



MALAYSIAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS

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**NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA**

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GUIDELINE HISTORY

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1	Original publication	April 2013
2	<p>1. Updates in line with ASEAN Variation Guideline for Pharmaceutical Products (Revision 1 & 2) and inclusion of country specific variation types & requirements as follows:</p> <p>a) Reclassification of variation types from MaV to MiV-PA</p> <ul style="list-style-type: none"> • Addition/Replacement of primary packaging site for non-sterile drug product <p>b) Reclassification of variation types from MiV-PA to MiV-N</p> <ul style="list-style-type: none"> • Change of outer carton pack sizes of drug product • Change in any part of the primary packaging material not in contact with the drug product • Addition/Replacement of secondary packaging site for drug product • Replacement of the company or manufacturer responsible for batch release <p>c) Addition of new variations types</p> <ul style="list-style-type: none"> • Administrative/Editorial changes to drug product labelling • Addition/Replacement of manufacturer/site of intermediate/starting material of drug substance where European Pharmacopoeial Certificate of Suitability (CEP) is not available] • Addition/Replacement of primary packaging site for non-sterile drug product • Addition/Replacement of the company/site responsible for quality control (QC) testing • Change of drug substance submission option • Change in the primary/secondary packaging material (not in contact with the drug product) • Change of name and/or address of the company/site responsible for quality control (QC) testing • Minor change in the manufacturing process of immediate-release solid oral dosage forms, semi solids or liquid dosage forms • Update of Bioequivalence (BE) Data/Status • Update of Certificate of Pharmaceutical Product (CPP) • Update of Good Manufacturing Practice (GMP) Certificate • Update of Halal Certificate or addition/deletion of Halal logo • Update of information following approval of Additional Indication • Update of approval for products exempted from Zone IV B stability data requirements • Update of stability data report for drug product (no changes to shelf life or storage condition) • Update of process validation report from Option 2 to Option 1 (conditional registration/fulfilling commitment) for local manufacturer • Update of Endorsement Letter (EL)/Acknowledgment Receipt (AR) from Medical Device Authority for drug-device combination 	July 2022

	<p>d) Amendment to existing variation types</p> <ul style="list-style-type: none">• Change of colouring agent/flavouring agent/capsule shell colour of the drug product• Change of release and/or shelf life/re-test specifications and/or test procedure of the drug product and/or drug substance and/or excipient following the updates in the compendium• Change in the primary/secondary packaging material (not in contact with the drug product) <p>e) Renumbering of variation types</p> <p>2. Revision of timelines</p> <p>3. Amendments to phrasing and layout</p> <p>4. Changes in the scope of Change of the manufacturing site (COS) of drug product applications</p> <p>5. Inclusion of Updated List of Minor Variation-Prior Approval (MiV-PA*) Changes Allowed to be Processed via the “Tell & Do” Procedure for Pharmaceutical Products</p>	
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1. INTRODUCTION

Throughout the life of a pharmaceutical product, the product registration holder (PRH) is responsible for the quality, safety and efficacy (QSE) of a pharmaceutical product that is placed in the market. The PRH is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the pharmaceutical product to be manufactured and checked by means of generally accepted scientific methods. Such amendments, regardless of their nature, are referred to as variations and have to be approved by National Pharmaceutical Regulatory Agency (NPRA).

This guidance document is adopted from the 31st ACCSQ-PPWG's ASEAN Variation Guideline for Pharmaceutical Products (Revision 2), incorporating Malaysia's country specific requirements and policies serving as a guide for establishing national requirements for the regulation of post-approval changes. This document shall be read in conjunction with the Drug Registration Guidance Document (DRGD), directives and circulars issued by NPRA as well as all relevant/related guidelines.

Updating of this guideline will be done on a periodic basis as and when required.

2. SCOPE OF THIS GUIDELINE

This Malaysian Variation Guideline concerns the variation applications submitted by the PRH for pharmaceutical products for human use only. It is intended to provide supportive information on the requirements for submission of a variation application to implement a change to a pharmaceutical product. There are separate guidelines for biological products, traditional medicines and health supplement products.

3. DEFINITION

Variation applications are categorized into major variation, minor variation (prior approval) and minor variation (notification).

3.1 Major variation (MaV)

Variation to a registered pharmaceutical product that may affect significantly and/or directly the aspects of quality, safety and efficacy and it does not fall within the definition of minor variation and new registration.

3.2 Minor Variation-Prior Approval (MiV-PA) & Notification (MiV-N)

Variation to a registered pharmaceutical product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of quality, safety and efficacy.

4. PROCEDURES AND TIMELINE

All applications should be submitted via the online QUEST system.

4.1 Major Variation (MaV) and Minor Variation–Prior Approval (MiV-PA)

Type of variation	MaV	MiV-PA
Procedure	<p>Prior approval</p> <p>If the application fulfils the requirements as per described, NPRA shall approve the proposed change.</p>	

4.1.1 Single variation application

For submissions that involve only 1 variation type. (e.g. one MaV or one MiV-PA)

Type of variation	MaV	MiV-PA
Correspondence or Approval	<p>First correspondence or approval shall be issued to PRH within 60 working days.</p> <p>Subsequent correspondences which fulfil the requirements will be granted approval within 30 working days.</p> <p>After the third correspondence, the application may be rejected if it still does not fulfil requirements.</p>	<p>First correspondence or approval shall be issued to PRH within 45 working days.</p> <p>Subsequent correspondences which fulfil the requirements will be granted approval within 20 working days.</p> <p>After the third correspondence, the application may be rejected if it still does not fulfil requirements.</p>
Timeline for PRH to reply	<p>Within 30 working days failing which application will be rejected.</p>	<p>Within 20 working days failing which application will be rejected.</p>

Note: For change of manufacturing site (COS) refer to 4.1.4

4.1.2 Grouping of variations

For submissions that involve:

- same variation type (e.g. multiple MaVs or multiple MiV-PAs)
- combination of different variation types (e.g. MaV and MiV-PA)

MaV & MiV-PA changes should be grouped together as one application when these are consequential changes.

The PRH may also group several minor (MiV-PA and/or MiV-N) including/excluding major variations (MaV) in a single submission. It must be noted that where a group of variations consist of different types of variations, it will be handled according to the 'highest' variation type. For example, a group consisting of MaV and MiV-PA will be handled as a major variation application.

Type of groupings	Including MaV	Excluding MaV
Correspondence or Approval	<p>First correspondence or approval shall be issued to PRH within 100 working days.</p> <p>Subsequent correspondences which fulfil the requirements will be granted approval within 45 working days.</p> <p>After the third correspondence, the application may be rejected if it still does not fulfil requirements.</p>	<p>First correspondence or approval shall be issued to PRH within 80 working days.</p> <p>Subsequent correspondences which fulfil the requirements will be granted approval within 30 working days.</p> <p>After the third correspondence, the application may be rejected if it still does not fulfil requirements.</p>
Timeline for PRH to reply	Within 60 working days failing which application will be rejected.	Within 45 workings days failing which application will be rejected.

4.1.3 Minor Variation–Prior Approval* via “Tell & Do” Procedure

Type of variation	MiV-PA*
Procedure	<p>“Tell & Do”</p> <p>If the application fulfils the requirements as per described, NPRA shall approve the proposed change.</p> <p><i>Changes can be implemented immediately after submission</i></p>

1. The changes may be implemented without prior approval from NPRA. PRH can continue to make changes to the product after the variation application has been submitted for regulatory approval by NPRA. This is in order to facilitate and expedite the implementation of the changes by the PRH.
2. The PRH has the flexibility to either implement the changes immediately after submission or within 6 months from the date that the variation is approved and updated in the QUEST system.
3. Certain MiV-PA changes are allowed to be processed via this procedure without any change to its original category of application, fees & timeline of evaluation. Please refer to Appendix A for the list of changes allowed via this procedure.
4. Changes may be submitted alone or together with other MaV, MiV-PA or MiV-N changes, provided that the “Tell & Do” changes are implemented only after submission of the application.
5. Timeline for NPRA to evaluate the variation application & timeline for PRH to reply will depend on the type of submission (single or grouping of variations).
6. All allowable changes via this procedure will be labeled with the asterisk* symbol in the QUEST system.
7. It should be highlighted that a “Tell & Do” variation may in specific circumstances be rejected with the consequence that the PRH must immediately cease to apply already implemented variations concerned. The PRH is responsible for:
 - withdrawing all changes that have been made to the product.
 - complying with the recall procedures as set out in the Guideline on Good Distribution Practice (GDP) for batches that have been marketed/manufactured with the proposed change.

4.1.4 Change of the manufacturing site (COS) of drug product (MaV-5)

Type of variation	MaV-5
Procedure*	<p>Once submitted, the application shall undergo an initial evaluation (screening process), to ensure that the submitted application is complete with the required data/information.</p> <p>Further evaluation shall be done after confirmation of payment.</p>
Timeline for NPRA to evaluate the variation application	<p>Maximum review period: 120 working days</p> <p>If correspondence is required, it shall be issued to PRH within the said timeline.</p> <p>After the third correspondence, the application may be rejected if it still does not fulfil requirements.</p>
Approval/Rejection	<p>Once NPRA deems the application is complete, the outcome of the application shall be decided by the Authority within 60 working days.</p>

* Refer to MaV-5 for more procedural information on COS in crisis situation (Type V) applications

All supporting documents are required to be submitted in accordance with the specified conditions for each type of COS (refer to MaV-5).

Application for COS will be rejected if the PRH failed to submit required data within **6 months** from the first correspondence date.

4.2 Minor Variation – Notification (MiV-N)

Type of variation	MiV-N
Procedure	<p>“Do & Tell”</p> <p>If the notification fulfils the requirements as per described, PRH must notify NPRA. NPRA shall acknowledge the valid notification.</p>
Timeline for NPRA to acknowledge the variation notification	<p>Within 30 working days following receipt of a notification. <i>(applicable for single or grouping of MiV-N)</i></p>
Reporting period	<p>Submit the changes to NPRA within 12 months following implementation of the specified changes.</p>
Correspondence	<p>Correspondences may be issued if deemed necessary.</p>

For convenience, PRHs may group several MiV-N changes in a single submission.

Generally, the evaluation of MiV-N applications is one-off. If queries are raised on the completeness of the application, the stop clock will apply, and the time is to be excluded from the set working days timeline.

A MiV-N application may be rejected in specific circumstances with the consequence that the PRH must cease to apply the already implemented changes.

4.3 Summary of implementation timelines

Type of variation	Implementation of the variation
MaV	<p>Within 6 months from the date the variation is approved and updated in the QUEST system**</p>
MiV-PA	
MiV-PA* “Tell & Do”	<p>Changes can be implemented immediately after submission or within 6 months from the date that the variation is approved and updated in the QUEST system**</p>
MiV-N “Do & Tell”	<p>Up to 12 months prior to the date of variation submission**</p>

** The manufacturing date (as printed on the label of a drug product) will serve as the measure to monitor the implementation of the variation within the allowable timelines.

