# APPENDIX 14 GUIDELINE ON MINOR VARIATION APPLICATIONS FOR BIOLOGICAL THERAPEUTIC PRODUCTS – DRAFT FOR CONSULTATION

# 1. Introduction

This guidance describes the requirements for the submission of Minor Variation Applications (MIVs) for registered biological therapeutic products in Singapore. It should be read together with the applicable provisions of the *Guidance on Therapeutic Product Registration in Singapore* and the governing legislation.

The checklist in the Annex sets out the applicable reporting categories, conditions and supporting data requirements for post-approval changes. Product registrants are responsible for assessing each proposed change in its entirety, including any consequential changes, and selecting the appropriate checklist item(s) and reporting category.

The reporting categories used in this guidance are:

- MIV-1
- MIV-2 Notification
- MIV-2 Do-and-Tell (MIV-2 D&T)

Changes that do not require notification to HSA are identified in the specific relevant sections of the checklist.

Where a proposed change is not covered by the checklist, or where there is uncertainty about the appropriate reporting category or supporting data requirements, product registrants should consult HSA before submission.

MIV-1 applications may be submitted under the abridged or verification evaluation route, as applicable. For further information, refer to the *Guidance on Therapeutic Product Registration in Singapore*.

For the purposes of this guidance, unless otherwise specified, a **change** refers to the addition, replacement or deletion of the relevant item.

The conditions and supporting data specified in the checklist represent the minimum requirements generally applicable to the corresponding variation. Product registrants are responsible for ensuring that all necessary studies and validations have been conducted to demonstrate that the proposed change does not adversely affect the quality, safety or efficacy of the therapeutic product. HSA may request additional information as necessary.

Where a supporting document specified in the applicable checklist is not submitted, a justification for its omission must be provided.

HSA reserves the right to request additional information or to require a different regulatory approach where warranted by the nature or impact of the proposed change.

# 2. Structure and Use of the Checklist

The checklist is organised according to the nature of the post-approval change:

- AD - Administrative Changes
- QS - Quality Drug Substance Changes

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- QP - Quality Drug Product Changes
- QR - Quality Regulatory Tools
- LB - Product Labelling Changes

Each checklist may comprise one or more checklist groups, with individual changes further classified into subcategories, where applicable. Each subcategory specifies the applicable conditions, reporting category and supporting data requirements.

For example, QS.02.A represents a checklist group, while QS.02.A.i, QS.02.A.ii and QS.02.A.iii represent individual subcategories within that group.

The conditions specified in the checklist are divided into:
- **Common Conditions** - conditions applicable to all relevant subcategories within the checklist or checklist group; and
- **Category-specific Conditions** - conditions applicable only to the individual subcategory concerned.

Product registrants should select the subcategory that best describes the proposed change. To qualify for the stated reporting category, all applicable Common Conditions and Category-specific Conditions must be fulfilled. If one or more conditions for a lower reporting category are not fulfilled, the change should be submitted under the applicable higher reporting category.

# 3. Application Submission Requirements

All proposed changes included in an MIV application must be clearly disclosed and identified in the application.

The applicable MIV checklist item(s) should be indicated for each proposed change. Where an application contains a primary change and one or more consequential changes, the main change should be identified as the primary change and the consequential change(s) as secondary change(s), as applicable.

Any variation embedded within the submitted data that has not been clearly disclosed as a proposed change, or any follow-on changes not specifically requested by HSA will not be considered part of the application.

The following should be submitted with the MIV application, as applicable:
- Cover letter
- Applicable MIV checklist(s)
- Table of Summary of Changes
- Supporting data specified in the checklist

The Table of Summary of Changes should provide a clear and concise description of each change and include, at minimum:
- Relevant dossier section(s) affected by the change
- Approved information
- Proposed information, with all changes from the approved information clearly highlighted
- Reason for the change
- Registration status of the proposed change in other countries or regulatory agencies, including the date of approval, where applicable, particularly for the country of origin and HSA's reference agencies

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| Dossier Section | Approved | Proposed | Reason for Change | Regulatory Status / Approval Date in Other Countries or Agencies |
|---|---|---|---|---|
| | | | | |
| | | | | |

# 4. Unexpected Events and Product Defect

An MIV application should not be submitted as a means of addressing an unresolved unexpected event that may result in a product defect.

Where an unexpected event, manufacturing deviation or quality issue that may affect the quality, safety or efficacy of the therapeutic product is identified, the product registrant should first assess and address the issue, including implementation of appropriate corrective and preventive actions (CAPAs), where applicable.

Relevant product defect reporting requirements should be followed in accordance with the *Product Defect Reporting and Recall Procedures* published on the HSA website.

An MIV application should be submitted, where required, after the relevant concerns have been appropriately addressed and the proposed change has been established as the intended post-approval change.

# 5. Additional Requirements and Clarifications

## 5.1 Recognised pharmacopoeial monograph

A recognised pharmacopoeial monograph refers to a monograph of the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), United States Pharmacopeia (USP), or Japanese Pharmacopoeia (JP).

## 5.2 Biological comparability

Where a proposed change to a manufacturing site, process, scale, cell or seed bank, raw material or other quality element may affect critical quality attributes, the supporting package should adequately demonstrate comparability of the pre-change and post-change material, as applicable.

## 5.3 Cell and seed banks

Any proposed change to the host cell line should be discussed with HSA prior to submission. Such a change may not be eligible for submission as an MIV and may require submission as a new application.

## 5.4 Solvent or diluent supplied with the drug product

A solvent or diluent supplied with the drug product is considered part of the drug product. Changes to its manufacturing facility, manufacturing process, specification, container closure system, shelf life or other quality attributes should be submitted under the applicable QP checklist(s), unless otherwise specified.

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## 5.5 Adjuvant

An adjuvant may be formulated with the drug product or supplied separately with the drug product.

Where an adjuvant is supplied as separate component with the drug product, it is considered part of the drug product. Changes to its manufacturing facility, manufacturing process, specification, container closure system, shelf life or other quality attributes should be submitted under the applicable QP checklist(s), unless otherwise specified.

Any proposed change to the type or structure of a chemical adjuvant, or the type or composition of a biological adjuvant, should be discussed with HSA prior to submission. Such changes may not be eligible for submission as an MIV and may require the filing of a new drug application.

## 5.6 Consequential product labelling changes

Where a change submitted under a QS, QP, QR or AD checklist results in a consequential change to the approved product labelling or product information, LB.02 - Changes to product labelling consequential to QS/QP/QR/AD changes should also be selected, unless otherwise specified.

LB.02 should be submitted together with the corresponding QS, QP, QR or AD change and should not be submitted as a standalone variation. Any additional labelling change that is not consequential to the corresponding QS/QP/QR/AD change should be assessed separately under LB.01.

## 5.7 Medical devices supplied with the drug product

For changes to a medical device supplied with the drug product:

- Refer to QP.05.A-C, as applicable, for an integral Class A/B medical device/device part forming part of the container closure system.
- Refer to QP.05.E for an integral Class C/D medical device/device part.
- Refer to QP.05.F for a co-packaged medical device.

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# Administrative Changes - AD

# AD.01. Change of drug product name

| **AD.01. Change of drug product name** | | | | | |
|---|---|---|---|---|---|
| **Common Conditions (Must be met for all subcategories)**<br>• There is no other change to the drug product, except for product name.<br>• The proposed name should not cause confusion with another product when spoken or written.<br>• The proposed name should not (i) suggest greater safety or efficacy than that supported by clinical data, (ii) imply superiority over another product; or (iii) imply the presence of any substance(s) not present in the product. | | | | | |
| **Code** | **Description of Change** | **Category-specific Conditions** | **Applicant Declaration (I confirm all applicable conditions are met)** | **Reporting Category** | **Supporting Data** |
| **AD.01** | Change of drug product name | None | ☐ Conditions met | MIV-2 Notification | 1 - 2 |
| **Supporting Data** | | | | | |
| **No.** | **Supporting data requirement** | | **Provided?** | **Remarks (e.g., include justification for not providing the required document)** | |
| 1. | An official letter from the product owner or product registrant authorising the change of the drug product name and committing to inform users of the relevant changes (where applicable). | | ☐ Yes<br>☐ N.A. | | |
| 2. | A declaration from the product registrant that there are no other changes to the product/label except for the drug product name change. | | ☐ Yes<br>☐ N.A. | | |

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# AD.02. Change of product owner / product owner name or address

**AD.02. Change of product owner / product owner name or address**

**Common Conditions (Must be met for all subcategories)**

- The product registrant and manufacturing site remain unchanged.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **AD.02.A** | Change of product owner | The legal transfer of product ownership is documented and the new product owner authorises the local registrant and manufacturer, as applicable. | ☐ Conditions met | MIV-2 D&T | 1 |
| **AD.02.B** | Change in the name and/or address of the existing product owner | There is no change in the legal product owner. | ☐ Conditions met | MIV-2 D&T | 2 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | For change of product owner,<br>a. A declaration on the transfer of ownership between the old product owner and new owner from the new product owner.<br>b. An official letter from the new product owner declaring the change and authorising the local registrant to be responsible for the product registration.<br>c. If the new product owner is not the manufacturer of the drug product, an official letter by the new product owner authorising the manufacturer to manufacture the drug product on its behalf. | ☐ Yes<br>☐ N.A. | |
| 2. | For change of name and/or address of product owner, an official letter from the product owner declaring the change and authorising the local registrant to be responsible for the product registration. | ☐ Yes<br>☐ N.A. | |

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# AD.03. Change of name and/or address of manufacturing facility

**AD.03. Change of name and/or address of manufacturing facility**

**Common Conditions (Must be met for all subcategories)**

- The manufacturing site remains unchanged, with no addition of new buildings or expansion of approved manufacturing areas, unless the new building or area is used solely for non-manufacturing activities (e.g. storage warehouse).

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **AD.03.A** | Change of name and/or address of an approved manufacturing facility of the drug substance (including QC testing). | None | ☐ Conditions met | MIV-2 D&T | 1 - 2 |
| **AD.03.B** | Change of name and/or address of an approved manufacturing facility of the drug product (including QC testing and batch release). | None | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Revised CTD Section S.2.1 or P.3.1, reflecting the new name and/or address. | ☐ Yes<br>☐ N.A. | |
| 2. | A valid GMP certificate, a CPP which covers the GMP certification or an official document from a relevant authority confirming the new name and/or address. | ☐ Yes<br>☐ N.A. | |
| 3. | An official letter from product owner authorising the manufacturer with the new name/address to manufacture the drug product. | ☐ Yes<br>☐ N.A. | |

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# AD.04. Change of batch numbering system

**AD.04. Change of batch numbering system**

**Common Conditions (Must be met for all subcategories)**

- The manufacturing site remains unchanged.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **AD.04.A** | Change of batch numbering system for the drug substance (where mentioned in the dossier) | None | ☐ Conditions met | MIV-2 D&T | 1 - 3 |
| **AD.04.B** | Change of batch numbering system for the drug product | None | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s), as applicable. | ☐ Yes<br>☐ N.A. | |
| 2. | Description of the new batch numbering system. | ☐ Yes<br>☐ N.A. | |
| 3. | Official letter stating the commencement date of the new batch numbering system. | ☐ Yes<br>☐ N.A. | |

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# AD.05. Update of Anatomical Therapeutic Chemical (ATC) code

**AD.05. Update of Anatomical Therapeutic Chemical (ATC) code**

**Common Conditions (Must be met for all subcategories)**

- The revised ATC code is assigned by the WHO Collaborating Centre for Drug Statistics Methodology and is consistent with the approved therapeutic use in Singapore.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **AD.05** | Update of ATC code | None | ☐ Conditions met | MIV-2 D&T | 1 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Evidence of the revised ATC code assigned by the WHO Collaborating Centre for Drug Statistics Methodology. | ☐ Yes<br>☐ N.A. | |

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# Quality Drug Substance Changes - QS

# QS.01. Change of manufacturing facility of drug substance / drug substance intermediate

**QS.01. Change of manufacturing facility of drug substance / drug substance intermediate**
**Note:**

- For changes to the manufacturing facility of cell bank / seed bank, refer to QS.08 checklist.

