# VARIATION INVOLVING DRUG SUBSTANCE

TRAINING COURSE ON MALAYSIA VARIATION GUIDELINE

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# Type of Drug Substance (DS) Variations

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|---|---|
| **MaV-3** | Change and/or addition of alternative manufacturer/site of DS (where CEP is not available) |
| **MaV-4** | Major change of manufacturing process of the DS (where CEP is not available) |
| **MiV-PA5** | Change and/or addition of alternative manufacturer/site of drug substance (where CEP is available) |
| **MiV-PA6** | Change of batch size of drug substance (where CEP is not available) |
| **MiV-PA7** | Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where CEP is not available] |
| **MiV-PA8** | Minor change of manufacturing process of the DS (where CEP is not available] |
| **MiV-PA11** | Change of shelf-life or retest period for DS |
| **MiV-PA12** | Change of storage condition for DS |
| **MiV-PA13** | Revision of CEP of DS |

| MaV-3 | Change and/or addition of alternative manufacturer/site of drug substance (where CEP is not available) |
|---|---|
| C | 1. Specifications of DS remain unchanged.<br>2. For Change and/or addition of alternative manufacturer/site of drug substance where CEP is available, please refer to MiV-PA5. |
| D | 1. Either one of the following options is applicable;<br>**a) Option 1 (DMF)**<br>i. DMF (Open and Closed part)<br>ii. GMP certificate<br>iii. Letter of Access.<br>**OR**<br>**b) Option 2 (Full ACTD)**<br>i. Full details of Part II S ACTD<br>ii.GMP certificate |
| | 2. Comparative tabulated format of the currently registered and revised DS manufacture information (where applicable).<br>3. Certificate of analysis and batch analysis data (in a comparative tabular format) for at least two pilot batches of the DS<br>4. A letter of commitment – Stability Studies for Product<br>5. TSE certificate of suitability or, other documentary evidence |

| MaV-4 | Major change of manufacturing process of the drug substance (where CEP) is not available) |
|---|---|
| C | 1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies.<br>2. The synthetic route is different. Refer to MiV-PA8 if the synthetic route remains unchanged.<br>3. Does not use any materials of human/animal origin for which assessment is required of viral safety.<br>4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged.<br>5. Specifications and stability performance of drug substance remain unchanged.<br>6. Refer to MiV-PA13 if this change resulted in revision of CEP. |

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| D | 1. Either one of the following options is applicable;<br>**a) Option 1 (DMF)** **OR** **b) Option 2 (Full ACTD)**<br>i. DMF (Open and Closed part) i. Full details of Part II S ACTD<br>ii. GMP certificate ii.GMP certificate<br>iii. Letter of Access.<br><br>2. Comparative tabulated format of manufacturing process of the DS<br><br>3. Certificate of analysis and batch analysis data (in a comparative tabular format) for at least two pilot batches of the DS<br><br>4. A letter of commitment - stability studies for the drug product<br><br>5. TSE certificate of suitability (where applicable) |

# QUALIFICATION OF IMPURITIES

## Definition:

- Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

# QUALIFICATION OF IMPURITIES (cont)

## When?

**Table1: Thresholds**

| Maximum Daily Dose | Qualification Threshold |
|---|---|
| ≤ 2g/day | 0.15% or 1.0 mg per day intake (whichever is lower) |
| > 2g/day | 0.05% |

## How?

- tested in safety and/or clinical studies (New Drug Substance) (ICH Q3A)
- limit specified for an identified impurity in an officially recognized pharmacopoeia (WHO)
- comparing the results of tests for impurities found in the existing API with those observed in an innovator product (WHO)

| MiV-PA5 | Change and/or addition of alternative manufacturer/site of drug substance (where CEP is available) |
|---|---|
| C | 1. Specifications of drug substances remain unchanged.<br>2. For change and/or addition of alternative manufacturer/site of drug substance where CEP is not available, please refer to MaV-3 |
| D | 1. A valid CEP for the DS, latest version, with all annexes<br>2. A letter of commitment – stability studies drug product<br>3. Certificate of analysis and batch analysis data (in a comparative tabular format).<br>4. Stability Studies for 2 pilot batches - If the re-test period is not stated in the CEP. |