4.4 Additional notes

- 4.4.1 NPRA reserves the right to re-categorize the application type, where deemed appropriate. Re-categorization may require the PRH to withdraw the original application and resubmit a new application according to the correct category.
- 4.4.2 Specific conditions (C) and documents to be submitted (D) are needed to support the variation application. Different types of changes have different conditions and requirements that need to be fulfilled. These are outlined for each variation type.
- 4.4.3 All PRHs are advised to attach a declaration letter of the intended variation application (attached under the Other Supporting Documents in the online QUEST system). The letter shall include the following:
- Variation category
 - Brief description of the variation with justification
 - Proposed changes affecting the dossier should be clearly outlined (i.e. tabulated format/ highlighted within the dossier)
 - Approvals from the regulatory agency of the country of origin/reference agencies (if any)
 - Declaration that there is no change except for the proposed change
 - Declaration that all of the conditions have been fulfilled based on the variation category
- 4.4.4 Variation application shall be submitted along with a declaration letter (attached under Other Supporting Documents in the online QUEST system) which is undersigned by the PRH that declares:
- The change will not adversely affect the quality, safety and efficacy of the product.
 - All conditions for the variation concerned are fulfilled based on the best fit category.
 - The required supporting documents as specified for the variation have been submitted.
 - The proposed change has been checked in reference to the approved data in the system.
- 4.4.5 PRHs are strongly encouraged to submit variation applications for multiple strengths of the same product at the same time.
- 4.4.6 Product labelling refers to blister/strips, immediate label and outer carton label. Submission of revised product labels, package insert and patient information leaflet are subject to current regulatory requirements as per latest DRGD, Directives and Circulars from NPRA.
- 4.4.7 Compendium refers to British Pharmacopeia (BP), European Pharmacopeia (EP), Japan Pharmacopoeia (JP) and United States Pharmacopeia (USP).
- 4.4.8 NPRA reserves the right to request for additional information, when deemed necessary or to define conditions not specifically described in this document in order to allow for adequate assessment of the quality, safety and efficacy of a pharmaceutical product. NPRA also reserves the right to reject the application when the submission is incomplete.
- 4.4.9 For variations that require generation of stability data on the drug substances or drug product, the stability studies required (including commitment batches) should be continued to cover the currently accepted retest or shelf life period. NPRA should be informed as soon as possible if any problems occur with the stability of drug substances or drug product during storage e.g. if found to be out-of or potentially out-of-specifications.

- 4.5.0 Drug Master File (DMF) holder should inform associated drug product manufacturers of relevant changes so that the drug product manufacturer can consider the implications of the changes for its own product and also determine whether a subsequent drug product variation is required. Since the drug product manufacturer can best determine the significance of a drug substance related change to its product, therefore, DMF holder/drug substance manufacturers are encouraged to inform all changes to their associated drug product manufacturers.
- 4.5.1 It remains the responsibility of the PRH to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product.
- 4.5.2 The list of variations outlined in this guideline is not exhaustive and will be amended from time to time as and when the need arises. Any variations not yet listed in this guideline should be justified and decided by NPRA. Appropriate reference can be made to:
- i. ASEAN Variation Guideline for Pharmaceutical Products
 - ii. European Medicine Agency Variation Guideline
 - iii. SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
 - iv. SUPAC-MR: Modified-release Solid, Oral Dosage Forms, Scale-Up and Post approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation
 - v. WHO Guidance on Variations to a Prequalified Product Dossier

5. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

The following changes are considered as a new product registration:

- 5.1 Changes to the drug substance/Active Pharmaceutical Ingredient (API)
- Change in the strength of one or more APIs
 - Change of the API to a different API (including change in the salt, isomer or polymorphic form of the API)
 - Inclusion of an additional API to a multi-component (combination) product
 - Removal of one API from a multi-component (combination) product
 - Increase in overage (except for vitamins and minerals as per pharmacopoeia)
- 5.2 Changes to the pharmaceutical dosage form.
- 5.3 Changes in the route of administration (except for parenteral route).
- 5.4 Addition of a new bulk manufacturing site (second source) to the approved site.

6. ABBREVIATIONS

ACTD	ASEAN Common Technical Dossier
API	Active Pharmaceutical Ingredient (<i>Interchangeable with drug substance</i>)
BSE	Bovine Spongiform Encephalopathy
C	Conditions to be fulfilled
CEP	Certificate of Suitability
CFS	Certificate of Free Sale
CoA	Certificate of Analysis
CPP	Certificate of Pharmaceutical Product
D	Documents to be submitted
DMF	Drug Master File
DRGD	Drug Registration Guidance Document
EDQM	European Directorate for the Quality of Medicines & Healthcare
GMP	Good Manufacturing Practice
MaV	Major Variation
MiV-N	Minor Variation-Notification
MiV-PA	Minor Variation-Prior Approval
PI	Package Insert
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIL	Patient Information Leaflet
PRH	Product Registration Holder
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

7. MAJOR VARIATION (MaV)

MaV-1	Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of drug product
C	<ol style="list-style-type: none"> 1. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document. 2. Not applicable to new/additional indication/extension of patient population/parenteral route of administration for new chemical entity (NCE). Please refer to DRGD for new or additional indication for NCE products.
D	<ol style="list-style-type: none"> 1. Justification for the proposed changes. 2. Approved PI/SmPC from reference regulatory agency or the country of origin containing the proposed changes (where applicable). 3. Approval letters from reference countries or country of origin, which have approved the new indication or dosing regimen (where applicable). 4. Clinical expert reports and/or clinical trial reports (where applicable). 5. Clinical documents as per ASEAN Common Technical Dossier (ACTD) part IV (where applicable). 6. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable).

MaV-2	Change of content of drug product labelling
C	<ol style="list-style-type: none"> 1. The change is not a minor variation and not within the scope of MaV-1. 2. As a subsequent change due to revision of SmPC or equivalent document.
D	<ol style="list-style-type: none"> 1. Approved PI/SmPC from reference regulatory agency or the country of origin containing the proposed changes (where applicable). 2. Justification for the proposed changes and supporting clinical documents (where applicable). 3. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable).

MaV-3	Addition/Replacement of manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. Specifications of drug substance remain unchanged. 2. For addition/replacement of manufacturer/site of drug substance where CEP is available, please refer to MiV-PA5. 3. For withdrawal/deletion of the alternative manufacturer(s) for drug substance, please refer to MiV-N8. 4. If there are changes to the specifications of drug substance, MiV-PA9 is also applicable.
D	<ol style="list-style-type: none"> 1. Either one of the following options is applicable: <ol style="list-style-type: none"> a) Option 1 (DMF) <ul style="list-style-type: none"> • DMF (Open and Closed part) • Current GMP certificate or any other evidence of GMP compliance from a regulatory Authority • Letter of Access or b) Option 2 (Full ACTD) <ul style="list-style-type: none"> • Full details of Part II S ACTD • Current GMP certificate or any other evidence of GMP compliance from a regulatory Authority. 2. Comparative tabulated format of the approved and proposed drug substance manufacture information (where applicable). 3. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance from the approved and proposed manufacturing sites. 4. Either a transmissible spongiform encephalopathy (TSE) European Pharmacopoeia certificate of suitability for any new source of material or, where applicable, documentary evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent Authority and shown to comply with the current guideline. 5. A letter of commitment from PRH to conduct long term and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall out-of-shelf life specifications (with proposed action) or when requested.

MaV-4	Major change in the manufacturing process of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. The synthetic route is different with potential change in qualitative and/or quantitative impurity profile, which would require further qualifications in safety studies. 2. Please refer to MiV-PA8 if the synthetic route remains unchanged. 3. Manufacturing process of drug substance does not use any materials of human/ animal origin for which assessment is required of viral safety; unless otherwise justified. 4. Stability performance of drug substance remain unchanged. 5. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 6. If there are changes to the specifications of drug substance, MiV-PA9 is also applicable.
D	<ol style="list-style-type: none"> 1. Either one of the following options is applicable. <ol style="list-style-type: none"> a) Option 1 (DMF) <ul style="list-style-type: none"> • DMF (Open and Closed part); and • Letter of Access <li style="text-align: center;">or b) Option 2 (Full ACTD) <ul style="list-style-type: none"> • Full details of Part II S ACTD 2. Comparative tabulated format of the approved and proposed process of the drug substance. 3. For sterile drug substance, process validation report is required (where applicable). 4. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance from the approved and proposed manufacturing sites. 5. Declaration letter from PRH/API manufacturer/DMF holder stating that the specifications of drug substance have not changed (where applicable). 6. Declaration letter from PRH/API manufacturer/DMF holder stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities, or that there is no increase in the levels of impurities, which require further safety studies. 7. Declaration letter from PRH stating that the relevant stability studies of the drug product in accordance with the ASEAN Guideline on Stability Study of Drug Product will be started and that the relevant stability studies will be finalized; data should be provided only if out-of-specifications (with proposed action).

MaV-5	Change of the manufacturing site (COS) of drug product
C	<ol style="list-style-type: none"> 1. Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. For replacement of the company or party responsible for batch release, please refer to MiV-N14. However, if the change of batch release site is a consequential change due to the change in bulk manufacturing site, the changes can be made simultaneously under this variation. 2. Not applicable if the change is only related to the primary or secondary packaging sites. <ul style="list-style-type: none"> • For change in primary packaging site, please refer to MaV-6/MiV-PA33. • For change in secondary packaging site, please refer to MiV-N15. <p>However, if there are changes to the company or party responsible for packaging (primary or secondary) as a consequential change due to the change in bulk manufacturing site, the changes can be made simultaneously under this variation.</p> 3. Changes in the manufacturing process to adapt to the new manufacturing site settings could be considered under this variation. 4. COS is <u>only applicable</u> for the following situations: <ol style="list-style-type: none"> a) a change in manufacturing site for the same company, including rationalization in the event of mergers b) a company that previously contracts out the manufacture of its product(s) transfers the manufacture of the product to its own manufacturing premises c) a company appoints a contract manufacturer (in or outside Malaysia) d) crisis situations as per scenarios described under Type V <p><i>Note: The change in manufacturing site for this condition will not be considered if the change is made without acceptable justification or submitted too frequently.</i></p>

Change of the manufacturing site (COS) of drug product are categorised into 5 types with minor differences in the documentations:

No.	Types of COS		Description
1.	Type I	Within Malaysia	Change of location of the site of manufacture within Malaysia only. This change may be due to upgrading of facilities, and/or expansion of manufacturing activities or moving to a newly constructed plant, or appointment of a contract manufacturer for pharmaceutical products.
2.	Type II	From foreign country to Malaysia	Change of location of the site of manufacture from outside Malaysia to a location in Malaysia. This change may be due to the ability of the local counterpart to manufacture the product, or appointment of a contract manufacturer for pharmaceutical products.
3.	Type III	Located outside Malaysia	Change of location of the site of manufacture to manufacturing facilities located outside Malaysia. a) From a manufacturer to its own/subsidiary manufacturing premise <ul style="list-style-type: none"> • This may be due to a merger or rationalization of manufacturing sites in line with manufacturing strategies. b) From a manufacturer (its own/subsidiary/contract) to a contract manufacturing premise c) From a local manufacturing site (in Malaysia) to manufacturing facilities located outside Malaysia (its own/subsidiary/contract)
4.	Type IV	For sterile products	Change of location of the site of manufacture for sterile products: <ul style="list-style-type: none"> • within Malaysia • from outside Malaysia to a location in Malaysia • from Malaysia to manufacturing facilities located outside Malaysia • between sites located outside Malaysia a) From a manufacturer to its own/subsidiary manufacturing premise <ul style="list-style-type: none"> • This may be due to a merger or rationalization of manufacturing sites in line with manufacturing strategies. b) From a manufacturer (its own/subsidiary/contract) to a contract manufacturing premise
5.	Type V	In crisis situation	i. Change of location of the site of manufacture that is deemed necessary due to certain circumstances such as natural disasters, closure or suspension of premise (revocation of manufacturing license), bankruptcy and matters related to breach of product quality, safety and efficacy ONLY. ii. Prior to submission of Type V COS, approval letter issued by the secretariat of the Authority shall be obtained. iii. Application for Type V COS must be made within 6 months from the date of the crisis.