**Notification to HSA is not required for:**

- Change of quality control (QC) testing location within the same approved manufacturing site, where the analytical procedure is unchanged and successful verification/transfer has been completed in accordance with GMP requirements.

**Common Conditions (Must be met for all subcategories)**

- Drug substance specification, route/process, batch size, container closure, retest period/shelf life and storage condition should remain unchanged unless the corresponding QS. checklist(s) is also selected.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.01.A** Addition or replacement of a manufacturing facility of the drug substance or drug substance intermediate (including sterilisation site) | | | | | |
| **i.** | Addition or replacement of a manufacturing facility of the drug substance or drug substance intermediate (including sterilisation site) | None (This category also applies where one or more of the conditions specified for categories A.ii to A.iii are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 7, 10 |
| **ii.** | Addition or replacement of a manufacturing site of the chemical drug substance intermediate | The change is limited to the manufacturing location of chemical drug substance intermediate, with no change to the approved manufacturing process, | ☐ Conditions met | MIV-2 Notification | 1 - 4, 8, 10 |

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| | | including the synthetic route, starting materials, intermediates, or reagents. | | | |
| **iii.** | Addition or replacement of facility (building/suite) within an existing approved manufacturing site of the drug substance or drug substance intermediate | The proposed facility (building/suite) is located within an existing approved manufacturing site, operates under the same pharmaceutical quality system (PQS), and any changes to the manufacturing process and/or controls are limited to those necessary to duplicate the approved manufacturing operation, such that product quality is unlikely to be adversely affected and does not require an extensive comparability assessment. | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **QS.01.B** Addition or replacement of a QC testing site responsible for release and stability testing of the drug substance | | | | | |
| **i.** | Addition or replacement of a QC testing site of the drug substance for biological / immunological / immunochemical analytical procedure | There is no change to the specification and analytical procedures. Analytical procedure transfer/verification at the proposed site has been successfully completed. | ☐ Conditions met | MIV-2 Notification | 1 - 3, 9 |
| **ii.** | Addition or replacement of QC testing site of the drug substance for non-biological analytical procedure | The analytical procedure is not a biological/immunological/immunochemical procedure.<br><br>There is no change to the specification and analytical procedures. Analytical procedure transfer/verification at the proposed site has been successfully completed. | ☐ Conditions met | MIV-2 D&T | 1 - 3, 9 |
| **QS.01.C** | Deletion of an approved manufacturer of the drug | At least one approved manufacturer remains for the relevant manufacturing activity, and the deletion is not due to | ☐ Conditions met | MIV-2 D&T | 2 - 3 |

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| | substance or drug substance intermediate | critical deficiencies in manufacturing or quality systems. | | | |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant CTD section(s) including stability studies as per relevant guidelines. | ☐ Yes<br>☐ N.A. | |
| 2. | Revised CTD Section S.2.1 from drug product manufacturer, reflecting the name, address and manufacturing responsibilities of approved and proposed drug substance manufacturing facilities. | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | Valid evidence of GMP compliance for the proposed manufacturing facility in accordance with the *Guidance on Therapeutic Product Registration in Singapore*. | ☐ Yes<br>☐ N.A. | |
| 5. | Comparability study of the approved and proposed drug substance or any intermediate of the drug substance with respect to physico-chemical characterisation, biological activity and impurity profile, including comparative batch analysis data of at least two production batches of the drug substance manufactured from the approved and proposed facilities or a justification for not submitting such a study. | ☐ Yes<br>☐ N.A. | |
| 6. | Process validation protocol and validation report for the manufacturing, sterilisation, and container closure system integrity, as applicable. | ☐ Yes<br>☐ N.A. | |
| 7. | A commitment letter to conduct relevant stability studies of the drug product in accordance with relevant guidelines 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. | ☐ Yes<br>☐ N.A. | |
| 8. | Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the drug substance from the current and proposed manufacturing facilities. | ☐ Yes<br>☐ N.A. | |

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| 9. | Declaration that specifications and analytical procedures remain unchanged, analytical procedure transfer/verification has been successfully completed, and comparative analysis from the current and proposed testing sites are comparable. | ☐ Yes<br>☐ N.A. | |
| 10. | A letter of appointment for the proposed site to manufacture the drug substance or drug product and stating the types of activity to be performed (where applicable). | ☐ Yes<br>☐ N.A. | |

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# QS.02. Change of manufacturing process / batch size of drug substance

**QS.02. Change of manufacturing process / batch size of drug substance**
**Note:**

- For introduction or extension of a design space or method operable design region (MODR), refer to QR.02.

**Notification to HSA is not required for:**

- For decommissioning of a duplicate manufacturing line where the approved manufacturing process and all registered quality attributes remain unchanged.

**Common Conditions (Must be met for all subcategories)**

- The manufacturing site and specifications remain unchanged unless the corresponding checklist(s) are also selected. The change should not be used to address unresolved unexpected events, product defects or stability concerns.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.02.A** Change (including addition or replacement) of manufacturing process and/or batch size of the drug substance or drug substance intermediate | | | | | |
| **i.** | Major change of manufacturing process and/or batch size of the drug substance or drug substance intermediate | None (This category also applies where one or more of the conditions specified for category A.ii are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 6 |
| **ii.** | Moderate change to the manufacturing process and/or batch size that does not require a comparability assessment | The change is limited to a non-critical process change that does not require a comparability assessment, and does not adversely affect the impurity profile, physicochemical characteristics, biological activity or control strategy, e.g. changes to harvesting or pooling with the same manufacturing method, recovery and storage conditions, duplication of line or addition of identical bioreactors. | ☐ Conditions met | MIV-2 Notification | 1 - 5 |

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| | | The proposed manufacturing process does not introduce any new materials of human or animal origin for which an assessment of viral safety is required. | | | |
| **iii.** | Minor change of manufacturing process and/or batch size of chemical drug substance intermediate | The synthetic route remains unchanged with no introduction of new reagents, catalysts or solvents, and no adverse qualitative or quantitative change in the impurity profile requiring additional qualification.<br><br>Changes to the synthetic route should be submitted under A.i.<br><br>Introduction of new reagents, catalysts or solvents with no change to the synthetic route should be submitted under A.ii. | ☐ Conditions met | MIV-2 D&T | 1 - 3, 7 |
| **QS.02.B** | Deletion of an approved alternative manufacturing process of the drug substance | At least one approved manufacturing process remains for the relevant manufacturing activity, and the deletion is not due to critical deficiencies in manufacturing or quality systems. | ☐ Conditions met | MIV-2 D&T | 2 - 3 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed information presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s) including stability studies as per relevant guidelines. | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |

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|---|---|---|---|
| 4. | Comparability study of the approved and proposed drug substance or any intermediate of the drug substance with respect to physico-chemical characterisation, biological activity and impurity profile, including comparative batch analysis data of at least two production batches of the drug substance from the approved and proposed manufacturing processes/batch size or a justification for not submitting such a study. | ☐ Yes<br>☐ N.A. | |
| 5. | Process validation protocol and validation report for the manufacturing, sterilisation, and container closure system integrity, as applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | A commitment letter to complete the ongoing stability studies to support the approved shelf life of the drug substance. 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. | ☐ Yes<br>☐ N.A. | |
| 7. | Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the chemical drug substance intermediate from the current and proposed manufacturing processes/batch size. | ☐ Yes<br>☐ N.A. | |

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# QS.03. Change of in-process controls applied during manufacture of drug substance

| QS.03. Change of in-process controls applied during manufacture of drug substance | | | | | |
|---|---|---|---|---|---|
| **Common Conditions (Must be met for all subcategories)**<br>• Specifications of drug substance and drug substance intermediate remain unchanged unless the corresponding QS. checklist(s) is also selected. | | | | | |
| **Code** | **Description of Change** | **Category-specific Conditions** | **Applicant Declaration (I confirm all applicable conditions are met)** | **Reporting Category** | **Supporting Data** |
| **QS.03.A** Change of in-process controls including test, acceptance criteria and corresponding analytical procedure of the drug substance | | | | | |
| **i.** | Major change of in-process control of the drug substance | None (This category also applies where one or more of the conditions specified for categories A.ii to A.iv are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 6 |
| **ii.** | Addition or replacement of an in-process control of the drug substance with its corresponding analytical procedure | The change does not concern assay, potency, purity and impurity, and the new analytical procedure does not involve a novel non-standard technique or a standard technique used in a novel manner, and is not a biological, immunological or immunochemical procedure. | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **iii.** | Tightening of in-process control of the drug substance | The analytical procedure remains the same, or changes in the test procedures are minor. | ☐ Conditions met | MIV-2 D&T | 1 - 6 |
| **iv.** | Deletion of obsolete/non-significant in-process test of the drug substance | The parameter is obsolete or non-significant (e.g., solubility), and the change does not concern a critical attribute, such as identity, assay, potency, purity and impurity. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

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| **QS.03.B** Change of an analytical procedure for an in-process control of the drug substance | | | | | |
|---|---|---|---|---|---|
| **i.** | Change of a biological / immunological / immunochemical analytical procedure used for an in-process control of the drug substance | Appropriate studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the current analytical procedure. | ☐ Conditions met | MIV-2 Notification | 2 - 6 |
| **ii.** | Change to an analytical procedure used for an in-process control of the drug substance | The analytical procedure is not a biological / immunological / immunochemical procedure.<br><br>Appropriate studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the current analytical procedure. | ☐ Conditions met | MIV-2 D&T | 2 - 6 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed in-process controls and acceptance criteria presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including a risk assessment where applicable. Where a specification parameter is proposed for deletion, a risk assessment demonstrating that the parameter is non-significant, obsolete, or no longer necessary shall be submitted. | ☐ Yes<br>☐ N.A. | |
| 4. | Batch analysis data for at least two batches (minimum pilot scale) of the drug substance, where applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | Description of the analytical procedures, including summary of validation data where applicable. | ☐ Yes<br>☐ N.A. | |

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| 6. | Comparative analytical results demonstrating that the proposed analytical procedure is equivalent to the approved analytical procedure, where applicable. | ☐ Yes<br>☐ N.A. | |

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# QS.04. Change of specification / analytical procedure of drug substance / drug substance intermediate

**QS.04. Change of specification / analytical procedure of drug substance / drug substance intermediate**

**Notification to HSA is not required for:**

- Update to the pharmacopoeial reference to the current edition of a recognised monograph (e.g. USP 41 to USP 42), where the dossier already refers to the "current edition" and no change to the approved specification (or the update is editorial in nature only).
- Change of pharmacopoeial reference for analytical procedures, with no change to the analytical procedure.

