability, such as change in harvesting and/or pooling procedures without a change in the method of manufacturing, recovery, storage conditions or production scale; duplication of a fermentation train; addition of identical or similar/comparable bioreactors. • No adverse change in the qualitative and/or quantitative impurity profile or in physico-chemical characteristics and other relevant properties. • Proposed manufacturing process of the active substance, critical starting materials and/or CTGTP does not use any new materials of human/animal origin for which assessment is required for viral safety. • Specification of the active substance, critical starting materials or CTGTP remains unchanged. If there is a change in the specification, MIV-1 A3 or MIV-2 B5 is also applicable.
1. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 2. Description of the new manufacturing process and justifications for the change. 3. Validation scheme and/or report of the proposed manufacturing process should be provided upon submission. 4. A copy of the approved release and shelf-life specifications, and a letter of declaration from the product registrant stating that the specifications of the active substance, critical starting materials or CTGTP have not changed. 5. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the active substance, critical starting materials or CTGTP of at least two production batches manufactured according to the approved and proposed processes, where appropriate. 6. A commitment letter to complete the relevant on-going stability studies of the active substance, critical starting materials or CTGTP in accordance with the relevant guideline. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be

provided to the Health Sciences Authority upon request.

B5 Change of specification of active substance, critical starting materials, CTGTP, process intermediates and/or in-process control tests

a) Specification limits are tightened.

b) Addition of new test parameter and limits.

c) Deletion of non-significant parameter (e.g., obsolete parameter).

- Test procedures remain unchanged. If there are changes to the test procedures, MIV-1 A12 or MIV-2 B10 is also applicable.
- For widening of specification limits and deletion of test parameter and limits, refer to MIV-1 A3.
- 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.

a) Specification limits are tightened

1. Justification for the change.
2. Comparative tabulated format of the approved and proposed specification with changes highlighted.
3. Test results of two production batches, unless otherwise justified, of the active substance, critical starting materials, CTGTP, process intermediates or in-process controls, for all tests in the revised specification.

b) Addition of new test parameter and limits.

In addition to the above documents,

4. Description of any new analytical method and summary of the validation data (where applicable).
5. Justification of the new specification parameter and the limits.
6. For stability indicating parameter, stability data as per the relevant guidelines on the stability study of the active substance, critical starting materials or CTGTP. 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.

c) Deletion of non-significant parameter

In addition to paragraphs (a) and (b),

7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.

B6 Deletion of solvent/ diluent for CTGTP

- The proposed change does not result in any change in the dosage form, regimen, indication or method of administration of the CTGTP.

1. Revised drafts of the package insert and labelling incorporating the proposed

variation (where applicable).
2. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent.
3. Amended relevant CTD Section P (where applicable).

B7 Change of specification of non-compendial excipient
• Release and shelf life specifications of CTGTP remain unchanged. • The change should not be the result of unexpected events arising during manufacture or because of stability concerns. • Applicable to non compendial excipients. For compendial excipients, refer to MIV-2 B19.
1. A declaration from the product registrant that the change does not impact the quality and safety of the CTGTP. 2. Description of new method and summary of analytical validation (applicable for addition or replacement of new parameter). 3. Comparative tabulated format of the approved and proposed specification of the excipient with changes highlighted. 4. Certificate of analysis or batch analysis data of the excipient for all tests in the proposed specification.

B8 Addition or replacement of manufacturer for secondary packaging
1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorised (accredited by the authority) for the packaging activity concerned, such as a valid GMP certificate (Note: GMP Conformity Assessment is required if the proposed site is not currently registered with HSA). 3. Official letter from the product owner authorising the new manufacturer or packager to perform secondary packaging.

B9 Replacement or change of working cell/seed bank
• Establishing a new working cell/seed bank derived from a previously approved master cell/seed bank according to approved protocols.
1. Comparative summary characterisation and testing of the approved and proposed working cell/seed banks. 2. Certificate of analysis or batch analysis data (in a comparative tabulated format) of at least three batches, unless otherwise justified, of active substance derived from the approved and proposed cell/seed banks. 3. A declaration that the release and shelf life specifications of the CTGTP have not been changed. 4. A commitment letter to complete the on-going stability studies to support the approved shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required but the data shall be

provided to the Health Sciences Authority upon request.