Ref: Drug Registration Guidance Document (DRGD)

No.	Documents To Be Submitted	Type I	Type II	Type III	Type IV	Type V
1.	Letter of authorisation/appointment from the product owner to authorise PRH to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product at the proposed site and stating the types of activity to be performed.	✓	✓	✓	✓	✓
2.	Letter from the manufacturer/product owner to clarify/explain the need to change site of manufacture.	✓	✓	✓	✓	✓
3.	Written declaration from the manufacturer to certify that the manufacturing process and the release and shelf life specifications of the product remain unchanged. <i>OR</i> If there are minor changes, to declare the minor changes & justify the need for such changes.	✓	✓	✓	✓	✓
4.	Release and shelf life specifications from proposed site.	✓	✓	✓	✓	✓
5.	<u>For imported products</u> Good Manufacturing Practice (GMP) and Certificate of Pharmaceutical Product (CPP)/ Certificate of Free Sale (CFS) from the source country of the proposed manufacturing site <i>OR</i> <u>For locally manufactured products</u> Letter of confirmation on GMP status or valid manufacturer's license for the proposed manufacturing site.	✓	✓	✓	✓	✓
6.	Batch Manufacturing Formula and/or product formula.	✓	✓	✓	✓	✓
7.	Certificate of Analysis (CoA) of drug product for at least 2 production/pilot scale batches from the proposed manufacturing site.	✓	✓	✓	✓	
8.	Comparative batch analysis data of drug product of at least 2 production batches (or one production batch and two pilot scale batches) from the proposed site and last 3 batches from the approved site; batch analysis data on the next 2 full production batches should be available upon request or reported if out-of-specifications (with proposed action).	✓	✓	✓	✓	

9.	Long term and accelerated stability data as per ASEAN Guideline on Stability Study of Drug Product and a letter of commitment to submit updated/completed long term stability data. <i>* In-use stability data may be required if there are changes that may have an impact on the drug product stability & quality characteristics.</i>	✓	✓	✓	✓	
10.	Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable).	✓	✓	✓	✓	✓
11.	Process validation report as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration.	✓	✓	✓	✓	
12.	Holding time studies of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).	✓	✓	✓	✓	
13.	Letter of commitment to submit stability data, CoA, and process validation report (where applicable) within 6 months of approval of site change.					✓
14.	i) Comparative dissolution profile data of the drug product (of at least one pilot/production batch) between approved and proposed manufacturing site for oral solid dosage forms as per US FDA SUPAC-IR/MR Guidelines ii) Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).	✓	✓	✓		
15.	Letter of commitment to submit comparative dissolution profile data between the approved and proposed site for oral solid dosage forms					✓

MaV-6	Addition/Replacement of primary packaging site for sterile drug product
C	<ol style="list-style-type: none"> 1. No other changes except for the addition or replacement of primary packaging site (direct contact with drug product). 2. For addition or replacement of primary packaging site for non-sterile drug product, please refer to MiV-PA33.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned such as a valid GMP Certificate and/or a CPP which covers GMP certification. 3. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 4. Process validation scheme and/or report on primary packaging processes as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration at the proposed site. 5. Holding time studies of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 6. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

<p>MaV-7</p>	<p>Change of specifications of drug product and/or drug substance [where European Pharmacopeial Certificate of Suitability (CEP) is not available]</p> <p>a) Specification limits are widened b) Deletion of test parameter and limits</p>
<p>C</p>	<ol style="list-style-type: none"> 1. Test procedures remain the same, or changes in the test procedure are minor. 2. Not applicable to compendial drug substances/drug products. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 4. If there are changes to the test procedure, MiV-PA10/MiV-PA28 is also applicable. 5. For change of specifications of drug substance where a CEP is available, please refer to MiV-PA13. 6. For tightening of specification limits and addition of new test parameter and limits of drug product/drug substance, please refer to MiV-PA25/MiV-PA9. 7. For widening of specification limits and deletion of test parameter and limits of drug product/drug substance following changes between compendiums and from non-compendial to compendial, please refer to MiV-PA25/MiV-PA9. 8. For changes in specifications within the same compendium, please refer to MiV-N10.
<p>D</p>	<p>(a) <u>Specification limits are widened</u></p> <ol style="list-style-type: none"> 1. Revised specifications of drug product/drug substance. 2. Comparative tabulated format of the approved and proposed specifications of drug substance/drug product with changes highlighted. 3. Certificate of analysis and batch analysis data: Drug product: CoA and batch analysis data (in a comparative tabulated format) for all tests in the proposed specification for at least 2 production/pilot scale batches. Drug substance: CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) for all tests in the proposed specification. 4. Justification for change substantiated with scientific data to be provided. 5. For change of drug substance specification that involve stability-indicating parameters: Stability data of drug substance and report if any results fall out-of-re-test/shelf life specifications (with proposed action). 6. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). <p>(b) <u>Deletion of test parameter and limits</u> All of the above documents except D5 & D6.</p>

MaV-8	Change of batch size of sterile drug product
C	<ol style="list-style-type: none"> 1. The product formulation remains unchanged. 2. The change does not affect consistency of production. 3. Release and shelf life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available, or validation of the manufacturing process has been successfully carried out according to protocol with at least 3 batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration.
D	<ol style="list-style-type: none"> 1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Process validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration of the proposed batch size. 3. Release and shelf life specifications of drug product. 4. CoA of the drug product for at least 2 production scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed batch size. 5. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

MaV-9	Change of batch size of non-sterile drug product (more than 10-fold)
C	<ol style="list-style-type: none"> 1. The product formulation remains unchanged. 2. The change does not affect consistency of production. 3. Release and shelf life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available, or validation of the manufacturing process has been successfully carried out according to protocol with at least 3 batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. 5. This is applicable for change of batch size more than 10-fold compared to the approved batch size. For change of batch size up to 10-fold compared to the registered batch size, please refer to MiV-PA14.
D	<ol style="list-style-type: none"> 1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Process validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration of the proposed batch size. 3. Revised ACTD Section P3.1 to P3.4 (where applicable). 4. Release and shelf life specifications of drug product. 5. CoA of the drug product for at least 2 production scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed batch size. 6. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). 7. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed batch size for oral solid dosage forms as per US FDA SUPAC-IR/MR Guidelines.

MaV-10	Major change in the manufacturing process of drug product
C	<ol style="list-style-type: none"> 1. Applicable for sterile and non-sterile drug product. 2. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 3. The manufacturing site remains unchanged. If there is a change in manufacturing site, MaV-5 is also applicable. 4. For minor changes in the manufacturing process for non-sterile products, please refer to MiV-PA21/MiV-N12.
D	<ol style="list-style-type: none"> 1. Description of the proposed manufacturing process and technical justification for the change. 2. Process validation scheme and/or report of the proposed manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. 3. Release and shelf life specifications of drug product. Or, alternatively, the release and shelf life specifications that supports the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 4. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed processes. 5. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). 6. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms as per US FDA SUPAC-IR/MR Guidelines. 7. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MaV-11	<p>Qualitative and/or quantitative change of excipient</p> <p>a) For immediate-release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)</p> <p>b) For modified-release oral dosage forms</p> <p>c) For other critical dosage forms such as sterile preparations</p>
C	<ol style="list-style-type: none"> 1. Replacement of an excipient with a comparable excipient of the same functional characteristics. 2. The dissolution profile of the proposed product is comparable to that of the approved product. 3. Process validation scheme and/or report is available, or validation of the manufacturing process has been successfully carried out according to protocol with at least 3 batches of the proposed new product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. 4. Release and shelf life specifications of drug product remain unchanged; except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 5. For other qualitative or quantitative changes of excipient for immediate-release oral dosage forms and other non-critical dosage forms, please refer to MiV-PA16.
D	<ol style="list-style-type: none"> 1. Justification for the change must be given by appropriate development of pharmaceuticals. 2. Revised batch manufacturing formula. 3. Comparative tabulated format of the approved and proposed product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 4. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 5. Specifications of the proposed excipient. 6. For proposed excipients made of ruminant's source, TSE-free certificate or BSE-free certificate issued from relevant Authority of the issuing country and/or documentary evidence from the supplier (where applicable). 7. A declaration that the proposed excipient does not interfere with the drug product release and shelf life specifications test method (where applicable). 8. Process validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula. 9. Revised ACTD Section P3.1 to P3.4 (where applicable). 10. Release and shelf life specifications of drug product. 11. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed product formulation. 12. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). 13. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms as per US FDA SUPAC-IR/MR Guidelines. 14. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 15. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).

MaV-12	Quantitative change in coating of tablets and/or size of capsule shell for modified-release oral dosage form
C	<ol style="list-style-type: none"> 1. The dissolution profile of the proposed product is comparable to that of the approved product. 2. Release and shelf life specifications of drug product remain unchanged except for the weight and/or size (where applicable). 3. For quantitative change in coating of tablets and/or size of capsule shell for immediate-release oral solid dosage form, please refer to MiV-PA17.
D	<ol style="list-style-type: none"> 1. Comparative tabulated format of approved and proposed product and batch manufacturing formula. 2. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 3. Release and shelf life specifications of drug product. 4. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product. 5. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). 6. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms as per US FDA SUPAC-MR Guidelines. 7. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 8. A declaration that the change does not interfere with the drug product release and shelf life specifications test method.

MaV-13	Change in primary packaging material for sterile drug product a) Type of container b) Addition of primary packaging material c) Qualitative and quantitative composition
C	<ol style="list-style-type: none"> 1. Release and shelf life specifications of drug product remain unchanged. 2. For change in the primary packaging material for non-sterile drug product, please refer to MiV-PA29.
D	<ol style="list-style-type: none"> 1. Appropriate scientific data on proposed packaging (comparative data on permeability, e.g. moisture, O₂, CO₂). 2. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 3. Comparative tabulated format of specifications of the approved and proposed primary packaging material. 4. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 5. Process validation scheme and/or report of the manufacturing and sterilization process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in primary packaging material. 6. Revised ACTD Section P3 and/or P7 (where applicable). 7. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

MaV-14	Change/Addition of pack size/fill volume and/or change of shape or dimensions of container or closure for sterile solid and liquid drug product
C	<ol style="list-style-type: none"> 1. The packaging material remains unchanged. 2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Release and shelf life specifications of drug product are not affected, except pack size/fill volume specification. 4. For change/addition of pack size/fill volume and/or change of shape or dimensions of container or closure for non-sterile drug product, please refer to MiV-PA31.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Validation data of the manufacturing process, sterilization and container closure system (where applicable). 4. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

MaV-15	Inclusion/Replacement of the solvent/diluent for drug product
C	<ol style="list-style-type: none"> 1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product. 2. For deletion of the solvent/diluent, please refer to MiV-PA19. 3. For change of shelf life and/or storage condition of the drug product after first opening and/or after dilution/reconstitution, please refer to MaV-16/MiV-PA35 and/or MaV-17/MiV-PA36 (where applicable).
D	<ol style="list-style-type: none"> 1. Approved PI/SmPC from reference regulatory agency or the country of origin containing the proposed changes (where applicable). 2. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 3. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 4. Revised ACTD Section P for the solvent/diluent and reconstitution stability data (where applicable). 5. A letter of authorization from product owner to authorize the manufacturing site to manufacture and package the solvent/diluent (where applicable). 6. Declaration from PRH that the release and shelf life specifications of drug product are not affected.