**Common Conditions (Must be met for all subcategories)**

- The proposed analytical procedure should be appropriately validated.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.04.A** Change in specifications of the drug substance or drug substance intermediate, including tests, acceptance criteria and corresponding analytical procedures. | | | | | |
| **i.** | Major change in the specification of the drug substance or drug substance intermediate | None (This category also applies where one or more of the conditions specified for categories A.ii to A.iv are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 8 |
| **ii.** | Addition or replacement of a specification test of the drug substance or drug substance intermediate that does not involve assay, potency, impurity or novel technique | The change does not concern assay, potency, purity and impurity, and the new analytical procedure does not involve a novel non-standard technique or a standard technique used in a novel manner, and is not a biological, immunological or immunochemical procedure. | ☐ Conditions met | MIV-2 Notification | 1 - 8 |
| **iii.** | Tightening of a specification limit of the drug substance or drug substance intermediate | The analytical procedure remains the same, or changes in the test procedures are minor. | ☐ Conditions met | MIV-2 D&T | 1 - 6 |

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| **iv.** | Deletion of obsolete/non-significant test of the drug substance or drug substance intermediate | The parameter is obsolete or non-significant (e.g., solubility), and the change does not concern a critical attribute, such as identity, assay, potency, purity and impurity. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |
| **QS.04.B** Change in the analytical procedures for the drug substance or drug substance intermediate<br>* ***Note:*** *Including consequential updates to analytical procedure reference codes in the specification. For other specification changes, refer to QS.04.A.* | | | | | |
| **i.** | Addition, replacement or major modification of a biological / immunological / immunochemical / novel analytical procedure of the drug substance or drug substance intermediate | None (This category also applies where one or more of the conditions specified for categories B.ii to B.iii are not fulfilled) | ☐ Conditions met | MIV-1 | 2 - 6 |
| **ii.** | Other changes to an approved analytical procedure of the drug substance or drug substance intermediate | The change is limited to:<br>• Addition, replacement or modification of a non-novel/non-biological analytical procedure<br>• Minor changes to an approved biological, immunological, immunochemical or novel analytical procedure without changes to the method of analysis.<br><br>Results of analytical procedure validation show that the new analytical procedure is at least equivalent to the current procedure. | ☐ Conditions met | MIV-2 Notification | 2 - 6 |
| **iii.** | Deletion of an alternative analytical procedure of the drug substance or drug substance intermediate | At least one approved analytical procedure for the same specification attribute remains registered. | ☐ Conditions met | MIV-2 D&T | 2 - 6 |
| **QS.04.C** Change in the specification and/or analytical procedure to comply with recognised pharmacopoeial monograph<br>* ***Note:*** *For any in-house tests, acceptance criteria and/or analytical procedures that are not specified in the recognised pharmacopoeial monograph, refer to QS.04.A or QS.04.B* | | | | | |

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|---|---|---|---|---|---|
| **i.** | Change in the specification of the drug substance or drug substance intermediate to comply with recognised pharmacopoeial monograph | None (This category also applies where one or more of the conditions specified for categories C.ii are not fulfilled) | ☐ Conditions met | MIV-2 Notification | 1 - 9 |
| **ii.** | Change in the specification of the drug substance or drug substance intermediate to comply with a recognised pharmacopoeial monograph excluding potency/purity/impurity | Applies to the following:<br>• Change from one recognised pharmacopoeial drug substance monograph to another (e.g. USP to Ph.Eur.), or from an in-house standard to a recognised pharmacopoeial standard, provided the change does not concern, potency, purity or impurities.<br>• Change resulting from an update to the edition of a recognised pharmacopoeial drug substance monograph (e.g. USP 41 to USP 42), provided the same pharmacopoeial standard continues to apply and the change does not concern, potency, purity or impurities.<br>• Change to comply with recognised pharmacopoeial general monograph for microbial control. | ☐ Conditions met | MIV-2 D&T | 1 - 9 |
| **QS.04.D** | Change of testing from routine to skip/periodic testing and vice versa for the drug substance or drug substance intermediate | The specification acceptance criteria and analytical procedure remain unchanged. | ☐ Conditions met | MIV-2 Notification | 1 - 3 |

**Supporting Data**

| **No.** | **Supporting data requirement** | **Provided?** | **Remarks (e.g., include justification for not providing the required document)** |
|---|---|---|---|
| 1. | Approved and proposed specifications presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |

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|---|---|---|---|
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including a risk assessment where applicable. Where a specification parameter is proposed for deletion, a risk assessment demonstrating that the parameter is non-significant, obsolete, or no longer necessary shall be submitted. | ☐ Yes<br>☐ N.A. | |
| 4. | Batch analysis data for at least two batches (minimum pilot scale) of the drug substance. | ☐ Yes<br>☐ N.A. | |
| 5. | Description of the analytical procedures, including validation data where applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | Comparative analytical results demonstrating that the proposed analytical procedure is equivalent to the approved analytical procedure. | ☐ Yes<br>☐ N.A. | |
| 7. | For change of drug substance specification that involved any stability-indicating parameters, stability studies as per relevant guidelines. | ☐ Yes<br>☐ N.A. | |
| 8. | A commitment letter to complete the ongoing stability studies to support the approved shelf life of the drug substance. 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. | ☐ Yes<br>☐ N.A. | |
| 9. | Relevant recognised pharmacopoeial monograph, as applicable. | ☐ Yes<br>☐ N.A. | |

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# QS.05. Change of container closure system of drug substance

**QS.05. Change of container closure system of drug substance**

**Note:**

- This checklist also applies to changes of container closure system of the critical drug substance intermediate such as cytotoxic intermediate and monoclonal antibody intermediate used in the manufacture of antibody-drug conjugates (ADCs).

**Notification to HSA is not required for:**

- Change in supplier of the primary packaging material if the material and specification remain unchanged and continue to comply with the applicable international standards or pharmacopoeia requirements.
- For a change in the sterilisation site of primary packaging material, provided that the specification and sterility status of the primary packaging material remain unchanged.
- For a change in the secondary packaging material of a drug substance, bulk drug substance or process intermediate, provided that the retest period, shelf-life or hold time, as applicable, remains unchanged.

**Common Conditions (Must be met for all subcategories)**

- The change should not adversely affect identity, strength, quality, purity, stability, sterility or container-closure integrity.
- Specifications, retest period/shelf life of the drug substance remain unchanged unless the corresponding QS. checklist(s) is also selected.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.05.A** Change in primary packaging material of the drug substance | | | | | |
| **i.** | Addition or replacement of primary packaging of the drug substance | None (This category also applies where the condition specified for category A.ii is not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 7 |
| **ii.** | Addition or replacement of primary packaging of non-sterile drug substance | The change is limited to non-sterile drug substance. The proposed packaging material must be at least equivalent to the approved material with respect to relevant protective and functional properties. | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **iii.** | Deletion of primary packaging of the drug substance | At least one approved primary packaging remains registered. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

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| **QS.05.B** Change in specification of primary packaging material of the drug substance<br>**** Note:** The primary packaging system remains unchanged. Otherwise, refer to QS.05.A.* | | | | | |
|---|---|---|---|---|---|
| **i.** | Major change in the specification of primary packaging of the drug substance | None (This category also applies where one or more of the conditions specified for categories B.ii are not fulfilled) | ☐ Conditions met | MIV-2 Notification | 1 - 3 |
| **ii.** | Minor change in the specification of primary packaging of the drug substance | The change does not involve widening or deletion of critical quality attribute (e.g., identification). | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed container closure system information presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | Declaration of compliance to the appropriate international standards or pharmacopoeia. | ☐ Yes<br>☐ N.A. | |
| 5. | Appropriate data on the proposed packaging (comparative data on permeability, e.g. for O2, CO2 and moisture). Where appropriate, evidence should be provided to demonstrate that no adverse interaction occurs between the drug substance and the packaging material, including migration of components from the proposed packaging material into the drug substance or loss of drug substance components into the packaging material. | ☐ Yes<br>☐ N.A. | |
| 6. | Stability studies as per relevant guidelines and a commitment letter to complete the ongoing stability studies to the approved or proposed retest period or shelf life, as applicable. 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. | ☐ Yes<br>☐ N.A. | |

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| 7. | Process validation protocol and validation report for the manufacturing, sterilisation, and container closure system integrity, as applicable. | ☐ Yes<br>☐ N.A. | |

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# QS.06. Change of shelf life / retest period / storage condition / stability protocol of drug substance

**QS.06. Change of shelf life / retest period / storage condition / stability protocol of drug substance**
**Note:**

- This checklist also applies to changes of shelf life / retest period / storage condition / stability protocol of the critical drug substance intermediate such as cytotoxic intermediate and monoclonal antibody intermediate used in the manufacture of antibody-drug conjugates (ADCs).

**Notification to HSA is not required for:**

- The following changes to stability protocol where the approved retest period/shelf life of drug substance remains unchanged:
  a. Change of sampling frequency in accordance with relevant ICH guidelines, e.g., adjust sampling frequency to annual time-points after completion of the stability study of primary batches.
  b. Change of time-points beyond the approved retest period/shelf life.

**Common Conditions (Must be met for all subcategories)**

- Stability studies must demonstrate compliance with the specification under the storage condition.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.06.A** Change of storage condition of drug substance with corresponding shelf life or retest period | | | | | |
| **i.** | Change of storage condition of the drug substance with corresponding shelf life or retest period | None | ☐ Conditions met | MIV-1 | 1 - 3 |
| **ii.** | Change to more restrictive storage condition of the drug substance with corresponding shelf life or retest period | The proposed storage condition is more restrictive. | ☐ Conditions met | MIV-2 Notification | 1 - 3 |
| **QS.06.B** Change of shelf life / retest period / storage period of the drug substance with no change in storage condition | | | | | |

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|---|---|---|---|---|---|
| **i.** | Change of shelf life or retest period of the drug substance based on extrapolation | The extrapolation should be scientifically justified and supported by available long-term stability data in accordance with the relevant ICH stability guideline. | ☐ Conditions met | MIV-1 | 1 - 3 |
| **ii.** | Change of shelf life or retest period of the drug substance supported with complete real time stability data | Complete real time stability data covering the proposed shelf life /retest period is available. | ☐ Conditions met | MIV-2 Notification | 1 - 3 |
| **QS.06.C** | Change to the approved stability protocol of the drug substance | The change is not due to stability concerns or unexpected manufacturing events and does not involve widening of acceptance criteria or removal of stability-indicating parameters. | ☐ Conditions met | MIV-2 Notification | 1 - 2, 4 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 2. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 3. | Results of stability studies for at least three pilot-scale or production-scale batches, comprising either:<br>a. Complete real time stability data supporting the proposed retest period or shelf life; or<br>b. Available stability data, together with a scientific justification for the extrapolation in accordance with relevant stability guidelines and a commitment letter to continue the ongoing stability studies up to the proposed retest period or shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required, but the data shall be provided to the Health Sciences Authority upon request. | ☐ Yes<br>☐ N.A. | |

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|---|---|---|---|
| 4. | Approved and proposed stability protocols presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |

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# QS.07. Change of specification / source of raw material for drug substance

**QS.07. Change of specification / source of raw material for drug substance**
**Note:**

- This checklist also applies to changes of specification of chemical starting materials. For changes relating to biological starting materials (e.g., cell banks, seed banks), refer to QS.08 checklist.

**Notification to HSA is not required for**

- Change in the supplier / manufacturer of a raw material which is not of mammalian or avian origin if the specification of the raw material remains unchanged.
- Change in the supplier / manufacturer for the chemical starting material with the same specification.