B10 Minor change of test procedure
• Applicable to change of test procedure to comply with the updated general monograph in official pharmacopoeia, such as Ph. Eur., USP, BP and JP. This includes standard compendial microbiological methods. • For change of test procedure of the active substance, critical starting materials, CTGTP, excipient, and/or in-process control where the test method is a biological/ immunological/ immunochemical method, or a method using a biological reagent, refer to MIV-1 A12. • The specification of the active substance, critical starting materials, CTGTP, excipient and/or in-process test remain unchanged. If there are changes made to the specification, submit MIV-1 A3 or MIV-2 B5 at the same time.
1. Justification for the proposed change. 2. Description of the proposed analytical methodology. 3. Appropriate verification/validation data. 4. Comparative test results between the approved and proposed test procedure, or certificate of analysis or comparative batch analysis of two production batches, unless otherwise justified, of the active substance, critical starting materials, CTGTP, excipient, or in-process control.

B11 Minor change of reference standard
• For change of in-house/non-compendial reference standard prepared and qualified by an approved preparation and calibration/qualification protocols. If there is a change of the approved protocol, refer to MIV-1 A13. • For change of compendial reference standard or change from a non-compendial/in house to a compendial reference standard.
1. Amended relevant CTD Sections. 2. A declaration that there is no change to the preparation and calibration/qualification protocols, if applicable. 3. Certificate of analysis of the proposed reference standard. 4. Certificate of analysis or batch analysis data (in a comparative tabulated format) of the active substance or CTGTP on at least two production batches, unless otherwise justified, using the approved and proposed reference standard.

B12 Change in supplier of animal-derived material
• For animal-derived material of mammalian or avian origin used as an excipient or active substance in the CTGTP, or as an adjuvant. • There is no change in the animal species from which the animal-derived material is obtained from. • Animal derived material from other species (e.g. insects and fish) is exempted from this variation.
1. Information on all countries which the animal was sourced from*.

*not required for animal derived products from milk and certain milk derivatives such as lactose.

2. Declaration on the nature of the animal tissue and/or fluid used.
3. Certificate of analysis for the animal-derived material used, stating the name and address of the supplier.
4. Relevant information to demonstrate that the manufacturing process is capable of inactivating adventitious agents, where applicable.
5. For materials derived from TSE-relevant animals (i.e. cattle, sheep, goat, deer, elk, non-human primates):
   a) A valid CEP for the TSE risk evaluation;
   b) If CEP is not available,
      i. Description of the tissue/organ/fluid-collection procedures and measures in place to avoid cross-contamination.
      ii. Details of the risk factors associated with the route of administration and maximum therapeutic dosage of the CTGTP.
      iii. Relevant information demonstrating that the manufacturing process is capable of inactivating TSE agents.

B13 Change in packaging material not in contact with CTGTP

- The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the CTGTP.

1. Amendment of the relevant section(s) of the dossier (presented in the CTD format), including revised product labelling as appropriate.

B14 Change of product owner or change in name and/or address (e.g. postal code, street name) of product owner

- The product registrant remains unchanged.
- The manufacturing site remains unchanged.
- There are no other variation applications pending approval. All changes should be submitted and approved before the registration transfer takes place.

a) For change of product owner:

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. A declaration on the transfer of ownership between the old product owner and new owner.
3. An official letter from the new product owner declaring the change and authorising the local registrant to be responsible for the product registration.
4. If the new product owner is not the manufacturer of the CTGTP, an official letter by the new product owner authorising the manufacturer to manufacture the CTGTP on its behalf.

b) For change of name and/or address of product owner:

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).

2. An official letter from the product owner declaring the change and authorising the local registrant to be responsible for the product registration.