MaV-16	Extension of the shelf life of drug product a) As a package for sale b) After first opening c) After dilution/reconstitution
C	<ol style="list-style-type: none"> 1. For (a) & (b) – The studies must show conformance to the approved shelf life specification. 2. For (c) – The studies must show conformance to the approved shelf life specification for the reconstituted product. 3. For reduction of shelf life, please refer to MiV-PA35.
D	<ol style="list-style-type: none"> 1. Technical justification for the proposed change (where applicable). 2. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 3. Revised ACTD Section P for the solvent/diluent and reconstitution stability data (where applicable). 4. Results of appropriate long term stability studies covering the duration of proposed shelf life of the product in the authorized packaging material <ol style="list-style-type: none"> a) as a package for sale b) after first opening c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate). 5. A letter of commitment from product owner/PRH to inform users of the relevant change (where applicable).

MaV-17	Change of storage condition of drug product (lowering from the approved storage condition) a) As a package for sale b) After first opening c) After dilution/reconstitution
C	<ol style="list-style-type: none"> 1. For (a) & (b) – The studies must show conformance to the approved shelf life specification. 2. For (c) – The studies must show conformance to the approved shelf life specification for the reconstituted product. 3. For change of storage condition (increasing from the approved storage condition), please refer to MiV-PA36.
D	<ol style="list-style-type: none"> 1. Technical justification for the proposed change. 2. Results of appropriate long term stability studies covering the duration of approved shelf life (at proposed storage condition) of the product and in the authorized packaging material <ol style="list-style-type: none"> a) as a package for sale b) after first opening c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of microbiological testing should be included (where appropriate). 3. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable).

8. MINOR VARIATION PRIOR APPROVAL (MiV-PA)

MiV-PA1	Change of drug product name
C	<ol style="list-style-type: none"> 1. There is no change to the product formulation, release and shelf life specifications, manufacturing source and process except for the product name change. 2. No confusion with another drug product either when spoken or written. 3. The new name does not: <ul style="list-style-type: none"> • imply a therapeutic use • imply superiority over another similar product • imply the presence of substance(s) not present in the product • suggest greater safety or efficacy than supported by clinical data
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Updated CPP (where applicable). 3. Official letter from product owner or PRH authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 4. Declaration letter from PRH stating that there are no other changes to the product/label except for the drug product name change. 5. Trademark certificate (where applicable).

MiV-PA2	<p>Change of drug product labelling (in accordance to country specific labelling requirement)</p> <p>Includes:</p> <ol style="list-style-type: none"> a) Changes to the artwork design. b) Addition/replacement of pictures, diagrams, logos and/or texts that do not imply an unapproved indication. c) Addition/strengthening of warnings, precautions, contraindications and/or adverse events/effects to the approved product labelling. d) Tightening of product's target population. e) Deletion of indication.
C	The change is not a MaV and does not contain promotional information. For major change in product labelling, please refer to MaV-2.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Relevant document/reference to support the changes (where applicable). 3. Declaration letter from PRH stating that there are no other changes on the label except for the intended change.

MiV-PA3	Change of patient information leaflet (PIL)
C	Changes to the content (e.g. ACTD Section A, C) that has been approved.
D	Proposed PIL – a clean and annotated version highlighting the changes made.

MiV-PA4	Addition/Replacement of manufacturer/site of intermediate/starting material of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. Specifications (including in-process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed drug substance route of synthesis remains unchanged. 2. The impurity profile of the drug substance intermediate/starting material is essentially the same and drug substance manufacturer's intermediate/starting material specifications remain unchanged. 3. Specifications and route of synthesis of intermediate remain unchanged.
D	<ol style="list-style-type: none"> 1. Either one of the following options is applicable. <ol style="list-style-type: none"> a) Option 1 (DMF) <ul style="list-style-type: none"> • Replacement of relevant sections of DMF (Open and Closed part). Closed part can be sent directly to NPRA by API manufacturer/DMF holder • Letter of Access. or b) Option 2 (Full ACTD) <ul style="list-style-type: none"> • Replacement of relevant sections of Part II S ACTD 2. Current intermediate manufacturer GMP certificate or any other evidence of GMP compliance. 3. Comparative tabulated batch data of intermediate for approved & proposed intermediate manufacturers. 4. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance from the approved and proposed manufacturing sites. 5. Either a transmissible spongiform encephalopathy (TSE) European Pharmacopoeia certificate of suitability for any new source of material or, where applicable, documentary evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent Authority and shown to comply with the current guideline.

MiV-PA5	Addition/Replacement of manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
C	<ol style="list-style-type: none"> 1. Specifications of drug substance remain unchanged. 2. For addition/replacement of manufacturer/site of drug substance where CEP is not available, please refer to MaV-3. 3. For withdrawal/deletion of the alternative manufacturer(s) for drug substance, please refer to MiV-N8.
D	<ol style="list-style-type: none"> 1. A valid CEP for the drug substance, latest version, with all annexes issued by the EDQM together with the following: <ul style="list-style-type: none"> • A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision • A declaration from the API Manufacturer that the PRH and NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety • Revised relevant ACTD Section S (where applicable) 2. A letter of commitment from PRH to conduct long term and accelerated stability studies for the drug product manufactured with the drug substance from the proposed manufacturing site, and report if any results fall out-of-shelf life specifications (with proposed action) or when requested. 3. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance from the approved and proposed manufacturing sites. 4. Additional data to address any relevant parameter(s) not addressed in the CEP such as <ul style="list-style-type: none"> • stability data (S7), If CEP did not specify a retest period with specific storage condition (CCS and specific temperature) or CCS (in S6 & S7) is different from CCS (in CEP), long term and accelerated stability data up to the proposed re-test period on 3 pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided • physicochemical characteristics (e.g. particle size, polymorphism, etc), (where applicable)

MiV-PA6	Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. Specifications of drug substance remain unchanged. 2. The change does not affect the reproducibility of the process.
D	<ol style="list-style-type: none"> 1. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) with specification and results of the drug substance manufactured to both the approved and proposed batch sizes. Batch analysis data on the next 3 full production batches should be available on request or reported if out-of-specification (with proposed action). 2. Revised relevant ACTD Section S (where applicable). 3. Declaration letter from PRH stating that the specifications of drug substance have not changed, and the reproducibility of the process has not been affected.

MiV-PA7	Change of in-process controls applied during the manufacture of drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. In-process limits are tightened, or new tests are added. 2. The change is not a consequence of any commitment from previous assessments to review specification limits. 3. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 4. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way. 5. If the change results in the revision of CEP, please refer to MiV-PA13.
D	<ol style="list-style-type: none"> 1. A description of the analytical method and summary of validation data must be provided for all new analytical methods (where applicable). 2. Comparative tabulated format of the approved and proposed in-process controls and the relevant changes. 3. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance for all tests in the proposed specification (where applicable).

MiV-PA8	Minor change in the manufacturing process of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
C	<ol style="list-style-type: none"> 1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. The synthetic route remains unchanged (for example, intermediates and starting material remain unchanged). Please refer to MaV-4 if the synthetic route is different. 3. Manufacturing process of drug substance does not use any materials of human/ animal origin for which assessment is required of viral safety. 4. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 5. Specifications and stability performance of drug substance remain unchanged.
D	<ol style="list-style-type: none"> 1. Drug Master File (DMF) or ACTD Section S (where applicable) relevant updated drug substance section. 2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 3. For sterile drug substance, process validation report is required (where applicable). 4. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance. 5. Declaration letter from PRH stating that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the levels of impurities, which require further safety studies. 6. Declaration letter from PRH stating that the specifications of the drug substance have not changed. 7. Declaration letter from PRH stating that the relevant stability studies of the drug product in accordance with the 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 out-of-specification (with proposed action).

<p>MiV-PA9</p>	<p>Change of specifications of drug substance a) Specification limits are tightened b) Addition of new test parameter and limits c) Specification limits are widened following compendium d) Deletion of test parameter and limits following compendium</p>
<p>C</p>	<ol style="list-style-type: none"> 1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns, unless otherwise justified. 2. Test procedures remain the same, or changes in the test procedure are minor. If there are changes to the test procedure, MiV-PA10 is applicable. 3. For change of specifications of drug substance where a CEP is available, please refer to MiV-PA13. 4. For (a) and (b), this applies for specification changes <ol style="list-style-type: none"> i. between non-compendial ii. from non-compendial to compendial iii. from one compendium to another 5. For (c) and (d), this applies for specification changes <ol style="list-style-type: none"> i. from non-compendial to compendial ii. from one compendium to another 6. For changes in the specifications of drug substance following the updates within the same compendium, please refer to MiV-N10. 7. For widening or deletion of non-compendial specifications of drug substance, please refer to MaV-7.
<p>D</p>	<p>(a) <u>Specification limits are tightened</u></p> <ol style="list-style-type: none"> 1. Technical justification for the proposed change. 2. Revised specifications of drug substance. 3. Comparative tabulated format of the approved and proposed specifications of drug substance with changes highlighted. 4. COA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance for all tests in the proposed specification. 5. Stability study data of drug substances (where applicable) and report if any results fall out-of-shelf life specifications (with proposed action). <p>(b) <u>Addition of new test parameter and limits</u> In addition to the above documents:</p> <ol style="list-style-type: none"> 6. Description of any new analytical method and summary of the validation data. 7. For change of drug substance specification that involved stability-indicating parameters: stability data of drug substances and report if any results fall out-of-re-test/shelf life specifications (with proposed action). <p>(c) <u>Specification limits are widened (following compendium)</u></p> <ol style="list-style-type: none"> 1. Revised specifications of drug substance. 2. Comparative tabulated format of the approved and proposed specifications of drug substance with changes highlighted. 3. COA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance for all tests in the proposed specification. 4. For change of drug substance specification that involved stability-indicating parameters: stability data of drug substances and report if any results fall out-of-re-test/shelf life specifications (with proposed action). <p>(d) <u>Deletion of test parameter and limits (following compendium)</u></p> <ol style="list-style-type: none"> 1. Revised specifications of drug substance. 2. Comparative tabulated format of the approved and proposed specifications of drug substance with changes highlighted. 3. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance for all tests in the proposed specification.

MiV-PA10	Change in test procedure for non-compendial drug substance
C	<ol style="list-style-type: none"> 1. Results of method validation/verification show new test procedure to be at least equivalent to the approved procedure. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns, unless otherwise justified. 3. If the change results in the revision of CEP, please refer to MiV-PA13. 4. This applies for non-compendial test procedures and/or changes in test procedures from one compendium to another. For the update within the same compendium, please refer to MiV-N10.
D	<ol style="list-style-type: none"> 1. Description of the proposed test procedure with a summary of changes from the approved test procedure. 2. Comparative tabulated format of the approved and proposed test method of the drug substance. 3. Description of the analytical methodology. 4. Appropriate verification/validation data of the proposed test procedure and comparative analytical result between the approved and proposed test (where applicable). A declaration statement may be provided if no verification/validation data is required for minor/editorial changes. 5. Specifications of the drug substance. 6. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance from the approved and proposed test procedure.