**Common Conditions (Must be met for all subcategories)**

- Specifications for in-process control, drug substance intermediate and drug substance remain unchanged unless the corresponding QS. checklist(s) is also selected.
- Any viral safety or TSE risks arising from changes to animal-derived materials should be appropriately assessed and demonstrated not to adversely affect the quality, safety or efficacy of the drug substance.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.07.A** Change in specification of chemical starting material | | | | | |
| **i.** | Major change of specification of chemical starting material | None (This category also applies where the condition specified for category A.ii is not fulfilled) | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **ii.** | Minor change of specification of chemical starting material | The change is limited to the addition of new tests, tightening of existing acceptance criteria, deletion of obsolete or non-significant tests (e.g. solubility), and/or alignment with a recognised pharmacopoeial monograph, provided | ☐ Conditions met | MIV-2 D&T | 1 - 6 |

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| | | that no new impurity is introduced into the specification and existing impurity acceptance criteria are not widened or deleted. | | | |
| **QS.07.B** Change in the specification of raw material (including solvents, reagents, catalyst) | | | | | |
| **i.** | Major change of specification of raw material | None (This category also applies where the condition specified for category B.ii is not fulfilled) | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **ii.** | Minor change of specification of raw material | The change is limited to the addition of new tests, tightening of existing acceptance criteria, deletion of obsolete or non-significant tests (e.g. solubility), and/or alignment with a recognised pharmacopoeial monograph. | ☐ Conditions met | MIV-2 D&T | 1 - 6 |
| **QS.07.C** Change of an animal-derived material used in drug substance manufacture | | | | | |
| **i.** | Introduction of, or change to, a TSE-relevant material not covered by a valid TSE CEP | The proposed material is TSE-relevant and is not covered by a valid TSE CEP. | ☐ Conditions met | MIV-2 Notification | 2 - 4, 7 - 8 |
| **ii.** | Introduction of, or change to, a TSE-relevant material covered by a valid TSE CEP | The proposed material is TSE-relevant and is covered by a valid TSE CEP applicable to the proposed material and its intended use. | ☐ Conditions met | MIV-2 D&T | 2 - 4, 7, 9 |
| **iii.** | Introduction of, or change to, a non-TSE-relevant animal-derived material | Both the existing and proposed materials are animal-derived and the proposed material is not TSE-relevant (e.g., porcine, avian, etc.). | ☐ Conditions met | MIV-2 D&T | 2 - 4, 10 |
| **iv.** | Change from an animal-derived material to a non animal-derived material | The proposed material must not be animal-derived (e.g., vegetable or synthetic) and must not introduce any new quality, safety, viral risks. | ☐ Conditions met | MIV-2 D&T | 2 - 4 |

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| Supporting Data | | | |
|---|---|---|---|
| **No.** | **Supporting data requirement** | **Provided?** | **Remarks (e.g., include justification for not providing the required document)** |
| 1. | Approved and proposed specifications presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | Batch analysis data for the starting material/raw material, as applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | Declaration that the change does not adversely impact the quality of the drug substance, including its qualitative and quantitative impurity profile, and does not result in impurities requiring additional safety qualification. | ☐ Yes<br>☐ N.A. | |
| 6. | Relevant recognised pharmacopoeial monograph, as applicable. | ☐ Yes<br>☐ N.A. | |
| 7. | Information on the animal-derived material, including the type of the tissue/fluid, species, source country and supplier, as applicable. | ☐ Yes<br>☐ N.A. | |
| 8. | Relevant information supporting the TSE risk assessment, including the tissue/fluid collection procedures and measures to prevent cross-contamination, risk factors associated with the route of administration and maximum therapeutic dose of the drug product, and the capacity of the manufacturing process to inactivate and/or remove TSE agents. | ☐ Yes<br>☐ N.A. | |
| 9. | A valid TSE Risk Evaluation CEP. | ☐ Yes<br>☐ N.A. | |
| 10. | Information on the type of the tissue/fluid and a declaration that the manufacturing process is capable of inactivating new adventitious agents. | ☐ Yes<br>☐ N.A. | |

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# QS.08. Change of cell bank / seed bank

**QS.08. Change of cell bank / seed bank**
**Note:**

- This checklist applies to changes involving the Master Cell Bank (MCB), Working Cell Bank (WCB), Master Seed Bank (MSB), and Working Seed Bank (WSB).
- For change of a cell bank/seed bank involving the introduction or revision of a qualification protocol, both 08.A and 08.B checklists are applicable.

**Notification to HSA is not required for:**

- Change of storage site, storage condition and/or shelf life for the cell bank/seed bank, where complete real time stability data demonstrate compliance with specifications throughout the proposed shelf life at the proposed storage condition.
- Change of QC site for the cell bank/seed bank, where the specification and analytical procedures remain unchanged and successful verification/transfer has been completed in accordance with GMP requirements.

**Common Conditions (Must be met for all subcategories)**

- Applicable to 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.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.08.A** Generation of a new cell bank/seed bank at an approved or new manufacturing site | | | | | |
| **i.** | Generation of a new MCB/MSB | The new MCB/MSB is derived from an approved bank according to approved protocol. | ☐ Conditions met | MIV-1 | 1 - 5 |
| **ii.** | Generation of a new WCB/WSB | No change in master bank or host cell line; qualification follows approved procedures. | ☐ Conditions met | MIV-2 Notification | 1 - 5 |
| **QS.08.B** Change of cell bank/seed bank qualification protocol | | | | | |

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|---|---|---|---|---|---|
| **i.** | Major change of cell or seed bank qualification protocol | None (This category also applies where one or more of the conditions specified for categories B.ii are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 2, 6 |
| **ii.** | Minor change of cell or seed bank qualification protocol | The protocol is considered more stringent (e.g., addition of new tests or tightening of acceptance criteria). | ☐ Conditions met | MIV-2 Notification | 1 - 2, 6 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 2. | Justification for the proposed change, including a risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |

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| 3. | Relationship to the approved bank and supporting qualification data, including:<br>a. For a new or replacement master bank (MCB/MSB):<br>• Description of the source, origin, history and passage level of the proposed bank, including documentation of raw materials of human or animal origin used during its establishment, where applicable.<br>• Identity and characterisation data, including relevant genetic, phenotypic and/or expression characteristics.<br>• Results of qualification testing, as applicable, including sterility, mycoplasma and adventitious agent testing.<br>• For recombinant expression systems, data demonstrating genetic stability and consistency of expression throughout the anticipated production cycle.<br>• For viral seed bank, information on seed derivation and characterisation, including any genetic modification, attenuation, reassortment or recombinant manipulation, where applicable.<br>• Validated cell stability under the freezing and storage conditions using cell recovery or viability data.<br>• Stability data as per the relevant guidelines on the stability study of the drug substance.<br>b. For a new or replacement working bank (WCB/WSB):<br>• Appropriate characterisation and qualification data demonstrating suitability for manufacture, including identity and other relevant tests, where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | Comparability assessment of drug substance manufactured from the approved and proposed bank, including physicochemical characterisation, biological activity, impurity profile and comparative batch analysis data. | ☐ Yes<br>☐ N.A. | |
| 5. | Commitment to complete any ongoing stability studies supporting the approved shelf life. Any out-of-specification result, together with the proposed actions, shall be reported to HSA. Submission of a final stability report is not required but should be made available to HSA upon request. | ☐ Yes<br>☐ N.A. | |
| 6. | Revised cell/seed bank qualification protocol, and supporting validation/qualification data, as applicable. | ☐ Yes<br>☐ N.A. | |

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# QS.09. Change to in-house biological reference standard / material

**QS.09. Change to in-house biological reference standard / material**
**Note:**

- This checklist also applies to changes of reference standard used in the drug product.
- For change of an in-house reference standard involving the introduction or revision of a qualification protocol, both 09.A and 09.B checklists are applicable.

**Notification to HSA is not required for:**

- Introduction of a new reference standard which is qualified in accordance with the approved qualification protocol, and when the old reference standard material is available for direct comparison with the new material.
- Extension of the reference standard shelf life or retest period if the reference standard within the limits/conditions as detailed in the approved qualification protocol.

**Common Conditions (Must be met for all subcategories)**

- The proposed reference standard should preserve traceability and ensure continuity of the analytical control strategy.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.09.A** Addition or replacement of an in-house reference standard / material | | | | | |
| **i.** | Addition or replacement of an in-house reference standard not covered by an approved qualification protocol, without direct comparative data | None (This category also applies where one or more of the conditions specified for categories A.ii to Aiii are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 4 |
| **ii.** | Addition or replacement of an in-house reference standard not covered by an approved qualification protocol, with direct comparative data | Comparative test results, showing that the current in-house reference standard and the proposed one are equivalent. | ☐ Conditions met | MIV-2 Notification | 1 - 4 |

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| **iii.** | Addition or replacement of an in-house reference standard in accordance with an approved qualification protocol, without direct comparative data | All approved qualification acceptance criteria are met. | ☐ Conditions met | MIV-2 Notification | 1 - 4 |
| **QS.09.B** Change to the qualification protocol for an in-house reference standard / material | | | | | |
| **i.** | Introduction or major change of a reference standard qualification protocol | None | ☐ Conditions met | MIV-1 | 1 - 2, 5 |
| **ii.** | Minor change to a reference standard qualification protocol | The protocol is considered more stringent (e.g., addition of new tests or tightening of acceptance criteria). | ☐ Conditions met | MIV-2 Notification | 1 - 2, 5 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 2. | Justification for the proposed change, including a risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 3. | Information on the qualification of the proposed reference standard, e.g., characterisation, information regarding the manufacturing process used to establish the reference standard, certificate of analysis, comparability data, expiry date, storage condition, stability and re-qualification. | ☐ Yes<br>☐ N.A. | |
| 4. | Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the drug substance/drug product using the current and proposed reference standard. | ☐ Yes<br>☐ N.A. | |
| 5. | Qualification protocol for the proposed reference standard. | ☐ Yes<br>☐ N.A. | |

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# QS.10. Change to vaccine strain / serotype / antigen / coding sequence

**QS.10. Change to vaccine strain / serotype / antigen / coding sequence**
**Note:**

- Non-consequential unrelated changes should be submitted separately. (Note: additional changes other than strain changes will require additional supporting documents, which may delay the evaluation timeline).

**Common Conditions (Must be met for all subcategories)**

- The change in drug substance is in accordance with the official recommendations from relevant authorities (e.g., WHO) or established global forum, where the efficacy and safety of the modified vaccine can be inferred from the data of the approved vaccine.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.10.A** Change of the strain(s) for seasonal influenza vaccine<br>** **Note:** The proposed product labels (outer carton, inner label and package insert) should clearly indicate strain type, Year/Year and southern hemisphere or northern hemisphere.* | | | | | |
| **i.** | Change of the strain(s) in seasonal influenza vaccine | None | ☐ Conditions met | MIV-1 | 1 - 9 |
| **ii.** | Change to seasonal influenza vaccine without strain change | The change is limited to the seasonal update with no change to the approved influenza virus strains. | ☐ Conditions met | MIV-2 Notification | 1, 9c |
| **QS.10.B** | Change of the strain(s) for SARS-CoV-2 Vaccine | None | ☐ Conditions met | MIV-1 | 1 - 8, 10 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |

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| 2. | Validation study reports and/or summaries of the critical manufacturing process (e.g., inactivation, splitting efficiency) for drug substance(s) to demonstrate manufacturing consistency. | ☐ Yes<br>☐ N.A. | |
| 3. | Revised release and/or shelf life specification for the drug substance(s), together with scientific and/or clinical justification, where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | Update and re-validation of analytical procedures and reference standards for the proposed strain (s), where applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | Batch analyses data for drug substance(s). | ☐ Yes<br>☐ N.A. | |
| 6. | Revised composition of the vaccine to reflect the proposed change. | ☐ Yes<br>☐ N.A. | |
| 7. | Release and/or shelf life specification for the vaccine. | ☐ Yes<br>☐ N.A. | |
| 8. | Batch analysis data (in a comparative tabular format) of the vaccines manufactured using the approved and proposed strains. | ☐ Yes<br>☐ N.A. | |
| 9. | For influenza vaccine:<br>a. Identification of working seed stock as per the pharmacopoeial requirements.<br>b. Validation study reports of single radial diffusion (SRD) test for the proposed strain(s).<br>c. Stability study result of at least 6 months of the vaccine from the preceding year or season and commitment to complete the ongoing 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. | ☐ Yes<br>☐ N.A. | |

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| 10. | For SARS-CoV-2 vaccine:<br>a. Details of changes to the starting material, e.g., construction and synthesis of DNA template, virus seed.<br>b. Justification for not submitting new clinical data for the proposed strain(s).<br>c. Revised Risk Management Plan, if required.<br>d. Demonstration of the applicability of the approved shelf life of the drug substance(s) and finished product to the modified vaccine, e.g., with real time stability data, accelerated and/or stress stability data, or predictive stability models.<br>e. A commitment letter to complete the ongoing 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. | ☐ Yes<br>☐ N.A. | |

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# QS.11. Addition or Replacement of Plasma Master File (PMF)

**QS.11. Addition or Replacement of Plasma Master File (PMF)**
**Note:**

- This checklist applies to the introduction or replacement of a PMF for human plasma-derived materials used in drug substance or drug product manufacture. Refer to Appendix 8 for further information.