B15 Change in ownership of manufacturer

- The manufacturing site remains unchanged.
- No other changes except for the change in ownership of manufacturer.

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. A letter of justification on the transfer of ownership, such as a valid GMP certificate.
3. An official letter stating the transfer of ownership from old manufacturer to the new manufacturer (where applicable).
4. In case of a contract manufacturer, an official letter from the product owner declaring the change and authorising the new manufacturer to manufacture the CTGTP on its behalf.

B16 Change of name or address (e.g. postal code, street name) of manufacturer of active substance, critical starting materials or CTGTP

- The manufacturing site remains unchanged.
- No other changes except for the change of the name and/or address of a manufacturer of CTGTP.
- Not applicable to the case involving a change in ownership of the manufacturer. For a change in ownership of manufacturer, refer MIV-2 B15.

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. A valid GMP certificate or an official document from a relevant authority confirming the new name and/or address.
3. An official letter from the product owner authorising the manufacturer with the new name/address to manufacture the active substance, critical starting materials or CTGTP.

B17 Change of name or address (e.g. postal code, street name) of company or manufacturer responsible for batch release

- The manufacturer of the CTGTP remains unchanged.
- The batch release site remains unchanged.
- Not applicable to the case involving a change in ownership of the manufacturer. For a change in ownership of manufacturer, refer MIV-2 B15.

1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. A valid GMP certificate or an official document from a relevant authority confirming the new name or address (where applicable).
3. An official letter from the product owner authorising the company/manufacturer with the new name/address that is responsible for batch release.

4. A declaration from the product registrant that the change does not involve a change of batch release site.

B18 Withdrawal/deletion of alternative manufacturer(s) for active substance, critical starting materials, CTGTP, packager or batch releaser
• An alternative manufacturer is registered.
1. Reason for withdrawal/deletion.

B19 Change of specification of excipient to comply with pharmacopoeia
• Applicable to compendial specifications only. • Change is made to comply with an update of the relevant monograph of the compendium or from one recognised pharmacopoeia to another. • Pharmacopoeia recognised by HSA: United States Pharmacopeia, European Pharmacopoeia, British Pharmacopoeia and Japanese Pharmacopoeia.
1. Specification of the excipient. 2. Tabulation of the approved and proposed specification of the excipient(s) with changes highlighted. 3. Certificate of analysis or batch analysis of the excipient(s) for all tests in the new specification of at least two batches, unless otherwise justified. 4. A declaration that the change has no impact on the manufacturing process and quality of the CTGTP.

B20 Deletion of pack size for CTGTP
• The remaining pack sizes are adequate to accommodate the dosing regimen as per the current approved product labelling. • For addition of pack size for CTGTP, refer to MIV-1 A6.
1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Reason for deletion.

B21 Change of batch numbering system
• The manufacturing site remains unchanged.
• Description of the revised batch numbering system. • An official letter stating the commencement date of the change.

B22 Change of name of quality control testing laboratory
• No other changes except for the change of the name and/or address of the approved laboratory(ies) for stability tests or any quality control tests.
1. Updated information of the testing laboratory.

2. Proof that the change of name on relevant accreditation certificates or licences (e.g. GMP, CAP, ISO 13485, ISO/IEC 17025).
3. An official letter from the product owner authorising the testing laboratory with the new name/address.

B23 Addition or replacement of site responsible for quality control testing laboratory
• For addition or replacement of the approved laboratories for release and/or stability test that is of compendial method.
1. Proof that the proposed site is appropriately authorised, such as valid and relevant accreditation certificates or licences (e.g. GMP, CAP, ISO 13485, ISO/IEC 17025). 2. Approved release and shelf life specification. 3. Analytical procedures to be carried out at the proposed site. 4. Certificate of analysis or batch analysis data (in a comparative tabular format) of at least two production batches, unless otherwise justified, tested at the approved and proposed site.

REVISION HISTORY
Guidance Version (Publish Date)
ATPB-GN-010-000 (March 2021)