MiV-PA11	Change of the shelf life or re-test period of drug substance
C	<ol style="list-style-type: none"> 1. The stability studies must show compliance with specification. 2. There is no change in storage condition. 3. If the change results in the revision of CEP, please refer to MiV-PA13.
D	<ol style="list-style-type: none"> 1. Specifications of drug substance. 2. Stability data of drug substance should be presented on at least 3 pilot or production scale batches of the requested shelf life or retest period.

MiV-PA12	Change of storage condition of drug substance
C	<ol style="list-style-type: none"> 1. There is no change in shelf life/retest period. 2. The stability studies must show compliance with specification. 3. If the change results in the revision of CEP, please refer to MiV-PA13.
D	<ol style="list-style-type: none"> 1. Specifications of drug substance. 2. Stability data of drug substance should be presented on at least 3 pilot or production scale batches of the requested storage condition.

MiV-PA13	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
C	None
D	<ol style="list-style-type: none"> 1. A valid CEP for the drug substance, latest version, with all annexes issued by EDQM together with the following: <ul style="list-style-type: none"> • A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision • A declaration from the API Manufacturer that the PRH and NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety 2. If this change is due to drug substance specification change, a declaration 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 out-of-specification (with proposed action). 3. Revised relevant ACTD Section S (where applicable). 4. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance manufacturer* demonstrating compliance with the EP monograph and including additional test/limits listed on the CEP (where applicable). 5. Additional data pertaining to any relevant parameters not addressed in the CEP such as <ul style="list-style-type: none"> • If the CEP did not specify a retest period with specific storage condition [Container Closure System (CCS) and specific temperature] or CCS (in S6 & S7) is different from CCS (in CEP), long term and accelerated stability data up to the proposed re-test period on 3 pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided • physicochemical characteristics e.g. particle size, polymorphism, etc (where applicable) 6. Comparative tabulated format of approved and newly revised CEP. <p>* If the drug substance 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.</p>

MiV-PA14	Change of batch size of non-sterile drug product (up to 10-fold)
C	<ol style="list-style-type: none"> 1. The product formulation remains unchanged. 2. The change does not affect consistency of production. 3. Release and shelf life specifications of drug product remain unchanged. 4. Process validation scheme and/or report is available, or validation of the manufacturing process has been successfully carried out according to protocol with at least 3 batches appropriate to the proposed batch size in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. 5. This is applicable to change of batch size up to 10-fold compared to the registered batch size. For change of batch size for sterile products, please refer to MaV-8. For change of batch size more than 10-fold compared to the registered batch size, please refer to MaV-9.
D	<ol style="list-style-type: none"> 1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Process validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration of the proposed batch size. 3. Revised ACTD Section P3.1 to P3.4 (where applicable). 4. Release and shelf life specifications of drug product. 5. CoA of the drug product for at least 2 production scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed batch size. 6. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

MiV-PA15	Reduction/Removal of overage of drug substance
C	<ol style="list-style-type: none"> 1. This applies to changes made to the approved manufacturing overages of drug substance only. 2. Release and shelf life specifications of drug product remain unchanged.
D	<ol style="list-style-type: none"> 1. Justification for the proposed change. 2. Comparative tabulated format of approved and proposed batch manufacturing formula. 3. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed product formulation. 4. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

MiV-PA16	<p>Qualitative and/or quantitative change of excipient</p> <p>a) For immediate-release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline)</p> <p>b) For other non-critical dosage forms e.g. oral liquid, external preparation</p>
C	<ol style="list-style-type: none"> 1. Replacement of an excipient with a comparable excipient of the same functional characteristics (where applicable). 2. The dissolution profile of the proposed product is comparable to that of the approved product. 3. Process validation scheme and/or report is available, or validation of the manufacturing process has been successfully carried out according to protocol with at least 3 batches of the proposed product formula in accordance with the ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. 4. Release and shelf life specifications of drug product remain unchanged; except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 5. For qualitative or quantitative change of excipient for immediate-release (Level 2 and 3 change as per SUPAC) and modified-release oral dosage forms and other critical dosage forms, please refer to MaV-11.
D	<ol style="list-style-type: none"> 1. Justification for the change must be given by appropriate development of pharmaceuticals. 2. Revised batch manufacturing formula. 3. Comparative tabulated format of the approved and proposed product formulation with calculated changes highlighted (please state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable). 4. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 5. Specifications of the proposed excipient. 6. For proposed excipients made of ruminants source, TSE-free certificate or BSE-free certificate issued from relevant Authority of the issuing country and/or documentary evidence from the supplier (where applicable). 7. A declaration that the proposed excipient does not interfere with the drug product release and shelf life specifications test method (where applicable). 8. Process validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change in product formula (where applicable). 9. Revised ACTD Section P3.1 to P3.4 (where applicable). 10. Release and shelf life specifications of drug product. 11. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed product formulation. 12. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). 13. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed formulation for oral solid dosage forms as per US FDA SUPAC-IR Guidelines. 14. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).

MiV-PA17	Quantitative change in coating of tablets and/or size of capsule shell for immediate-release oral solid dosage form
C	<ol style="list-style-type: none"> 1. The dissolution profile of the proposed product is comparable to that of the approved product. 2. Release and shelf life specifications of drug product remain unchanged except for the weight and/or size. 3. For quantitative change in coating of tablets and/or size of capsule shell for modified-release oral solid dosage forms, please refer to MaV-12.
D	<ol style="list-style-type: none"> 1. Proposed product labelling – a clean and annotated version highlighting the changes made (where applicable). 2. Comparative tabulated format of approved and proposed product and batch manufacturing formula. 3. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed composition for oral solid dosage forms as per US FDA SUPAC-IR Guidelines. 4. Release and shelf life specifications of drug product. 5. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product. 6. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action); except for the change in size of capsule shell, a declaration letter that the relevant stability studies of the drug product in accordance with ASEAN Guideline on Stability Study of Drug Product have been started will suffice. 7. Declaration from PRH that the change does not interfere with the drug product release and shelf life specifications test method.

MiV-PA18	Change of colouring agent/flavouring agent/capsule shell colour of drug product
C	<ol style="list-style-type: none"> 1. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. 2. The proposed colouring/flavouring agents/capsule shell must not have been rejected for pharmaceutical use. 3. Release and shelf life specifications of drug product remain unchanged except for the update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 4. If there is a change to the source of capsule shell, MiV-PA24 is also applicable.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. A letter of commitment from product owner or PRH to inform users of the relevant change (where applicable). 3. Revised product formulation and batch manufacturing formula. 4. Qualitative and quantitative information of the approved and proposed colouring agent/flavouring agent/capsule shell colour in a comparative table. 5. For proposed excipients made of ruminants source, TSE-free certificate or BSE-free certificate issued from relevant Authority of the issuing country and/or documentary evidence from the supplier (where applicable). 6. Release and shelf life specifications of drug product. 7. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product. 8. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). 9. CoA of proposed coloring agent/flavoring agent/capsule shell (where applicable). 10. Declaration from PRH that the change does not interfere with the drug product release and shelf life specifications test method.

MiV-PA19	Deletion of the solvent/diluent for drug product
C	<ol style="list-style-type: none"> 1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent. 3. Revised relevant ACTD Section P (where applicable).

MiV-PA20	Change of in-process controls applied during the manufacture of drug product (including tightening and addition of new in-process test)
C	<ol style="list-style-type: none"> 1. Release and shelf life specifications of drug product remain unchanged. 2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 3. Any new test method does not concern a novel non-standard technique, or a standard technique used in a novel way.
D	<ol style="list-style-type: none"> 1. Comparative tabulated format of approved and proposed in-process controls. 2. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 3. Proposed in-process specifications together with justification and relevant process validation data. 4. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product.

MiV-PA21	Minor change in the manufacturing process of non-sterile drug product
C	<ol style="list-style-type: none"> 1. The manufacturing site remains unchanged. If there is a change in manufacturing site, MaV-5 is also applicable. 2. The overall manufacturing principle remains unchanged. 3. The change does not cause negative impact on the quality, safety and efficacy of the drug product. 4. The dissolution profile of the proposed product is comparable to that of the approved product. 5. Release and shelf life specifications of drug product remain unchanged. 6. For major change in the manufacturing process for drug product, please refer to MaV-10. 7. For minor change (as per Level 1, Part VI Manufacturing, SUPAC Guideline) in the manufacturing process of an immediate-release solid oral dosage form, semi-solid or oral solutions, please refer to MiV-N12.
D	<ol style="list-style-type: none"> 1. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing process for oral solid dosage forms as per US FDA SUPAC-IR/MR Guidelines. 2. Description of the proposed manufacturing process and technical justification for the change. 3. Comparative tabulated format of approved and proposed process with changes highlighted. 4. Process validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. 5. Release and shelf life specifications of drug product. 6. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed processes. 7. Declaration from PRH stating that the relevant stability studies of the drug product in accordance with the 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 out-of-specification (with proposed action).

MiV-PA22	Change of specifications of non-compendial excipient a) Specification limits are tightened/widened b) Addition/replacement/deletion of test parameter and limits
C	<ol style="list-style-type: none"> 1. Release and shelf life specifications of drug product remain unchanged. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns, unless otherwise justified. 3. Applicable to non-compendial excipients and/or changes in specification from one compendium to another. For updates within the same compendium. i.e. for which the product was initially approved for during registration, please refer to MiV-N10.
D	<ol style="list-style-type: none"> 1. Description of new method and summary of analytical validation (applicable for addition/replacement of new parameter). 2. Comparative tabulated format of the approved and proposed specifications of the excipient with changes highlighted. 3. CoA of the excipient for all tests in the new specification.

MiV-PA23	Change in test procedure for excipient (including replacement of an approved test procedure by a new test procedure)
C	<ol style="list-style-type: none"> 1. Appropriate method validation studies have been performed in accordance with the ASEAN Guidelines for Validation of Analytical Procedures. 2. Results of method validation show proposed test procedure to be at least equivalent to the former procedure. 3. The change does not result in changes of the total impurity limits. 4. Only applicable to the approved test parameters and limits. For addition/replacement/deletion of test parameter and limits, please refer to MiV-PA22/ MiV-N10. 5. No new unqualified impurities are detected. 6. Applicable for non-compendial excipients and/or changes in test procedure from one compendium to another. For the update within the same compendium, please refer to MiV-N10.
D	<ol style="list-style-type: none"> 1. Description of the proposed analytical methodology with a comparative tabulation of the changes. 2. For quantitative test change, comparative analytical validation results showing that the approved and proposed tests are equivalent.