**Common Conditions (Must be met for all subcategories)**

- The PMF should be current and applicable to the authorised product. The product-specific impact of PMF changes should be assessed and documented.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QS.11** | Addition or replacement of PMF | None | ☐ Conditions met | MIV-1 | 1 - 7 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 2. | New or latest version of the PMF. | ☐ Yes<br>☐ N.A. | |
| 3. | Letter of Access issued by the PMF holder to the product owner. | ☐ Yes<br>☐ N.A. | |
| 4. | Latest EMA annual recertification letter and recertification assessment report, if available. | ☐ Yes<br>☐ N.A. | |
| 5. | An expert statement outlining all changes introduced to the PMF with evaluation of the potential impact on the drug product, including specific risk assessments. | ☐ Yes<br>☐ N.A. | |

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| 6. | Batch analysis data of at least three production batches of drug substance or drug product manufactured using the previous and new PMF, where applicable. | ☐ Yes<br>☐ N.A. | |
| 7. | Stability data as per the relevant guidelines, and a commitment letter to continue the ongoing stability studies up to the approved retest period or shelf life, as applicable. 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. | ☐ Yes<br>☐ N.A. | |

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# Quality Drug Product Changes - QP

# QP.01. Change of manufacturing facility responsible for any manufacturing operations of drug product

**QP.01. Change of manufacturing facility responsible for any manufacturing operations of drug product**
**Note:**

- This checklist is also applicable to changes to the manufacturing facility of a drug product intermediate, adjuvant, diluent and/or solvent.
- For changes to package insert and labelling incorporating the proposed change, refer to LB checklist(s).

**Notification to HSA is not required for:**

- Change in the location of QC testing within the same approved manufacturing site, provided that the specification and analytical procedures remain unchanged and analytical procedure transfer/verification has been completed in accordance with GMP requirements.

**Common Conditions (Must be met for all subcategories)**

- Drug product specification, manufacturing process, batch size, container closure, shelf life and storage condition should remain unchanged unless the corresponding the Q.P. checklist is also selected.
- The product formulation and drug product specifications must remain common across the current and proposed manufacturing facilities.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.01.A** Change of facility responsible for bulk production of the drug product, including associated packaging, QC testing and batch release functions at the same site | | | | | |
| **i.** | Addition or replacement of a site responsible for manufacture of the drug product (including sterilisation site) | None (This category also applies where one or more of the conditions specified for A.ii are not fulfilled). | ☐ Conditions met | MIV-1 | 1 - 11 |
| **ii.** | Addition or replacement of facility (building/suite) within an existing | The proposed facility (building/suite) is located within an existing approved manufacturing site, operates under the | ☐ Conditions met | MIV-2 Notification | 1 - 6 |

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| | approved manufacturing site of the drug product | same pharmaceutical quality system (PQS), and any changes to the manufacturing process and/or controls are limited to those necessary to duplicate the approved manufacturing operation. | | | |
| **QP.01.B** Change of a site responsible for primary and/or packaging of the drug product | | | | | |
| **i.** | Addition or replacement of a site responsible for primary packaging of sterile drug product, performing primary packaging only or both primary and secondary packaging | The packaging material and specification remain unchanged. For a change to the packaging material, refer to QP.05 checklist(s). | ☐ Conditions met | MIV-1 | 1 - 7, 11 |
| **ii.** | Addition or replacement of a site responsible for primary packaging of non-sterile drug product, performing primary packaging only or both primary and secondary packaging | The drug product is non-sterile.<br><br>The packaging material and specification remain unchanged. For a change to the packaging material, refer to QP.05. | ☐ Conditions met | MIV-2 Notification | 1 - 7, 11 |
| **iii.** | Addition or replacement of a site responsible for secondary packaging of the drug product | The secondary packaging material remains unchanged. For a change to the packaging material, refer to QP.05. | ☐ Conditions met | MIV-2 Notification | 1 - 4, 11 |
| **QP.01.C** Addition or replacement of a QC testing site responsible for release and stability testing of the drug product | | | | | |
| **i.** | Addition or replacement of a QC testing site of the drug product for biological / immunological / immunochemical analytical procedure | There is no change to the specification and analytical procedures. Analytical procedure transfer/verification at the proposed site has been successfully completed. | ☐ Conditions met | MIV-2 Notification | 1 - 2, 9 |
| **ii.** | Addition or replacement of a QC testing site of the drug product for non-biological analytical procedure | The analytical procedure is not a biological / immunological / immunochemical procedure.<br><br>There is no change to the specification and analytical procedures. Analytical | ☐ Conditions met | MIV-2 D&T | 1 - 2, 9 |

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| | | procedure transfer/verification at the proposed site has been successfully completed. | | | |
| **QP.01.D** | Addition or replacement of a site responsible for batch release of the drug product | The drug product manufacturer remains unchanged. The change is limited to the batch release function. | ☐ Conditions met | MIV-2 Notification | 1 - 4, 11 |
| **QP.01.E** | Deletion of an approved site for any manufacturing operations of the drug product | At least one approved site remains for the relevant activity, and the deletion is not due to critical deficiencies in manufacturing or quality systems. | ☐ Conditions met | MIV-2 D&T | 1 - 2 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 2. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 3. | Batch numbering system (where applicable). | ☐ Yes<br>☐ N.A. | |
| 4. | Valid evidence of GMP compliance for the proposed manufacturing facility in accordance with the *Guidance on Therapeutic Product Registration in Singapore*. For overseas manufacturers, application form for GMP Evidence Evaluation or for an Overseas GMP Audit, as applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | Process validation protocol and validation report for the manufacturing, sterilisation, and container closure system integrity, as applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | Batch analysis data (in a comparative tabular format) for at least two batches (preferably production scale) of the drug product from the current and proposed manufacturing facilities. | ☐ Yes<br>☐ N.A. | |
| 7. | Holding time studies of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). | ☐ Yes<br>☐ N.A. | |

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| 8. | Stability studies as per relevant guidelines and a commitment letter to complete the ongoing stability studies to the approved or proposed 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. | ☐ Yes<br>☐ N.A. | |
| 9. | Declaration that specifications and analytical procedures remain unchanged, analytical procedure transfer/verification has been successfully completed, and comparative analysis from the current and proposed testing sites are comparable. | ☐ Yes<br>☐ N.A. | |
| 10. | Comparability study with respect to physico-chemical characterisation, biological activity and impurity profile or a justification for not submitting such a study. | ☐ Yes<br>☐ N.A. | |
| 11. | A letter of appointment for the proposed site to manufacture the drug product and stating the types of activity to be performed (where applicable). | ☐ Yes<br>☐ N.A. | |

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# QP.02. Change of manufacturing process / batch size of drug product

**QP.02. Change of manufacturing process / batch size of drug product**
**Note:**

- For introduction or extension of a design space or method operable design region (MODR), refer to QR.02.
- This checklist is also applicable to changes in the manufacturing process and/or batch size of drug product intermediate, adjuvant, diluent and/or solvent.

**Notification to HSA is not required for:**

- For decommissioning of a duplicate manufacturing line where the approved manufacturing process and all registered quality attributes remain unchanged

**Common Conditions (Must be met for all subcategories)**

- The change does not affect reproducibility and/or consistency of the drug product.
- The formulation, batch size, release/shelf life specification, container closure system, shelf life and storage condition remain unchanged unless the corresponding QP. checklist(s) is also selected.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.02.A** Change (including addition or replacement) of manufacturing process of the drug product, including corresponding change in batch size | | | | | |
| **i.** | Major change of manufacturing process of the drug product that may have significant impact on product quality, safety or efficacy | None (This category also applies where one or more of the conditions specified for categories A.ii are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 7 |
| **ii.** | Minor change of manufacturing process of the drug product | The overall manufacturing principle remains unchanged, and the change does not have a significant impact on product quality or performance. | ☐ Conditions met | MIV-2 Notification | 1 - 7 |
| **QP.02.B** Chang of batch size of the drug product with process changes limited to scale-up or downscaling | | | | | |
| **i.** | Change in batch size of sterile drug product or drug product | The drug product is sterile or is manufactured by novel or complex | ☐ Conditions met | MIV-1 | 1 - 6 |

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| | manufactured by novel or complex manufacturing processes | manufacturing processes (e.g. continuous manufacturing).<br><br>Any changes to the manufacturing process and/or the in-process controls are only those necessitated by scale-up or downscaling, e.g., use of different-sized equipment. | | | |
| **ii.** | Change of batch size of non-sterile drug product | The drug product is non-sterile and is not manufactured using a novel or complex manufacturing processes.<br><br>Any changes to the manufacturing process are only those necessitated by scale-up or downscaling, e.g., use of different-sized equipment. | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **iii.** | Change of batch size through duplication of an approved manufacturing line | The change is limited to duplication of an approved manufacturing line, with no changes to the manufacturing process, control strategy, critical process parameters or approved specifications. | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **QP.02.C** | Change in the holding time and/or storage condition of bulk product or process intermediate | The change does not affect the shelf life of the drug product. | ☐ Conditions met | MIV-2 Notification | 1 - 3, 8 - 9 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed information presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including an appropriate risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |

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| 4. | Batch analysis data (in a comparative tabular format) for at least two batches (preferably production scale) of the drug product from the current and proposed manufacturing processes and/or batch size. | ☐ Yes<br>☐ N.A. | |
| 5. | Process validation protocol and validation report for the manufacturing, sterilisation, and container closure system integrity, as applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | Stability studies as per relevant guidelines and a commitment letter to complete the ongoing stability studies to the approved or proposed 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. | ☐ Yes<br>☐ N.A. | |
| 7. | Comparability study with respect to physico-chemical characterisation, biological activity and impurity profile or a justification for not submitting such a study. | ☐ Yes<br>☐ N.A. | |
| 8. | Data to validate the proposed change in holding time and/or storage conditions of the bulk product or process intermediate. | ☐ Yes<br>☐ N.A. | |
| 9. | Declaration that the finished product shelf life is set in accordance with the *EMA Note for guidance on start of shelf life of the finished dosage form*, or otherwise justified. | ☐ Yes<br>☐ N.A. | |

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# QP.03. Change of in-process controls applied during manufacture of drug product

| QP.03. Change of in-process controls applied during manufacture of drug product | | | | | |
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| **Common Conditions (Must be met for all subcategories)**<br>• The release and shelf life specifications of drug product remain unchanged unless the corresponding QP.04 checklist(s) is also selected. | | | | | |
| **Code** | **Description of Change** | **Category-specific Conditions** | **Applicant Declaration (I confirm all applicable conditions are met)** | **Reporting Category** | **Supporting Data** |
| **QP.03.A** Change of in-process controls including test, acceptance criteria and corresponding analytical procedure | | | | | |
| **i.** | Major change of in-process control of the drug product (including widening of acceptance criteria and/or deletion of a significant test) | None (This category also applies where one or more of the conditions specified for categories A.ii to A.iv are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 6 |
| **ii.** | Addition or replacement of an in-process control of the drug product with its corresponding analytical procedure | The change does not concern assay, potency, purity and impurity, and the new analytical procedure does not involve a novel non-standard technique or a standard technique used in a novel manner, and is not a biological, immunological or immunochemical procedure. | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **iii.** | Tightening of in-process control of the drug product | The analytical procedure remains the same, or changes in the test procedures are minor. | ☐ Conditions met | MIV-2 D&T | 1 - 6 |
| **iv.** | Deletion of obsolete/non-significant in-process test of the drug product | The parameter is obsolete or non-significant (e.g., solubility), and the change does not concern a critical | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