| MiV-PA6 | Change of batch size of drug substance (where CEP is not available) |
|---|---|
| C | 1. The change does not affect the reproducibility of the process.<br>2. Specifications of drug substance remain unchanged.<br><br>Refer to MiV-PA13 if this change resulted in revision of CEP. |
| D | 1. A letter of declaration from marketing authorized holder that the specifications of drug substance have not changed and the reproducibility of the process has not been affected<br><br>2. Certificate of analysis and comparative batch analysis data with specification and results (in a comparative tabulated format) on a minimum of one production or pilot batch manufactured to both the currently approved and proposed batch sizes. Batch data on the next two full production batches should be available on request or reported if outside specification (with proposed action).<br><br>3. Amended relevant ACTD Section S (where applicable). |

| MiV-PA7 | Change of in-process controls applied during the manufacture of the drug substance (including tightening and addition of new in-process test and where CEP is not available) |
|---|---|
| C | 1. In-process limits are tightened or addition of new tests.<br>2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.<br>3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.<br>4. Refer to MiV-PA13 if this change resulted in revision of CEP. |
| D | 1. A description of the analytical method and summary of validation data must be provided for all new analytical methods (where applicable).<br>2. Comparative tabulated format of the proposed and current in-process controls and the relevant changes.<br>3. Comparative batch analysis data of two production batches of the drug substance for all tests in the proposed specification (where applicable). |

| MiV-PA8 | Minor change of manufacturing process of the drug substance (where CEP is not available) |
|---|---|
| C | 1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies.<br>2. The synthetic route remains the same (for example, intermediates remain the same). Refer to MaV-4 if the synthetic route is different.<br>3. Manufacturing process of drug substance does not use any materials of human/animal origin for which assessment is required of viral safety.<br>4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged.<br>5. Specifications and stability performance of drug substance remain unchanged.<br>6. Refer to MiV-PA13 if this change resulted in revision of CEP. |

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| D | 1. DMF, or relevant updated drug substance (DS) section (ACTD Part II S)<br><br>2. Comparative tabulated format of the currently approved and new processes with changes highlighted (where available).<br><br>3. For sterile drug substance, process validation report (where applicable).<br><br>4. A declaration from product registration holder or DMF holder where applicable that there is no change in qualitative and quantitative impurity profile or in physicochemical properties that the synthesis route remains the same and that the specifications of active substance or intermediate are unchanged.<br><br>5. Certificate of analysis for two batches of the drug substance.<br><br>6. A declaration - stability studies of the drug product |

| MiV-PA11 | Change of shelf-life or re-test period for drug substance |
| --- | --- |
| C | 1. The stability studies must show compliance with specification.<br>2. No change in storage condition.<br>3. Refer to MiV-PA13 if this change resulted in revision of CEP. |
| D | 1. Specifications of the drug substance.<br>2. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested shelf-life or retest period. |

| MiV-PA12 | Change of storage condition for drug substance |
| --- | --- |
| C | 1. The stability studies must show compliance with specification.<br>2. No change in shelf-life/retest period.<br>3. Refer to MiV-PA13 if this change resulted in revision of CEP. |
| D | 1. Specifications of the drug substance.<br>2. Stability data of the drug substance should be presented on at least two pilot |

| MiV-PA13 | Revision of CEP of DS |
|---|---|
| C | None |
| D | 1. A valid CEP for the drug substance, latest version, with all annexes issued by EDQM.<br>2. If this change is due to drug substance specification change, a declaration from the applicant that the relevant stability studies of the drug product in accordance with ASEAN Guideline On Stability Study Of Drug Product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action); (where applicable).<br>3. Specifications of drug substance (where applicable).<br>4. Certificate of analysis and results of batch analysis from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP<br>5. Additional data to address any relevant parameter(s) not addressed in the CEP such as stability data (S7), if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc),<br><br>* If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted. |

# THANK YOU