MiV-PA24	Change in the source of empty hard capsule
C	<ol style="list-style-type: none"> 1. The change is from TSE-risk material to vegetable-sourced or synthetic empty hard capsules or vice versa. 2. The formulation and manufacturing process of drug product remain unchanged. 3. Not applicable to change from hard capsule to soft gel. 4. Excipient and drug product release and shelf life specifications remain unchanged.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Declaration letter from the manufacturer or the PRH stating that the material is purely of vegetable, animal or synthetic origin. 3. Technical specifications and composition of the empty hard capsule of the proposed source. 4. For empty hard capsule made of ruminants source, TSE-free certificate or BSE-free certificate issued from relevant Authority of the issuing country and/or documentary evidence from the supplier. 5. Comparative dissolution profile data of at least one pilot/production batch of the drug product using hard capsule between the 2 sources for oral solid dosage as per as per US FDA SUPAC-IR/MR Guidelines (where applicable). 6. CoA of the empty hard capsule of the proposed source. 7. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product. 8. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

<p>MiV-PA25</p>	<p>Change of release and/or shelf life specifications of drug product a) Specification limits are tightened b) Addition of new test parameter and limits c) Specification limits are widened following compendium d) Deletion of test parameter and limits following compendium</p>
<p>C</p>	<ol style="list-style-type: none"> 1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns unless otherwise justified. 2. The test methods remain unchanged or changes in the test methods are minor. 3. If there are changes to the test procedure, MiV-PA28 is also applicable. 4. For (a) and (b) This applies for specification changes: <ol style="list-style-type: none"> i. between non-compendial ii. from non-compendial to compendial iii. from one compendium to another 5. For (c) and (d) This applies for specification changes: <ol style="list-style-type: none"> i. from non-compendial to compendial ii. from one compendium to another 6. For widening or deletion of non-compendial specifications of drug product, please refer to MaV-7. 7. For changes in the specifications of drug product following the updates within the same compendium, please refer to MiV-N10.
<p>D</p>	<p>(a) <u>Specification limits are tightened</u></p> <ol style="list-style-type: none"> 1. Technical justification for the change. 2. Revised specifications of drug product. 3. Comparative tabulated format of the approved and proposed release and shelf life specifications of the drug product with changes highlighted. 4. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed product specifications. <p>(b) <u>Addition of new test parameter and limits</u> In addition to the above documents:</p> <ol style="list-style-type: none"> 5. Description of any new method and summary of analytical validation data for non-compendial method. 6. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). (where applicable) <p>(c) <u>Specification limits are widened (following compendium)</u></p> <ol style="list-style-type: none"> 1. Revised specifications of drug product. 2. Comparative tabulated format of the approved and proposed release and shelf life specifications of drug product with changes highlighted. 3. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed product specifications. 4. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action). <p>(d) <u>Deletion of test parameter and limits (following compendium)</u></p> <ol style="list-style-type: none"> 1. Revised specifications of drug product. 2. Comparative tabulated format of the approved and proposed release and shelf life specifications of drug product with changes highlighted. 3. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed product specifications.

MiV-PA26	Change of imprints, embossing/debossing or other markings (including break/score-line) on tablets or printing on capsules including addition/change of inks used for product marking
C	<p>(a) <u>Change in imprints, embossing/debossing or other markings</u></p> <ol style="list-style-type: none"> 1. Proposed markings do not cause confusion with other registered products. 2. Any ink proposed must comply to relevant pharmaceutical legislation or be of food grade and not a listed banned substance. 3. Release and shelf life specifications of the drug product remain unchanged except for appearance. <p>(b) <u>Change in score/break-line</u></p> <p>In addition to the above conditions:</p> <ol style="list-style-type: none"> 4. Score/break-line is not meant for cosmetic purpose. 5. Applicable to addition or removal of score/break-line.
D	<p>(a) <u>Change in imprints, embossing/debossing or other markings</u></p> <ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Detailed drawing or written description of the approved and proposed imprint/bossing/markings. 3. Details and specifications of the proposed inks (where applicable). 4. Certificate of analysis of ink/printing material (pharmaceutical grade and of food grade) (where applicable). 5. Release and shelf life specifications of drug product with the proposed product description. 6. A letter of commitment from product owner or PRH to inform users of the relevant change (where applicable). <p>(b) <u>Change in score/break-line</u></p> <p>In addition to the above documents:</p> <ol style="list-style-type: none"> 7. Justification for the change (i.e. change in dosing regimen). 8. Data on test of uniformity of the subdivided parts of the tablets at release as conformed to compendial requirement. 9. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product.

MiV-PA27	Change of shape or dimensions of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass
C	<ol style="list-style-type: none"> 1. If appropriate, the dissolution profile of the proposed product is comparable to that of the approved product. 2. Release and shelf life specifications of drug product remain unchanged except for dimensions and/or shape.
D	<p>(a) <u>Immediate-release oral solid dosage form, suppositories and pessaries</u></p> <ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Detailed drawing or written description of the approved and proposed appearance. 3. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed dimensions/shape for oral solid dosage forms as per as per US FDA SUPAC-IR/MR Guidelines (where applicable). 4. For scored tablets, data on test of uniformity of the subdivided parts of tablets at release as conformed to compendial requirement 5. Release and shelf life specifications of drug product with proposed dimensions and/or shape. <p>(b) <u>Other than immediate-release oral solid dosage forms, suppositories and pessaries</u></p> <p>In addition to the above documents:</p> <ol style="list-style-type: none"> 6. Justification for not submitting a new bioequivalence study according to the ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable).

MiV-PA28	Change in test procedure for drug product
C	<ol style="list-style-type: none"> 1. Drug product specifications are not adversely affected unless the specifications are tightened. 2. Results of method verification/validation show new test procedure to be at least equivalent to the approved procedure. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns, unless otherwise justified. 4. This applies for non-compendial test procedures and/or changes in test procedures from one compendium to another. For the update within the same compendium, please refer to MiV-N10.
D	<ol style="list-style-type: none"> 1. Justification for the proposed change. 2. Comparative tabulated format of the approved and proposed test method of the drug product. 3. Description of the analytical methodology. 4. Appropriate verification/validation data and comparative analytical results between the approved and proposed test (where applicable). A declaration statement may be provided if no verification/validation data is required for minor/editorial changes. 5. Specifications of the drug product (where applicable). 6. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product.

MiV-PA29	Change in primary packaging material for non-sterile drug product a) Type of container b) Addition of primary packaging material c) Qualitative and quantitative composition
C	<ol style="list-style-type: none"> 1. The proposed packaging material must be at least equivalent to or better than the approved material in respect of its relevant properties. 2. Release and shelf life specifications of drug product remain unchanged. 3. For addition or change in the primary packaging material for sterile drug product, please refer to MaV-13.
D	<ol style="list-style-type: none"> 1. Justification for the change in packaging material and appropriate scientific studies on the proposed packaging. 2. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 3. For semi-solid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). 4. Comparative tabulated format of the approved and proposed specifications of the primary packaging material (where applicable). 5. Revised ACTD Section P3 and/or P7 (where applicable). 6. Stability data as per ASEAN Guideline on Stability Study of Drug Product and report if any results fall out-of-shelf life specifications (with proposed action).

MiV-PA30	Update of process validation report from Option 2 to Option 1 (conditional registration/fulfilling commitment) for local manufacturer
C	This is only applicable for update of process validation report for products granted with conditional registration/fulfilling commitment to submit Option 1 reports and it does not involve any other change.
D	Process validation report as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration (Option 1).

MiV-PA31	Change/Addition of pack size/fill volume and/or change of shape or dimensions of container or closure for non-sterile drug product
C	<ol style="list-style-type: none"> 1. The change only concerns the same packaging type and material. 2. The proposed size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Change in the dimensions of the primary packaging material (where applicable). 4. Release and shelf life specifications of drug product remain unchanged. 5. For change of pack size/fill volume and/or change of shape or dimensions of container or closure for sterile solid and liquid drug product, please refer to MaV-14.
D	<ol style="list-style-type: none"> 1. Justification for the proposed pack size. 2. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 3. Revised ACTD Section P3 and/or P7 (where applicable). 4. Declaration from PRH stating that the relevant stability studies of the drug product in accordance with the 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 out-of-specification (with proposed action).

MiV-PA32	Change of drug substance submission option
C	<ol style="list-style-type: none"> 1. Drug substance manufacturer remained the same. 2. Submission option changed from DMF/ACTD to CEP only. For a change in drug substance submission option from CEP to DMF/ACTD, please refer to MaV-3 3. Manufacturing process/route of synthesis of the drug substance remain unchanged. 4. If the change involves changes in drug substance specification, please refer to MaV-7 or MiV-PA9 (where applicable). 5. If there are changes to the test procedure of drug substance, MiV-PA10 is also applicable.
D	<ol style="list-style-type: none"> 1. A valid CEP for the drug substance, latest version, with all annexes issued by EDQM together with the following: <ul style="list-style-type: none"> • A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision • A declaration from the API Manufacturer that the PRH and NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety 2. Revised relevant ACTD Section S (where applicable). 3. CoA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format) of the drug substance manufacturer demonstrating compliance with the EP monograph and including additional test/limits listed on the CEP (where applicable). 4. If CEP did not specify a retest period with specific storage condition, container closure system (CCS) and specific temperature, or CCS (in S6 & S7) is different from CCS (in CEP), long term and accelerated stability data up to the proposed re-test period on 3 pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided.

MiV-PA33	Addition/Replacement of primary packaging site for non-sterile drug product
C	<ol style="list-style-type: none"> 1. No other changes except for the addition or replacement of site for primary packaging (direct contact with drug product). 2. For addition or replacement of site for primary packaging (direct contact with drug product) for sterile product, please refer to MaV-6.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Proof that the proposed site is appropriately authorized for the packaging activity of the pharmaceutical form concerned such as a valid GMP Certificate and/or a CPP which covers GMP certification. 3. In case of a contract primary packager, letter of appointment and letter of acceptance for the proposed site to package the product and stating the types of activity to be performed by the packager (where applicable). 4. Process validation scheme and/or report of the manufacturing process as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration appropriate to the proposed change of alternative site for primary packaging (where applicable). 5. Holding time studies of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6. A letter of commitment from PRH to conduct long term and accelerated stability studies for the drug product packed at the proposed site, and report if any results fall out-of-shelf life specifications (with proposed action) or when requested.

MiV-PA34	Addition/Replacement of measuring device for oral liquid dosage forms and other dosage forms
C	<ol style="list-style-type: none"> 1. The size and where applicable, the accuracy of the proposed measuring device must be compatible with the approved posology. 2. The proposed device is compatible with the drug product.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Description of the device (including a drawing; where applicable). 3. The composition of the device material. The materials should comply with the pharmacopoeia (where applicable). 4. Justification that size and accuracy of the device are adequate for the posology as approved in the product labelling. 5. Data on test of uniformity of delivered dose as per compendium (where applicable).

MiV-PA35	<p>Reduction of the shelf life of drug product</p> <p>a) As a package for sale b) After first opening c) After dilution/reconstitution</p>
C	<ol style="list-style-type: none"> 1. For (a) & (b) - The studies must show conformance to the approved shelf life specification. 2. For (c) – The studies must show conformance to the approved shelf life specification for the reconstituted product. 3. For extension of shelf life, please refer to MaV-16.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Technical justification for the proposed change (where applicable). 3. A letter of commitment from product owner or PRH to inform users of the relevant change (where applicable). 4. Results of appropriate long term stability studies covering the duration of proposed shelf life of the product in the authorized packaging material <ol style="list-style-type: none"> a) as a package for sale b) after first opening c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate).