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| | | attribute, such as identity, assay, potency, purity and impurity. | | | |
| **QP.03.B** | Change of an analytical procedure for an in-process control of the drug product | Appropriate studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the current analytical procedure. | ☐ Conditions met | MIV-2 Notification | 2 - 6 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed in-process controls and acceptance criteria presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including a risk assessment where applicable. Where a specification parameter is proposed for deletion, a risk assessment demonstrating that the parameter is non-significant, obsolete, or no longer necessary shall be submitted. | ☐ Yes<br>☐ N.A. | |
| 4. | Batch analysis data for at least two batches (preferably production scale) of the drug product, where applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | Description of the analytical procedures, including summary of validation data where applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | Comparative analytical results demonstrating that the proposed analytical procedure is equivalent to the approved analytical procedure where applicable. | ☐ Yes<br>☐ N.A. | |

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# QP.04. Change of specification / analytical procedure of drug product

**QP.04. Change of specification / analytical procedure of drug product**
**Note:**

- This checklist is also applicable to changes to the specification and/or analytical procedure of drug product intermediate, adjuvant, diluent and/or solvent.

**Notification to HSA is not required for:**

- Update to the pharmacopoeial reference to the current edition of a recognised monograph (e.g. USP 41 to USP 42), where the dossier already refers to the "current edition" and no change to the approved specification (or the update is editorial in nature only).
- Change of reference standard if the analytical procedure remains unchanged.
- Change of pharmacopoeial reference for analytical procedures, with no change to the analytical procedure.

**Common Conditions (Must be met for all subcategories)**

- The new or revised analytical procedures should be appropriately validated and suitable for their intended purpose.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.04.A** Change in specification of drug product, including tests, acceptance criteria and corresponding analytical procedures | | | | | |
| **i.** | Major change in the specification of the drug product | None (This category also applies where one or more of the conditions specified for categories A.ii to A.iv are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 8 |
| **ii.** | Addition or replacement of a specification test of the drug product that does not involve assay, potency, impurity or novel technique | The change does not concern assay, potency, purity and impurity, and the new analytical procedure does not involve a novel non-standard technique or a standard technique used in a novel manner, and is not a biological, immunological or immunochemical procedure. | ☐ Conditions met | MIV-2 Notification | 1 - 8 |

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| **iii.** | Tightening of a specification limit of the drug product | The analytical procedure remains the same, or changes in the test procedures are minor. | ☐ Conditions met | MIV-2 D&T | 1 - 6 |
| **iv.** | Deletion of obsolete/non-significant test of the drug product | The parameter is obsolete or non-significant (e.g., solubility), and the change does not concern a critical attribute (e.g., identity, assay, potency, impurities, sterility-related attributes, critical physical characteristics, dosage form-specific test). | ☐ Conditions met | MIV-2 D&T | 1 - 3 |
| **QP.04.B** Change in the analytical procedure of the drug product<br>*** *Note:*** *Including consequential updates to analytical procedure reference codes in the specification. For other specification changes, refer to QP.04.A.* | | | | | |
| **i.** | Major change to an approved analytical procedure of the drug product | None (This category also applies where one or more of the conditions specified for categories B.ii to B.iii are not fulfilled) | ☐ Conditions met | MIV-1 | 2 - 6 |
| **ii.** | Minor change to an approved analytical procedure of the drug product | The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). Results of analytical procedure validation show that the new analytical procedure is at least equivalent to the current procedure. | ☐ Conditions met | MIV-2 Notification | 2 - 6 |
| **iii.** | Introduction of an alternative analytical procedure of the drug product | The new analytical procedure does not involve a biological, immunological, immunochemical or novel analytical technique, or a standard technique used in a novel manner, and results of analytical procedure validation show that the new analytical procedure is at least equivalent to the current procedure. | ☐ Conditions met | MIV-2 Notification | 2 - 6 |
| **iv.** | Deletion of an alternative analytical procedure of the drug product | At least one approved analytical procedure for the same specification attribute remains registered. | ☐ Conditions met | MIV-2 D&T | 2 - 3 |

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| **QP.04.C** | Change of testing from routine to skip/periodic testing and vice versa for the drug product | The specification acceptance criteria and analytical procedure remain unchanged. | ☐ Conditions met | MIV-2 Notification | 1 - 3 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed specifications presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including a risk assessment where applicable. Where a specification parameter is proposed for deletion, a risk assessment demonstrating that the parameter is non-significant, obsolete, or no longer necessary shall be submitted. | ☐ Yes<br>☐ N.A. | |
| 4. | Batch analysis data for at least two batches (preferably production scale) of drug product. | ☐ Yes<br>☐ N.A. | |
| 5. | Description of the analytical procedures, including validation data where applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | Comparative analytical results demonstrating that the proposed analytical procedure is equivalent to the approved analytical procedure. | ☐ Yes<br>☐ N.A. | |
| 7. | For change of drug product specification that involved any stability-indicating parameters, stability studies as per relevant guidelines and a commitment letter to complete the ongoing stability studies to the approved shelf life, as applicable. 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. | ☐ Yes<br>☐ N.A. | |
| 8. | Relevant recognised pharmacopoeial monograph, as applicable. | ☐ Yes<br>☐ N.A. | |

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# QP.05. Change of container closure system / pack size / medical device supplied with drug product

**QP.05. Change of container closure system / pack size / medical device supplied with drug product**
**Note:**

- Multiple packaging configurations may be included under a single product registration, provided the product has an identical dosage form, strength, product name, and product formula across all configurations, and does not use different container closure systems that serve as drug delivery devices. Where these conditions are not met, a new drug application should be submitted. Refer to Appendix 17 for further information.
- For changes to a medical device supplied with the drug product:
  a. Refer to QP.05.A - C, as applicable, for an integral Class A/B medical device forming part of the container closure system.
  b. Refer to QP.05.E for an integral Class C/D medical device.
  c. Refer to QP.05.F for a co-packaged Class A/B medical device (e.g., measuring cup, empty syringe, needle).

**Notification to HSA is not required for:**

- Change in supplier of the primary packaging material if the material and specification remain unchanged and continue to comply with the applicable international standards or pharmacopoeia requirements.
- Change in the sterilisation site of a purchased sterile primary packaging material where its specification and sterility status remain unchanged.
- Change in the secondary packaging material of bulk drug product or process intermediate, provided that the approved hold time remains unchanged.
- Change to medical device as per Section 2.3 of *GN21: Guidance on Change Notification for Registered Medical Devices*.

**Common Conditions (Must be met for all subcategories)**

- The change does not adversely affect drug product quality, stability, sterility, delivery, use, safety or dosing regimen.
- Specifications, storage condition and shelf life of the drug product remain unchanged unless the corresponding QP. checklist(s) is also selected.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.05.A** Change in type and/or material of container closure system for the drug product<br>**** Note:** Applicable to primary packaging and functional secondary packaging components* | | | | | |
| **i.** | Change in type and/or material of container closure system for the drug product | None (This category also applies where the condition specified for category A.ii is not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 7 |

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| **ii.** | Change in type and/or material of container closure system for non-sterile drug product | The change is limited to non-sterile drug product. The proposed packaging material must be at least equivalent to the approved material with respect to relevant protective and functional properties. | ☐ Conditions met | MIV-2 Notification | 1 - 6 |
| **iii.** | Change in packaging component not in contact with the drug product (such as colour of flip-off caps, colour code rings on ampoules) | The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |
| **QP.05.B** | Change in shape or dimensions of the primary packaging material for the drug product | The type and material of primary packaging component remain unchanged. Otherwise, refer to QP.05.A. | ☐ Conditions met | MIV-2 Notification | 1 - 3, 6 - 7 |
| **QP.05.C** Change in the specification of the primary packaging material for the drug product<br>* ***Note****: The type and material of primary packaging component remain unchanged. Otherwise, refer to QP.05.A.* | | | | | |
| **i.** | Major change in the specification of the primary packaging material for the drug product | None (This category also applies where one or more of the conditions specified for categories C.ii are not fulfilled) | ☐ Conditions met | MIV-2 Notification | 1 - 3 |
| **ii.** | Minor change in the specification of the primary packaging material for the drug product | The change does not involve widening of specification (e.g., water-vapour or oxygen permeability) or deletion of critical quality attribute (e.g., identification test). | ☐ Conditions met | MIV-2 D&T | 1 - 3 |
| **QP.05.D** Change of pack size / fill volume for the drug product<br>* ***Note****: The type/material, shape and specification of primary packaging component remain unchanged. Otherwise, refer to the applicable subcategory under QP.05.A, QP.05.B or QP.05.C. as applicable.* | | | | | |
| **i.** | Change in the fill volume for sterile drug product | The change is consistent with the approved dosing regimen and treatment duration. | ☐ Conditions met | MIV-1 | 1 - 3, 6 - 8 |
| **ii.** | Change in the fill volume for non-sterile drug product | The change is consistent with the approved dosing regimen and treatment duration. | ☐ Conditions met | MIV-2 Notification | 1 - 3, 8, 9 |

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| **iii.** | Change in the number of primary containers per pack for the drug product | The change only involves the number of primary containers (e.g., vials, ampoules) per pack where the fill volume per container remains unchanged. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |
| **QP.05.E** Change in integral Class C/D medical device for the drug product<br>*** Note:** *For changes to the material, specification, dimensions or shape of an integral Class A or Class B medical device, refer to the applicable subcategory under QP.05.A, QP.05.B or QP.05.C.* | | | | | |
| **i.** | Major Change of an integral Class C/D medical device for the drug product | None | ☐ Conditions met | MIV-1 | 1 - 7, 11 |
| **ii.** | Minor Change to an integral Class C/D medical device for the drug product | The intended use and operating principle remain unchanged. The change does not significantly affect dose delivery or accuracy, compatibility, usability, safety, device performance, or the quality, safety or efficacy of the drug product.<br><br>The proposed device change does not fall under Technical Change category under *GN21: Guidance on Change Notification for Registered Medical Devices.* | ☐ Conditions met | MIV-2 Notification | 1 - 6, 11 |
| **QP.05.F** | Change in co-packaged Class A/B medical device supplied with the drug product | The change does not adversely affect the intended use, dose delivery/accuracy, compatibility, usability, safety, performance, or quality, safety or efficacy of the drug product. | ☐ Conditions met | MIV-2 Notification | 1 - 4, 10 |
| **QP.05.G** | Deletion of an approved primary packaging material, container or pack size for the drug product | The remaining product presentation(s) must be adequate for the approved dosing regimen and treatment duration. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

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| Supporting Data | | | |
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| **No.** | **Supporting data requirement** | **Provided?** | **Remarks (e.g., include justification for not providing the required document)** |
| 1. | Approved and proposed container closure system information presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | Declaration of compliance to the appropriate international standards or pharmacopoeia, as applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | Appropriate data on the proposed packaging (comparative data on permeability, e.g. for $O_2$, $CO_2$ and moisture). Where appropriate, evidence should be provided to demonstrate that no adverse interaction occurs between the drug product and the packaging material, including migration of components from the proposed packaging material into the drug product or loss of drug product components into the packaging material. | ☐ Yes<br>☐ N.A. | |
| 6. | Stability studies as per relevant guidelines and a commitment letter to complete the ongoing stability studies to the approved shelf life, as applicable. 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. | ☐ Yes<br>☐ N.A. | |
| 7. | Process validation protocol and validation report for the manufacturing, sterilisation, and container closure system integrity, as applicable. | ☐ Yes<br>☐ N.A. | |
| 8. | Justification that the proposed pack size/fill volume is consistent with the approved dosing regimen and treatment duration. | ☐ Yes<br>☐ N.A. | |
| 9. | A commitment letter to conduct relevant stability studies of the drug product in accordance with relevant guidelines 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. | ☐ Yes<br>☐ N.A. | |

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| 10. | Justification that the size and accuracy of the device are adequate for the dosing regimen as approved in the product labelling. | ☐ Yes<br>☐ N.A. | |
| 11. | Additional supporting documents as per *GN21: Guidance on Change Notification for Registered Medical Devices*. | ☐ Yes<br>☐ N.A. | |

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# QP.06. Change of shelf life / storage condition / stability protocol of drug product

**QP.06. Change of shelf life / storage condition / stability protocol of drug product**
**Note:**

- This checklist is also applicable to changes to in-use storage condition and period (e.g., following first opening of a multidose container, reconstituted/diluted drug product) and user-convenience storage condition and period (e.g., removal from refrigerated or frozen storage).

