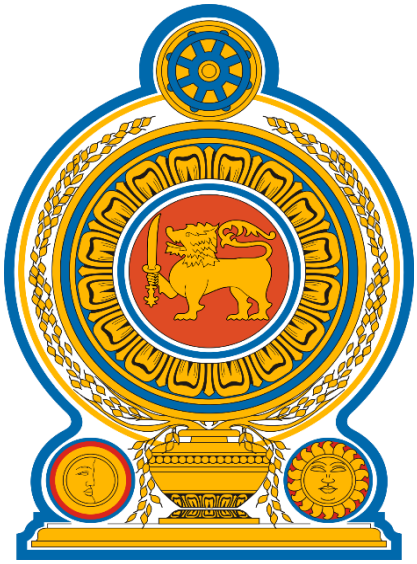

GUIDELINE ON VARIATIONS FOR MEDICINES

MAY 17, 2022

NATIONAL MEDICINE REGULATORY AUTHORITY
No.120, Norris Canal Rd, Colombo 01000, Sri Lanka

GUIDELINE ON VARIATIONS FOR MEDICINES

Content

1. INTRODUCTION

The marketing authorization holder is responsible for the quality, safety, and efficacy of a medicine (i.e. a finished pharmaceutical product) that is placed on the market, throughout its life cycle. Changes may be required to the content of particulars related to the medicine that were submitted to NMRA, due to various reasons such as technical and scientific advances, new findings that affects its quality, safety, efficacy, or simply changes of administrative nature. Marketing authorization holder is legally bound to inform any such changes to the NMRA.

Variation applications are categorized as major variations, minor variations requiring approval and, minor variations requiring notification based on the level of impact on the quality, safety, and efficacy of a registered medicine. The guideline will be updated periodically, as required.

2. PURPOSE

This guideline intends to provide the marketing authorization holders with information on requirements for submission of variation applications in order to implement the intended change.

The document would also serve as a guideline for the Medicines Evaluation Committee in terms of clause 47 of the NMRA Act No. 05 of 2015, and to respective reviewers who would be tasked with review of variation applications.

3. SCOPE

The document will serve as a guide to establish national requirements for regulation of post-approval changes relevant to finished pharmaceutical products. In this document, such post-approval changes are categorized depending on the level of risk to the public.

4. ABBREVIATIONS

API	-	Active Pharmaceutical Ingredient (drug substance)
BSE	-	Bovine Spongiform Encephalopathy
CEP	-	Certificate of Suitability
CPP	-	Certificate of a Pharmaceutical Product
CTD	-	Common Technical Document
EDQM	-	European Directorate for the Quality of Medicine
GMP	-	Good Manufacturing Practices
MAH	-	Marketing Authorization Holder
NMRA	-	National Medicines Regulatory Authority
PET	-	Preservative Effectiveness Tests
Ph Eur	-	European Pharmacopeia
PI	-	Package Insert
PIL	-	Patient information leaflet
SmPC	-	Summary of Product Characteristics
MAV	-	Major Variation
MIV_1	-	Minor variations requiring approval
MIV_2	-	Minor variations requiring notification
TSE	-	Transmitting Animal Spongiform Encephalopathy
USPI	-	United States Product Information

5. APPLICATION TYPES

There are 3 (three) types of application for variation registration as the following,

- **Major variations (MAV)**
  Proposed changes that may affect directly and/or significantly the aspects of its quality, safety and efficacy of a registered medicine and they do not fall within the definition of a minor variation or a new registration. Prior to implementation of such changes, approval of the NMRA is necessary.
- **Minor variations requiring approval (MIV_1)**
  Proposed changes may have minimum impact on the quality, safety, and efficacy of a registered medicine. NMRA approval for the change is still required prior to implementation.
- **Minor variations requiring notification (MIV_2)**
  These changes are mainly of administrative nature with no significant impact on quality, safety, and efficacy of the registered medicine. Marketing authorization holder requires only notifying the change to the NMRA.