MiV-PA36	<p>Change of storage condition of drug product (increasing from the approved storage condition)</p> <p>a) As a package for sale b) After first opening c) After dilution/reconstitution</p>
C	<ol style="list-style-type: none"> 1. For (a) & (b) - The studies must show conformance to the approved shelf life specification. 2. For (c) – The studies must show conformance to the approved shelf life specification for the reconstituted product. 3. For change of storage condition (lowering from the approved storage condition), please refer to MaV-17. 4. General precautionary statements on storage conditions in product labelling may be included but should not be used due to stability concerns.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Technical justification for the change of storage condition. 3. Results of appropriate long term stability studies covering the duration of approved shelf life (at proposed storage condition) of the product and in the authorized packaging material <ol style="list-style-type: none"> a) as a package for sale b) after first opening c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product, results of microbiological testing should be included (where appropriate). 4. Data on photosensitivity and/or moisture sensitivity test on drug product (where applicable).

MiV-PA37	Update of stability data report for drug product (no changes to shelf life or storage condition)
C	<ol style="list-style-type: none"> 1. This is applicable for update of stability data report or applications seeking for an exemption from Zone IV B stability requirements for renewal purpose. 2. The shelf life or storage condition of the drug product remains unchanged.
D	<ol style="list-style-type: none"> 1. Results of appropriate long-term stability studies covering the duration of approved shelf life and storage condition of the product and in the authorized packaging material <ol style="list-style-type: none"> a) as a package for sale b) after first opening c) after the dilution/reconstitution in accordance with the ASEAN Guidelines on Stability Study of Drug Product, results of microbiological testing should be included (where appropriate). In addition to D1 for exemption from Zone IV B: 2. Results that the product cannot meet the specifications during storage condition of long-term stability study on 30°C/75% RH for less than 18 months. 3. Scientific justification covering all aspects of the product as appropriate, e.g. drug substance, drug product, formulation, container closure, etc. 4. Letter of intent (from PRH/product owner/manufacturer) requesting exemption from Zone IV B.

9. MINOR VARIATION NOTIFICATION (MiV-N)

MiV-N1	Change of name and/or address of the product registration holder (PRH)
C	<ol style="list-style-type: none"> 1. For change on PRH details in product labelling only. 2. Applicable after a transfer procedure for the purpose of changing the existing PRH to a new PRH has been approved by the Authority. This requires a formal application prior to the submission of this variation type. Please refer to DRGD for the procedures & requirements for the change of PRH. 3. This is also applicable after the PRH details have been updated in the system. For example, renaming of the company and update of the existing PRH address (e.g. postal code, street name). 4. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Letter by the product owner authorizing the new name/address of PRH to hold the product license. 3. Official document from the Authority confirming the change with the new name and/or address (where applicable).

MiV-N2	Change of importer and/or store address
C	<ol style="list-style-type: none"> 1. Update of importer and/or store address in the system. 2. The batch release site remains the same. 3. The manufacturer of the drug product remains the same. 4. Only applicable for the change of importer and/or store address details in the product labelling. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	<ol style="list-style-type: none"> 1. Valid business license. 2. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable).

MiV-N3	Change of product owner
C	<ol style="list-style-type: none"> 1. The PRH remains the same. 2. The manufacturing site remains the same. 3. This includes renaming of the company and updating the address of the product owner (e.g. postal code, street name).
D	<ol style="list-style-type: none"> 1. Declaration letter on the transfer of ownership between approved and proposed product owner and counter-signed by both parties (where applicable). 2. Official letter from the proposed product owner declaring the change and authorizing the PRH to be responsible for the product license. 3. If the proposed product owner is not the manufacturer of the drug product, an official letter by the proposed product owner authorizing the manufacturer to manufacture the drug product on its behalf. 4. If the proposed product owner is not the manufacturer of the drug product, letter of acceptance from the manufacturer that it will be held responsible for manufacturing and ensuring the quality, safety and efficacy aspect of the drug product. 5. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made including changes to product registration number (where applicable).

MiV-N4	Change in ownership of manufacturer
C	<ol style="list-style-type: none"> 1. The manufacturing site remains the same. 2. No other changes except for the change in ownership of manufacturer. 3. For local manufacturers, this is only applicable after the formal application to update manufacturer's name in the system has been approved. 4. For overseas manufacturers, details will be updated in the system after the variation is approved. 5. Only applicable for the change of manufacturer details in the product labelling. Please refer to MaV-2 and MiV-PA2 if other changes are involved.
D	<ol style="list-style-type: none"> 1. Letter of justification on the transfer of ownership such as a valid GMP certificate. 2. Official letter stating the transfer to the proposed manufacturer (where applicable). 3. In case of a contract manufacturer, official letter from product owner declaring the change and authorizing the proposed manufacturer to manufacture the drug products on its behalf. 4. In case of a contract manufacturer, letter of acceptance from the proposed manufacturer that it will be held responsible for manufacturing and ensuring the quality, safety and efficacy aspect of the drug product. 5. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made including changes to product registration number (where applicable).

MiV-N5	Change of name and/or address of the manufacturer of drug product
C	<ol style="list-style-type: none"> 1. The manufacturing site remains the same. 2. No other changes except for the change of the name and/or address of the manufacturer of drug product (e.g. postal code, street name, district/state name). 3. For local manufacturers, this is only applicable after the formal application to update manufacturer's name in the system has been approved. 4. For overseas manufacturers, details will be updated in the system after the variation is approved. 5. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer to MiV-N4. 6. Only applicable for the change of manufacturer details in the product labelling. Please refer to MaV-2 and MiV-PA2 if other changes are involved.
D	<ol style="list-style-type: none"> 1. A valid GMP certificate or CPP which covers the GMP certification or official document from relevant Authority confirming the proposed name and/or address. 2. Official letter from product owner authorizing the manufacturer with proposed name/address to manufacture the drug product. 3. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made including changes to product registration number (where applicable).

MiV-N6	Change of name and/or address of the company or manufacturer responsible for batch release
C	<ol style="list-style-type: none"> 1. The manufacturer of the drug product remains the same. 2. The batch release site remains the same. 3. No other changes except for the change of the name and/or address of the company or manufacturer responsible for batch release (e.g. postal code, street name, district/state name). 4. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer to MiV-N4. 5. Only applicable for the change of batch releaser details in the product labelling. Please refer to MaV-2 and MiV-PA2 if other changes are involved.
D	<ol style="list-style-type: none"> 1. A valid GMP certificate or CPP which covers the GMP certification or official document from relevant Authority confirming the proposed name or address (where applicable). 2. Official letter from product owner authorizing company/manufacturer with proposed name/address responsible for batch release. 3. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made including changes to product registration number (where applicable). 4. Declaration from PRH that the change does not involve change of batch release site.

MiV-N7	Change of name and/or address of the manufacturer of drug substance
C	<ol style="list-style-type: none"> 1. The manufacturing site of drug substance remains the same. 2. No other changes except for the change of the name and/or address of the manufacturer of drug substance (e.g. postal code, street name, district/state name).
D	<ol style="list-style-type: none"> 1. Updated information of the manufacturer of the drug substance. 2. Official document/evidence (where applicable).

MiV-N8	Withdrawal/Deletion of a) primary and/or secondary packaging site(s) for drug product b) alternative manufacturer(s) for drug substance
C	An alternative manufacturer is registered.
D	<ol style="list-style-type: none"> 1. Reason for withdrawal/deletion. 2. For deletion of the drug product packager, proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made, including changes to product registration number (where applicable).

MiV-N9	Renewal of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
C	Only applicable if the renewal of CEP does not involve any other change.
D	A valid CEP of drug substance of the latest version, with all annexes issued by EDQM.

MiV-N10	Change of release and/or shelf life/re-test specifications and/or test procedure of a) drug product b) drug substance c) excipient following the updates in the compendium
C	<ol style="list-style-type: none"> 1. Applicable to compendial specifications and/or test procedure only. 2. Change is made exclusively to comply with an update of the relevant monograph within the same compendium. 3. For changes in specifications and/or test procedure from one compendium to another, please refer to: <ol style="list-style-type: none"> a) MiV-PA25 and/or MiV-PA28 for drug product b) MiV-PA9 and/or MiV-PA10 for drug substance c) MiV-PA22 and/or MiV-PA23 for excipient
D	<ol style="list-style-type: none"> 1. Tabulation of the approved and proposed release and/or shelf life/re-test specifications and/or test procedure with changes highlighted. 2. Certificate of analysis and batch analysis data: <ul style="list-style-type: none"> • Drug product: COA for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) according to approved and proposed product specifications. • Drug substance: COA (2 batches) and batch analysis data (at least 3 pilot batches in a comparative tabulated format). • Excipient: CoA and batch analysis data (in comparative tabulated format) for all tests in the proposed specifications of at least two batches (where applicable) 3. Copy of the relevant monograph from the compendium. 4. Revised release and/or shelf life/re-test specifications. 5. For change in test procedure, appropriate verification data of the proposed test procedure (where applicable). 6. Declaration from the PRH (where applicable) stating that the relevant stability studies of the drug product will be started and finalized; data should be provided only if out-of-specification (with proposed action).

MiV-N11	Deletion of pack sizes for drug product
C	<ol style="list-style-type: none"> 1. The remaining pack sizes are adequate to accommodate the approved dosing regimen. 2. For addition of pack size for sterile and non-sterile products, please refer to MaV-14 and MiV-PA31 respectively. For change in the outer carton pack size, please refer to MiV-N16. 3. Only applicable for the change of pack size in the product labelling. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	<ol style="list-style-type: none"> 1. Reason for deletion. 2. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable).

MiV-N12	Minor change in the manufacturing process of immediate-release solid oral dosage forms, semi-solids or liquid dosage forms
C	<ol style="list-style-type: none"> 1. The change, as per Level 1, Part VI Manufacturing, SUPAC Guideline. <ol style="list-style-type: none"> i. Change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients. ii. Change to alternative equipment of the same design and operating principles of the same or of a different capacity. iii. Process changes including changes such as mixing times and operating speeds within application/validation ranges. 2. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 3. The manufacturing principle for individual manufacturing steps remain unchanged, e.g. there are no changes in the processing intermediates and manufacturing solvent(s) used in the process. 4. The proposed process has to be controlled by relevant in-process controls used in the approved process and no changes (widening or deletion of limits) are required for these controls. 5. The specifications of the drug product and/or process intermediates remain unchanged. 6. The proposed process must lead to an identical product regarding all aspects of quality, safety and efficacy. 7. For minor changes of the manufacturing process of immediate-release solid oral dosage forms, semi solids or liquid dosage forms that are not as per Level 1, Part VI Manufacturing, SUPAC Guideline, please refer to MiV-PA21. 8. For minor changes of the manufacturing process for other dosage forms of non-sterile products, please refer to MiV-PA21.
D	<ol style="list-style-type: none"> 1. Revised relevant sections of the dossier, as appropriate, including a direct comparison of the approved and proposed processes. 2. Release and shelf life specifications of drug product. 3. CoA of the drug product for at least 2 production/pilot scale batches and batch analysis data (in a comparative tabulated format) of the drug product according to approved and proposed processes. 4. Declaration from PRH (where applicable) stating that the relevant stability studies of the drug product will be started and finalized; data should be provided only if out-of-specification (with proposed action).

MiV-N13	Change in the primary/secondary packaging material (not in contact with the drug product)
C	<ol style="list-style-type: none"> 1. For change of any part of the packaging material not in contact with drug product <ol style="list-style-type: none"> a) primary packaging, such as colour of flip-off caps, colour code rings on ampoules, change of needle shield. b) secondary packaging, such as paper/cardboard. 2. The change does not concern the part of the packaging material, which affects the delivery, use, safety or stability of the drug product.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Revised ACTD Section P1 and/or P7 (where applicable).