**Notification to HSA is not required for**:

- The following changes to stability protocol where the approved shelf life of drug product remains unchanged:
  a. Change of sampling frequency in accordance with relevant ICH guidelines, e.g., adjust sampling frequency to annual time-points after completion of the stability study of primary batches.
  b. Change of time-points beyond the approved shelf life.

**Common Conditions (Must be met for all subcategories)**

- Stability studies must demonstrate compliance with the specification under the storage condition.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.06.A** | Change of storage condition of the drug product with corresponding shelf life and/or in-use period | None | ☐ Conditions met | MIV-1 | 1 - 4 |
| **QP.06.B** Change of shelf life and/or in-use period of the drug product with no change in storage condition | | | | | |
| **i.** | Change of shelf life of the drug product based on extrapolation | The extrapolation should be scientifically justified and supported by available long-term stability data in accordance with the relevant ICH stability guideline. | ☐ Conditions met | MIV-1 | 1 - 4 |

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| **ii.** | Change of shelf life of the drug product with complete real time stability data | Complete real time stability data covering the proposed shelf life/in-use period are available. | ☐ Conditions met | MIV-2 Notification | 1 - 4 |
| **QP.06.C** | Change of the approved stability protocol of the drug product | The change is not due to stability concerns or unexpected manufacturing events and does not involve widening of acceptance criteria or removal of stability-indicating parameters. | ☐ Conditions met | MIV-2 Notification | 1 - 2, 5 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 2. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 3. | For changes to the shelf life or storage conditions of the drug product as packaged for sale, provide the following:<br>a. Results of stability studies as per relevant guidelines, comprising either:<br>• Complete stability data supporting the proposed shelf life; or<br>• Available stability data, together with a scientific justification for the extrapolation in accordance with relevant stability guidelines and a commitment letter to continue the ongoing stability studies up to the proposed shelf life. The product registrant shall report to the Health Sciences Authority of any out-of-specification result (with proposed action). Submission of the data in the form of a finalised report is not required, but the data shall be provided to the Health Sciences Authority upon request.<br><br>b. Where the drug product has approved in-use or user-convenience storage, provide stability data or a scientific justification, based on available stability data, demonstrating that these approved conditions and periods remain supported. | ☐ Yes<br>☐ N.A. | |

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| 4. | For changes to approved in-use and user-convenience storage, complete stability data for at least two batches (preferably production-scale) supporting the proposed condition and duration of use. | ☐ Yes<br>☐ N.A. | |
| 5. | Approved and proposed stability protocols presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |

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# QP.07. Change of composition of drug product

**QP.07. Change of composition of drug product**

**Note:**

- A single product registration shall contain only one drug product formulation. The proposed change must not result in multiple formulations under the same product registration.
- Where the proposed composition change involves the introduction or replacement of a human plasma-derived material supported by a Plasma Master File (PMF), QS.11 is also applicable.
- HSA reserves the right to re-categorise the application to NDA, if deemed appropriate.

**Common Conditions (Must be met for all subcategories)**

- The change in drug product formulation does not involve a change in the type or structure of adjuvant, lipid nanoparticle, liposome, or other delivery-system component. Applicant should consult HSA if such changes are proposed.
- The release and shelf life specifications remain unchanged except for justified product-description/appearance attributes, unless QP.04 is also selected.
- The proposed change must not adversely affect the functional characteristics or performance of the drug product (e.g., biological activities).

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.07.A** | Change in composition of the drug product | None | ☐ Conditions met | MIV-1 | 1 - 9 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed formulation/batch manufacturing formula presented in a comparative table, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s), including CTD P4 for new excipients, as applicable. | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including a risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |

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| 4. | Information on the animal-derived material, including the type of the tissue/fluid, species, source country and supplier, and demonstrate that the manufacturing process is capable of inactivating new adventitious agents, as applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | For new excipients derived from TSE-relevant animals (i.e. cattle, sheep, goat, deer, elk, non-human primates):<br>a. A valid TSE Risk evaluation CEP; or<br>b. Relevant information supporting the TSE risk assessment, including the tissue/fluid collection procedures and measures to prevent cross-contamination, risk factors associated with the route of administration and maximum therapeutic dose of the drug product, and the capacity of the manufacturing process to inactivate and/or remove TSE agents. | ☐ Yes<br>☐ N.A. | |
| 6. | Batch analysis data (in a comparative tabular format) for at least two batches (preferably production scale) of the drug product from the current and proposed drug product formulation. | ☐ Yes<br>☐ N.A. | |
| 7. | Process validation protocol and validation report for the manufacturing, sterilisation, and container closure system integrity, as applicable. | ☐ Yes<br>☐ N.A. | |
| 8. | Stability studies as per relevant guidelines and a commitment letter to complete the ongoing stability studies to 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. | ☐ Yes<br>☐ N.A. | |
| 9. | Comparability study with respect to physico-chemical characterisation, biological activity and impurity profile or a justification for not submitting such a study. | ☐ Yes<br>☐ N.A. | |

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# QP.08. Change of specification / analytical procedure of excipient

**QP.08. Change of specification / analytical procedure of excipient**

**Notification to HSA is not required for:**

- Change in the supplier / manufacturer of an excipient which is not of mammalian or avian origin if the specification of the excipient remains unchanged.

**Common Conditions (Must be met for all subcategories)**

- The drug product formulation, manufacturing process, specifications remain unchanged unless the corresponding QP. checklist(s) is also selected.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.08.A** Change in specification of excipient, including tests, acceptance criteria and corresponding analytical procedures. | | | | | |
| **i.** | Major change in the specification for excipient | None (This category also applies where one or more of the conditions specified for categories A.ii to A.iii are not fulfilled) | ☐ Conditions met | MIV-1 | 1 - 7 |
| **ii.** | Addition or replacement of a specification for excipient | The new analytical procedure does not involve a novel non-standard technique or a standard technique used in a novel manner, and is not a biological, immunological or immunochemical procedure. | ☐ Conditions met | MIV-2 Notification | 1 - 7 |
| **iii.** | Minor change in the specification for excipient | The proposed change shall be limited to the tightening of an acceptance criterion, deletion of an obsolete or non-significant test, or alignment with a recognised pharmacopoeial monograph. For compendial excipients, the change shall not involve deletion or widening of a critical in-house test. | ☐ Conditions met | MIV-2 D&T | 1 - 7 |
| **QP.08.B** Change in analytical procedure for excipient | | | | | |

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| ** **Note:** Including consequential updates to analytical procedure reference codes in the specification. For other specification changes for excipient, refer to QP.08.A.* | | | | | |
| **i.** | Major change in the analytical procedure for excipient | The excipient specification remains unchanged. Validation/verification demonstrates that the proposed procedure is suitable for its intended purpose. | ☐ Conditions met | MIV-2 Notification | 2 - 7 |
| **ii.** | Minor change in the analytical procedure for excipient | The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). Results of analytical procedure validation show that the new analytical procedure is at least equivalent to the current procedure. | ☐ Conditions met | MIV-2 D&T | 2 - 7 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed specifications for excipient presented in a comparative tabular format, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including a risk assessment where applicable. Where a specification parameter is proposed for deletion, a risk assessment demonstrating that the parameter is non-significant, obsolete, or no longer necessary shall be submitted. | ☐ Yes<br>☐ N.A. | |
| 4. | Batch analysis data for at least two batches of the excipient. | ☐ Yes<br>☐ N.A. | |
| 5. | Description of the analytical procedures, including validation data where applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | Comparative analytical results demonstrating that the proposed analytical procedure is equivalent to the approved analytical procedure, as applicable. | ☐ Yes<br>☐ N.A. | |

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| 7. | Relevant recognised pharmacopoeial monograph, as applicable. | ☐ Yes<br>☐ N.A. | |

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# QP.09. Change in animal-derived material used in drug product

**QP.09. Change in animal-derived material used in drug product**
**Note:**

- This checklist is applicable only to changes in the source and/or species of an animal-derived material that do not result in a change to the drug product composition. For changes that result in a change to the qualitative and/or quantitative composition of drug product, refer to QP.07.

**Notification to HSA is not required for:**

- Change in the supplier / manufacturer of a material which is not of mammalian or avian origin if the specification of the material remains unchanged.

**Common Conditions (Must be met for all subcategories)**

- The excipient specification remains unchanged unless QP.08 is also selected.
- Any viral safety or TSE risks arising from changes to animal-derived materials should be appropriately assessed and demonstrated not to adversely affect the quality, safety or efficacy of the drug product.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.09.A** | Introduction of, or change to, a TSE-relevant material not covered by a valid TSE CEP | The proposed material is TSE-relevant and is not covered by a valid TSE CEP. | ☐ Conditions met | MIV-2 Notification | 1 - 5 |
| **QP.09.B** | Introduction of, or change to, a TSE-relevant material covered by a valid TSE CEP | The proposed material is TSE-relevant and is covered by a valid TSE CEP applicable to the proposed material and its intended use. | ☐ Conditions met | MIV-2 D&T | 1 - 4, 6 |
| **QP.09.C** | Introduction of, or change to a non-TSE-relevant animal-derived material | The proposed material is derived from non TSE-relevant animals (e.g., porcine, avian, etc.). | ☐ Conditions met | MIV-2 D&T | 1 - 3, 7 |
| **QP.09.D** | Change from an animal-derived material to a non animal-derived material | The proposed material must not be animal-derived (e.g., vegetable or synthetic) and must not introduce any new quality, safety, viral risks. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

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| Supporting Data | | | |
|---|---|---|---|
| **No.** | **Supporting data requirement** | **Provided?** | **Remarks (e.g., include justification for not providing the required document)** |
| 1. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 2. | Justification for the proposed change, including risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 3. | Batch analysis data for at least two batches of the excipient. | ☐ Yes<br>☐ N.A. | |
| 4. | Information on the animal-derived material, including the type of the tissue/fluid, species, source country and supplier, as applicable. | ☐ Yes<br>☐ N.A. | |
| 5. | Relevant information supporting the TSE risk assessment, including the tissue/fluid collection procedures and measures to prevent cross-contamination, risk factors associated with the route of administration and maximum therapeutic dose of the drug product, and the capacity of the manufacturing process to inactivate and/or remove TSE agents. | ☐ Yes<br>☐ N.A. | |
| 6. | A valid TSE Risk Evaluation CEP. | ☐ Yes<br>☐ N.A. | |
| 7. | Information on the type of the tissue/fluid and a declaration that the manufacturing process is capable of inactivating new adventitious agents. | ☐ Yes<br>☐ N.A. | |

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# QP.10. Change of solvent / diluent supplied with the drug product

**QP.10. Change of solvent / diluent supplied with the drug product**
**Note:**

- This checklist is only applicable to addition, replacement or deletion of a solvent/diluent supplied with the drug product. Changes to an approved solvent/diluent (e.g., manufacturing site, manufacturing process, specification, container closure system, or shelf life) should be submitted under the relevant QP checklist(s), as applicable.
- A single product registration shall contain only one drug product formulation. The proposed change must not result in multiple drug product formulations under the same product registration, including presentations supplied with and without a solvent/diluent, or presentations supplied with different solvents/diluents. Otherwise, a new drug application should be submitted.

