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

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| 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.
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| 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.
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| B2 Change of product labelling1. 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.
2. Addition or amendment of information on “Instructions for Use” for products with special delivery system/device.
3. Tightening of product’s target population.
4. Deletion of indication.
5. Administrative/editorial changes that have no impact on safety, efficacy and quality.
6. Rearrangement/re-formatting of text/images without any change in information.
7. Addition/change of labelling intended for foreign markets (i.e. shared pack), e.g. other countries’ registration/ licence no./ in package insert.
8. Addition/update/deletion of barcode / QR code for logistic purposes.
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| * 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.
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| 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).
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| 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.
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| 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.
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| 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.
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| 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.
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| B5 Change of specification of active substance, critical starting materials, CTGTP, process intermediates and/or in-process control tests1. Specification limits are tightened.
2. Addition of new test parameter and limits.
3. Deletion of non-significant parameter (e.g., obsolete parameter).
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| * 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.
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| 1. **Specification limits are tightened**
2. Justification for the change.
3. Comparative tabulated format of the approved and proposed specification 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 controls, for all tests in the revised specification.
5. **Addition of new test parameter and limits.**

In addition to the above documents,1. Description of any new analytical method and summary of the validation data (where applicable).
2. Justification of the new specification parameter and the limits.
3. 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.
4. **Deletion of non-significant parameter**

In addition to paragraphs (a) and (b),1. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
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| 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.
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| 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).
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| 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.
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| 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.
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| 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.
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| 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.
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| 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.
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| 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.
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| 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.
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| 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.
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| 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.
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| 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.1. Declaration on the nature of the animal tissue and/or fluid used.
2. Certificate of analysis for the animal-derived material used, stating the name and address of the supplier.
3. Relevant information to demonstrate that the manufacturing process is capable of inactivating adventitious agents, where applicable.
4. For materials derived from TSE-relevant animals (i.e. cattle, sheep, goat, deer, elk, non-human primates):
5. A valid CEP for the TSE risk evaluation;
6. If CEP is not available,
7. Description of the tissue/organ/fluid-collection procedures and measures in place to avoid cross-contamination.
8. Details of the risk factors associated with the route of administration and maximum therapeutic dosage of the CTGTP.
9. Relevant information demonstrating that the manufacturing process is capable of inactivating TSE agents.
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| 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.
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| 1. Amendment of the relevant section(s) of the dossier (presented in the CTD format), including revised product labelling as appropriate.
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| 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.
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| 1. **For change of product owner:**
2. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
3. A declaration on the transfer of ownership between the old product owner and new owner.
4. An official letter from the new product owner declaring the change and authorising the local registrant to be responsible for the product registration.
5. 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.
6. **For change of name and/or address of product owner:**
7. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
8. An official letter from the product owner declaring the change and authorising the local registrant to be responsible for the product registration.
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| B15 Change in ownership of manufacturer |
| * The manufacturing site remains unchanged.
* No other changes except for the change in ownership of manufacturer.
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| 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.
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| 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.
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| 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.
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| B18 Withdrawal/deletion of alternative manufacturer(s) for active substance, critical starting materials, CTGTP, packager or batch releaser |
| * An alternative manufacturer is registered.
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| 1. Reason for withdrawal/deletion.
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| 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.
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| 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.
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| 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.
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| 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable).
2. Reason for deletion.
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| B21 Change of batch numbering system |
| * The manufacturing site remains unchanged.
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| * Description of the revised batch numbering system.
* An official letter stating the commencement date of the change.
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| 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.
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| 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.
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| 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.
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| 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.
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