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

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| 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).
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| * 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. For the change of manufacturing site for active substance or critical starting materials: 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. For the change of manufacturing site for CTGTP: 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.
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| 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.
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| 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. For the change of manufacturing process for active substance or critical starting materials: 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. For the change of manufacturing process for CTGTP: 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.
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| A3 Change of specification of active substance, critical starting materials CTGTP, process intermediates and/or in-process control tests1. Widening of specification limits.
2. Deletion of specification parameters which may have a significant effect on the overall quality of the CTGP.
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| * 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.
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| 1. **Widening of specification limits**
2. Justification for change substantiated with scientific data.
3. Revised specification of the active substance, critical starting materials, CTGTP, process intermediates or in-process control test.
4. 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.
5. 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.
6. 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.
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.
8. **Deletion of specification parameters**

All the above documents except 5 & 6. |

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| 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.
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| 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):
9. A valid CEP for the TSE risk evaluation;
10. If CEP is not available,
11. Description of the tissue/organ/fluid-collection procedures and measures in place to avoid cross-contamination.
12. Details of the risk factors associated with the route of administration and maximum therapeutic dosage of the CTGTP.
13. Relevant information demonstrating that the manufacturing process is capable of inactivating TSE agents.
14. Active substance or CTGTP release and shelf-life specifications.
15. 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.
16. Stability data as per relevant guidelines on the stability study of the active substance or CTGTP.
17. 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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| A5 Change in primary packaging material for active substance or CTGTP1. Change in qualitative and quantitative composition.
2. Change in type of container.
3. Inclusion of a new primary packaging material.
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| * 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. |

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| 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.
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| 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).
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| A8 Change of shelf-life of active substance or CTGTP 1. As a package for sale; and/or
2. After first opening; and/or
3. After dilution/reconstitution.
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| * 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.
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| * 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
1. as a package for sale; and/or
2. after first opening; and/or
3. after the dilution/reconstitution

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

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| A9 Change of storage condition of active substance or CTGTP 1. As a package for sale; and/or
2. After first opening; and/or
3. After dilution/reconstitution.
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| * 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 material1. as a package for sale; and/or
2. after first opening; and/or
3. after the dilution/reconstitution

in accordance with the relevant guidelines on the stability study of the active substance or CTGTP.* 1. 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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| 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.
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| 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.
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| 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.
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| 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.
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| 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.
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| A15 Change and/or addition of alternative cell/tissue procurement site |
| * Human cell/tissue procurement site including apheresis site and tissue bank.
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| 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.
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