**Common Conditions (Must be met for all subcategories)**

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

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QP.10.A** | Addition or replacement of solvent / diluent supplied with the drug product | None | ☐ Conditions met | MIV-1 | 1 - 6 |
| **QP.10.B** | Deletion of solvent / diluent supplied with the drug product | None | ☐ Conditions met | MIV-2 Notification | 1 - 3 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed solvent/diluent composition and pack configuration presented in a comparative table, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 2. | Relevant revised CTD section(s). For new solvent/diluent, complete CTD P sections (3.2.P.1 to 3.2.P.8) for the solvent/diluent, including reconstitution stability data, should be provided. | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including a risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |

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| 4. | Batch numbering system (where applicable). | ☐ Yes<br>☐ N.A. | |
| 5. | Valid evidence of GMP compliance for the proposed manufacturing facility in accordance with the *Guidance on Therapeutic Product Registration in Singapore*. For overseas manufacturers, application form for GMP Evidence Evaluation or for an Overseas GMP Audit, as applicable. | ☐ Yes<br>☐ N.A. | |
| 6. | 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). | ☐ Yes<br>☐ N.A. | |

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# Quality Regulatory Tools - QR

# QR.01. Post-approval change management protocol (PACMP)

**QR.01. Post-approval change management protocol (PACMP)**
**Note:**
- This checklist applies to both the drug substance and drug product.

**Common Conditions (Must be met for all subcategories)**
- The PACMP should prospectively define the proposed change(s), conditions, studies, acceptance criteria and implementation/reporting approach.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QR.01.A** | Introduction of a PACMP | The protocol provides sufficient scientific understanding and a predefined strategy for implementation and reporting of the proposed post-approval change(s). | ☐ Conditions met | MIV-1 | 1 - 3 |
| **QR.01.B** Change to an approved PACMP | | | | | |
| **i.** | Major change to an approved PACMP | The proposed amendment is clearly identified and scientifically justified. Any impact on the agreed implementation/reporting category is addressed. | ☐ Conditions met | MIV-1 | 1, 4 |
| **ii.** | Minor change to an approved PACMP | The changes do not change the overall strategy defined in the protocol and are not broader than the currently approved protocol. | ☐ Conditions met | MIV-2 Notification | 1, 4 - 5 |
| **QR.01.C** Implementation of change foreseen in an approved PACMP<br>** **Note:** In case the acceptance criteria and/or other conditions in the approved protocol are not met, the change cannot be implemented under this category and should instead be submitted as variation of the applicable category without PACMP.* | | | | | |

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| **i.** | Implementation in accordance with an approved PACMP via MIV-2 Notification | All acceptance criteria and conditions specified in the approved PACMP have been fulfilled. | ☐ Conditions met | MIV-2 Notification | 1, 6 -7 |
| **ii.** | Implementation in accordance with an approved PACMP via MIV-2 Do-and-Tell | All acceptance criteria and conditions specified in the approved PACMP have been fulfilled. | ☐ Conditions met | MIV-2 D&T | 1, 6 -7 |
| **QR.01.D** | Deletion of an approved PACMP | The deletion is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the PACMP and does not have any effect on the already approved information in the dossier. | ☐ Conditions met | MIV-2 D&T | 1, 8 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Relevant revised CTD section(s), as applicable. | ☐ Yes<br>☐ N.A. | |
| 2. | PACMP describing the scope, proposed change(s), conditions, studies, acceptance criteria and proposed implementation/reporting category. | ☐ Yes<br>☐ N.A. | |
| 3. | Relevant development studies, validation data and risk assessment supporting the PACMP. | ☐ Yes<br>☐ N.A. | |
| 4. | Amendment of the PACMP with justification for the proposed changes, including a risk assessment. | ☐ Yes<br>☐ N.A. | |
| 5. | Declaration that the changes do not change the overall strategy defined in the protocol and are not broader than the currently approved protocol. | ☐ Yes<br>☐ N.A. | |
| 6. | Results of the studies performed in accordance with the approved PACMP. | ☐ Yes<br>☐ N.A. | |
| 7. | Declaration that the change is in accordance with the approved PACMP and that the study results meet the acceptance criteria specified in the protocol. | ☐ Yes<br>☐ N.A. | |

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| 8. | Justification for the proposed deletion, and a declaration that the deletion is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the PACMP and does not have any effect on the already approved information in the dossier. | ☐ Yes<br>☐ N.A. | |

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# QR.02. Design space / method operable design region (MODR)

**QR.02. Design space / method operable design region (MODR)**
**Note:**
- This checklist applies to both the drug substance and drug product.

**Common Conditions (Must be met for all subcategories)**
- The release/shelf life specifications remain unchanged unless the corresponding QS.04 or QP.04 checklist(s) is also selected.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **QR.02.A** | New or expansion of design space in the manufacturing process, including the resulting in-process controls and/or analytical procedures | The design space comprises a multidimensional combination and interaction of relevant input variables and process parameters. | ☐ Conditions met | MIV-1 | 1 - 5 |
| **QR.02.B** | New or expansion of MODR for analytical procedure | The MODR is supported by appropriate analytical procedure development, validation and robustness data. | ☐ Conditions met | MIV-1 | 1 - 4 |
| **QR.02.C** | Reduction of an approved design space or MODR | The change is limited to reduce or limit the range of parameters used to define the design space or MODR and is not due to critical deficiencies in manufacturing or quality systems. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved and proposed design space/MODR information presented in a comparative table, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |

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|---|---|---|---|
| 2. | Relevant revised CTD section(s). | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including an appropriate risk assessment where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | The design space/MODR has been developed in accordance with the relevant international scientific guidelines. Results from development studies (including risk assessment and multivariate studies, as appropriate) should demonstrate a systematic understanding of the relationship between input variables and critical quality attributes and/or analytical procedure performance. | ☐ Yes<br>☐ N.A. | |
| 5. | Results of at least six months of real time stability studies and a commitment letter to complete the ongoing stability studies to the approved or proposed retest period or shelf life, as applicable. 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. | ☐ Yes<br>☐ N.A. | |

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# Product Labelling Changes - LB

# LB.01. Change of product labelling

**LB.01. Change of product labelling**

**For outer carton and inner/blister label, notification to HSA is not required** for the following labelling changes, provided that the revised label continues to meet the current Appendix 7 requirements:

- Editorial or layout changes without any change to label content or colour scheme, including:
  - Change in text font type or size (e.g., Calibri 11 to Arial 10)
  - Change in placement of text, batch number, manufacturing date and expiry date on label (e.g., shift from front panel to side flap)
  - Change in format of manufacturing or expiry date (e.g., from MMYY to DDMMYY)
- Content changes:
  - Deletion of information that is no longer a requirement in accordance with Appendix 7 (e.g., manufacturing date, name and address of either manufacturer or product owner or registrant)
  - Change of registration number, licence number or distributor information which are relevant only to a foreign country
  - Change of non-English text as long as the information is consistent with the approved English text
  - Change of machine-readable codes (e.g., barcode, QR code) for logistic purposes or e-labelling
  - Change of anti-counterfeit features
  - Addition/Deletion of poison label
  - Addition/Deletion of trademark
- Change in the dimensions of the outer carton or inner label, with no change in the label artwork or number of units per strip / pack size / primary packaging.

**Common Conditions (Must be met for all subcategories)**

- The proposed labelling change should be limited to the scope described in the applicable subcategory.
- Change is not within the scope of an MAV.
- Administrative/editorial changes should not alter the meaning of approved information or adversely affect quality, safety or efficacy.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|

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|---|---|---|---|---|---|
| **LB.01.A** | Change to the content of product labelling | None | ☐ Conditions met | MIV-1 | 1 - 4 |
| **LB.01.B** | Minor change to the content of product labelling | Applies to the following changes, provided that they do not fall under LB.01.C:<br>• Addition or amendment of warnings, precautions, contraindications, drug interactions, overdose and/or adverse events that results in strengthening of safety information or restriction of use.<br>• Addition or amendment of information on "Instructions for Use" for drug products with special delivery system/device (e.g. transdermal patches, inhalers, prefilled syringes etc).<br>• Tightening of product's target population.<br>• Deletion of indication.<br>• Alignment of a generic drug product labelling with that of the Singapore Reference Product.<br>• Minor change of content of product labelling that does not have any impact on the product's safety, efficacy and quality. | ☐ Conditions met | MIV-2 Notification | 1 - 3 |
| **LB.01.C** | Safety-related labelling update as requested by HSA | The change is limited to implementation of the HSA-requested safety information and any consequential editorial amendments. | ☐ Conditions met | MIV-2 Notification | 1 - 3 |
| **LB.01.D** | Administrative update of product labelling | The change is limited to the following administrative changes:<br>• Rearrangement / re-formatting of text without any change in information in PI/PIL. | ☐ Conditions met | MIV-2 D&T | 1 - 3 |

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| | | • Changes to non-English text (e.g., Chinese) in PI/PIL as long as the information is consistent with the approved English text.<br>• Addition / deletion / change of artwork (e.g., pantone colour), images and logos.<br>• Amendment of typographical errors.<br>• Alignment of product registrant, manufacturer, batch release site or product owner information in the product labelling with the approved registration record. | | | |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved product labelling. | ☐ Yes<br>☐ N.A. | |
| 2. | Proposed product labelling in pristine and annotated versions, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |
| 3. | Justification for the proposed change, including supporting clinical or administrative documents and relevant correspondence with HSA, where applicable. | ☐ Yes<br>☐ N.A. | |
| 4. | Approved PI/SmPC/PIL from an approved reference agency or the country of origin containing the proposed changes, where applicable. | ☐ Yes<br>☐ N.A. | |

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# LB.02. Change to product labelling consequential to AD/QS/QP/QR change

**LB.02. Change to product labelling consequential to AD/QS/QP/QR change**

**Common Conditions (Must be met for all subcategories)**

- This checklist is applicable only to labelling changes consequential to a corresponding AD/QS/QP/QR change and must be submitted together with that change. Any additional labelling change should be assessed separately under LB.01.

| Code | Description of Change | Category-specific Conditions | Applicant Declaration (I confirm all applicable conditions are met) | Reporting Category | Supporting Data |
|---|---|---|---|---|---|
| **LB.02** | Change to product labelling consequential to AD/QS/QP/QR change | None | ☐ Conditions met | Same reporting category as the corresponding AD/QS/QP/QR change | 1 - 2 |

**Supporting Data**

| No. | Supporting data requirement | Provided? | Remarks (e.g., include justification for not providing the required document) |
|---|---|---|---|
| 1. | Approved product labelling. | ☐ Yes<br>☐ N.A. | |
| 2. | Proposed product labelling in both pristine and annotated versions, with all changes clearly highlighted. | ☐ Yes<br>☐ N.A. | |

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