MiV-N14	Replacement of the company or manufacturer responsible for batch release
C	<ol style="list-style-type: none"> 1. Only applicable for batch release. 2. The manufacturer of the drug product remains unchanged. 3. Method transfer from the approved to the proposed site or test laboratory has been successfully completed.
D	<ol style="list-style-type: none"> 1. Proof that the proposed site is appropriately authorized (accredited by the Authority) to be responsible for batch release such as a valid GMP certificate or CPP which covers the GMP certification. 2. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable). 3. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable).

MiV-N15	Addition/Replacement of secondary packaging site for drug product
C	The manufacturer and primary packager of the drug product remains unchanged.
D	<ol style="list-style-type: none"> 1. Proof that the proposed site is appropriately authorized (accredited by the authority) for the packaging activity concerned such as a valid GMP certificate and/or CPP which covers the GMP certification. 2. Official letter from product owner authorizing the proposed manufacturer or packager to perform secondary packaging (where applicable). 3. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made including changes to product registration number (where applicable).

MiV-N16	Change of outer carton pack sizes of drug product
C	<ol style="list-style-type: none"> 1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a drug product. 3. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labelling.
D	<ol style="list-style-type: none"> 1. Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). 2. Declaration letter from PRH stating that there are no other changes except for the change of outer carton pack sizes for a drug product.

MiV-N17	Addition/Replacement of the company/site responsible for quality control (QC) testing a) drug product b) drug substance
C	<ol style="list-style-type: none"> 1. The manufacturer and primary packager of the drug product/drug substance remains unchanged. 2. Method transfer from the approved to the proposed site or test laboratory has been successfully completed.
D	<ol style="list-style-type: none"> 1. Declaration from the drug product/drug substance manufacturer/product owner on the following: <ul style="list-style-type: none"> • The change does not affect the release and shelf life specifications of the drug product/drug substance • The tests used by the proposed QC testing site are equivalent to the registered methods. • List of tests used by the proposed QC testing site with indication if the method suitability/transfer/validation has been completed for each test. 2. Documentary evidence that the proposed quality control testing site is appropriately accredited. 3. Official letter from product owner authorizing the company to be responsible for quality control testing site (where applicable). 4. Analytical method transfer data/verification data (where applicable). 5. Revised ACTD Section P3 and/or S2.

MiV-N18	Change of name and/or address of the company/site responsible for quality control (QC) testing a) drug product b) drug substance
C	<ol style="list-style-type: none"> 1. The quality control testing site remains the same. 2. The manufacturer of the drug product/drug substance remains the same. 3. No other changes except for the change of the name and/or address of the company/site responsible for quality control testing (e.g. postal code, street name, district/state name). 4. For change in ownership of manufacturer, please refer to MiV-N4.
D	<ol style="list-style-type: none"> 1. Documentary evidence that the proposed quality control testing site is appropriately accredited (where applicable). 2. Official letter from product owner authorizing company with proposed name/address to be responsible for quality control testing. 3. Declaration letter from PRH stating that the change does not involve change of quality control testing site.

MiV-N19	Administrative/Editorial changes to drug product labelling Includes: a) Addition of barcode b) Addition of trademark/registered trademark c) Change of distributor's details d) Change of box size/dimensions e) Change of colour of existing graphic f) Change of product logo/company logo/company registration number g) Change of layout (e.g. position of existing graphic & product information) h) Update of administrative code of product registration number (e.g. C/E/R/S) i) Update of label with product category code (e.g. X to A) j) Update of label with other country registration code k) Deletion of pictures, diagrams, barcode, logos and/or texts that do not imply an unapproved indication. l) Amendment of typographical errors
	C The change is not a MaV and MiV-PA and does not contain promotional information.
	D <ol style="list-style-type: none"> Proposed product labelling/PI/PIL – a clean and annotated version highlighting the changes made (where applicable). Declaration letter from the PRH stating that there are no other changes on the label except for the intended change. Trademark certificate (where applicable). Relevant document/reference to support the changes (where applicable).

MiV-N20	Update of Good Manufacturing Practice (GMP) Certificate
C	This is applicable if the update of GMP certificate does not involve any other change.
D	A valid GMP certificate for the drug product, issued by PIC/S Authority.

MiV-N21	Update of Certificate of Pharmaceutical Product (CPP)
C	This is applicable if the update of CPP certificate does not involve any other change.
D	A valid CPP certificate for the drug product, issued by the relevant Authority.

MiV-N22	Update of Halal Certificate or addition/deletion of Halal logo
C	This is applicable if the update of Halal certificate or addition/deletion of Halal logo does not involve any other change.
D	<ol style="list-style-type: none"> A valid Halal certificate for the drug product, issued by the relevant Authority. Proposed product labelling – a clean and annotated version highlighting the changes made (where applicable).

MiV-N23	Update of Endorsement Letter (EL)/Acknowledgment Receipt (AR) from Medical Device Authority for drug-device combination
C	This is applicable if the update of EL/AR does not involve any other change.
D	Official document issued by the relevant Authority.

MiV-N24	Update of approval for products exempted from Zone IV B stability data requirements
C	<ol style="list-style-type: none"> 1. This is only applicable after an exemption from Zone IV B stability has been approved in the system via MiV-PA37. 2. There is no change to the approved shelf life or storage condition.
D	Approval letter issued by the secretariat of the Authority exempting the product from Zone IV B stability data requirements.

MiV-N25	Update of Bioequivalence (BE) Data/Status
C	<ol style="list-style-type: none"> 1. This is applicable after bioequivalence data that has been reviewed and approved manually (e.g. to fulfil product registration renewal requirement). 2. This is also applicable for products that have been granted exemption from bioequivalence requirements.
D	<ol style="list-style-type: none"> 1. Approved letter issued by the secretariat of the Authority for the report of bioequivalence data/exempting the product from bioequivalence requirements. 2. The approved report of bioequivalence data according to the ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies.

MiV-N26	Update of information following approval of Additional Indication
C	<ol style="list-style-type: none"> 1. This is applicable for update of ACTD Section A as per package insert that has been reviewed and approved during Additional Indication application. 2. This is a post-approval update for additional indications approved via the Additional Indication application.
D	<ol style="list-style-type: none"> 1. Revised ACTD Section A. 2. Approval letter issued by the secretariat of the Authority.

10. GLOSSARY

Refer to ACTD/ACTR Glossary

11. REFERENCES

1. ASEAN Variation Guideline for Pharmaceutical Products (Rev 2) 2021
2. European Medicine Agency Variation Guideline, 2013 : Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures - Official Journal of the European Union (C 223 of 2.08.2013)
3. WHO Guidance on Variations to a Prequalified Product Dossier (WHO Technical Report Series, No. 981, 2013)
4. SUPAC-IR: Immediate-Release Solid Oral Dosage Forms, Scale-up and Post-approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, 1995
5. SUPAC-MR: Modified-Release Solid, Oral Dosage Forms, Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation, 1997
6. ASEAN Guideline on Stability Study of Drug Product, R1, 25th ACCSQ-PPWG
7. ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration
8. ASEAN Guideline for Validation of Analytical Procedures
9. ASEAN Guideline for the Conduct of Bioavailability and Bioequivalence Studies, 2015

Appendix A

LIST OF MINOR VARIATION-PRIOR APPROVAL (MIV-PA*) CHANGES ALLOWED TO BE PROCESSED VIA THE “TELL & DO” PROCEDURE FOR PHARMACEUTICAL PRODUCTS

No.	Variation Type	Variation Title
1.	MiV-PA3*	Change of patient information leaflet (PIL)
2.	MiV-PA5*	Addition/Replacement of manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
3.	MiV-PA7*	Change of in-process controls applied during the manufacture of drug substance [including tightening and addition of new in process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
4.	MiV-PA9(a)*	Change of specifications of drug substance (a) Specification limits are tightened <i>Note: This applies for specification changes</i> - between non-compendial - from non-compendial to compendial - from one compendium to another
5.	MiV-PA9(b)*	Change of specifications of drug substance (b) Addition of new test parameter and limits (following compendium) <i>Note: This applies for specification changes</i> - from non-compendial to compendial - from one compendium to another
6.	MiV-PA9(c)*	Change of specifications of drug substance (c) Specification limits are widened following compendium <i>Note: This applies for specification changes</i> - from non-compendial to compendial - from one compendium to another
7.	MiV-PA9(d)*	Change of specifications of drug substance (d) Deletion of test parameter and limits following compendium <i>Note: This applies for specification changes</i> - from non-compendial to compendial - from one compendium to another
8.	MiV-PA13*	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
9.	MiV-PA14*	Change of batch size of non-sterile drug product (up to 10-fold)
10.	MiV-PA15*	Reduction/Removal of overage of drug substance <i>Note: No other changes to the formulation can be made</i>
11.	MiV-PA18*	Change of colouring agent/flavouring agent/capsule shell colour of drug product
12.	MiV-PA20*	Change of in-process controls applied during the manufacture of drug product (including tightening and addition of new in-process test)
13.	MiV-PA22(a)*	Change of specifications of non-compendial excipient (a) Specification limits are tightened

14.	MiV-PA25(a)*	Change of release and/or shelf life specifications of drug product (a) Specification limits are tightened <i>Note: This applies for specification changes</i> - between non-compendial - from non-compendial to compendial - from one compendium to another
15.	MiV-PA25(b)*	Change of release and/or shelf life specifications of drug product (b) Addition of new test parameter and limits (following compendium) <i>Note: This applies for specification changes</i> - from non-compendial to compendial - from one compendium to another
16.	MiV-PA25(c)*	Change of release and/or shelf life specifications of drug product (c) Specification limits are widened following compendium <i>Note: This applies for specification changes</i> - from non-compendial to compendial - from one compendium to another
17.	MiV-PA25(d)*	Change of release and/or shelf life specifications of drug product d) Deletion of test parameter and limits following compendium <i>Note: This applies for specification changes</i> - from non-compendial to compendial - from one compendium to another
18.	MiV-PA26*	Change of imprints, embossing/debossing or other markings (including break/score-line) on tablets or printing on capsules including addition/change of inks used for product marking (a) Imprints, embossing/debossing or other markings on tablets or printing on capsules <i>Note: Proposed imprints/markings should not be of misleading logo/wordings and changes in the labels strictly for updating the new description only</i> (b) Removal of score/break-line that was included initially for cosmetic purposes is allowed
19.	MiV-PA29*	Change in primary packaging material for non-sterile drug product a) Type of container b) Addition of primary packaging material c) Qualitative and quantitative composition <i>Note: For upgrading purpose (reference paper to support the material upgrading is needed)</i>
20.	MiV-PA31*	Change/Addition of pack size/fill volume and/or change of shape or dimensions of container or closure for non-sterile drug product
21.	MiV-PA32*	Change of drug substance submission option
22.	MiV-PA34*	Addition/Replacement of measuring device for oral liquid dosage forms and other dosage forms <i>Note: As long as the device is not an integrated part of the primary packaging</i>
23.	MiV-PA35*	Reduction of the shelf life of drug product a) As a package for sale b) After first opening c) After dilution/reconstitution

*Subtype variation: Only relevant fields are opened in the online QUEST system