6. PROCEDURES

i. In terms of NMRA Act and regulations, a marketing authorization holder shall make a variation application to the Authority in the form specified in regulations for prior approval or notification of a change to the content of particulars relevant to a registered medicine.

ii. Each variation shall require a separate application. A processing fee shall be charged as specified in the gazette no. 2052/33 of the regulations for each application relevant to variations requiring prior approval.

iii. Nevertheless grouping of variations shall be allowed in certain cases, in order to facilitate smooth review and ease administrative burden. E.g. when several changes are interrelated such as variations leading to revision of product information (SmPC, PI and labelling) or when a change affects several marketing authorizations of the same marketing authorization holder (change of name of the manufacturer)

iv. For the purpose of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change.

v. For major variations and minor variations requiring prior approval, a letter shall be issued to the marketing authorization holder conveying whether the proposed change is acceptable to NMRA.

vi. Minor variations requiring only a notification shall make the variation application after the change has been implemented, but not more than 12 months of implementation. If NMRA does not issue an unfavourable opinion on a minor variation for notification within 30 days of receiving the notification, the variation deemed acceptable to NMRA.

vii. On certain instance, amendments may be also needed to the existing certificate of registration. E.g. Change of shelf life (MAV), deletion of a pack size (MIV_2)

viii. NMRA reserves the right to request for additional data in order to determine the acceptability of the variation.

ix. NMRA reserves the right to re-categorize the variation type indicated by the applicant, or to determine whether the change necessitate a new product registration altogether.

x. Category of any variation not listed in this guideline shall be determined by the Authority

7. TIMELINES

Type of variation	Timeline for the MAH	Procedure	Timeline for NMRA
Major variation	Prior to implementation	If the application fulfils the requirements, NMRA shall issue an approval for the proposed change	120 working days
Minor variation requiring approval	Prior to implementation	If the application fulfils the requirements, NMRA shall issue an approval for the proposed change	90 working days
Minor variation requiring notification	Within one year of implementation	To consider as approved if no response from NMRA within 30 working days	30 working days, if there is a concern

8. DOCUMENTARY REQUIREMENT FOR SUBMISSION OF VARIATION

8.1 All Documents in support of an application for variation should be submitted along with **administrative documents,** among other, as the following,

(i) A statement letter that declares there is no other change except for the proposed variation
(ii) A comparative table of the proposed changes including reference of changes.
(iii) Justification of the proposed changes.
(iv) Certificate of Registration and all prior approvals of Variation issued by the NMRA including the appendices
(v) Other required administrative documents.

8.2 Condition for variation to be fulfilled and the document to be submitted depend on the type of medicine.

(i) For medicines which contain chemical entity, the conditions and documentary requirements are listed in **APPENDIX I**. Biological products and vaccines are not covered in the list.

(ii) Refer to the WHO's guidelines, for the condition and documentary requirements relevant to biological / biotech products, and vaccines. It should be bear in mind that there are differences of naming or term of categories of variation in the WHO's guideline and the term used in this guideline. However, the classification is the same. The different terms used are as follows:

No	Classification in the WHO Guideline	Category of Variation in this Guideline

1	Major	Major Variations (**MAV**)
2	Moderate	Minor Variation Requiring Approval (**MIV_1**)
3	Minor	Minor Variations Requiring Notification (**MIV_2**)

- For ease of reference, **APPENDIX II** of this guideline list examples of Major Variations, Minor Variations requiring Approval and Minor Variations requiring Notification for biological/ biotech products.
- For detailed condition and documentary requirements for variations relevant to biological/biotech products and vaccines, respective WHO's guidelines should be referred.

8.3 Changes Leading To a New Product Registration

Certain variations to the product, which are mostly not listed in this guideline, may lead to a new product registration and, it may be necessary to submit a new application for marketing authorization of the varied product. E.g. Change of API, change of dosage form, change of release profile such as normal release to sustained release, change of coating of tablets such as sugar coated to film coated, and change of primary packaging type such as vial to ampoule or a pre-filled syringe. NMRA would consider whether a new registration is required, case by case. NMRA would also consider addition or replacement of the manufacturing site of the drug product (sterile) as a new registration ~~or a registration of variation following the condition and documentary requirement in APPENDIX I and II.~~

9. RELATED LEGISLATIONS

1. National Medicine Regulatory Authority Act No. 05 of 2015
2. National Medicines Regulations 2145/1, 14th October 2019

10. REFERENCES

1. ASEAN variation guideline for pharmaceutical products, R1, June 2019
2. WHO general guidance on variations to multisource pharmaceutical products, Annex 10, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fiftieth report.
3. WHO Guideline on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products, 2017
4. Annex 4 WHO TRS 993, Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines, 2015
5. Scale-Up and Postapproval Changes (SUPAC); Guidance for Industry, CDER, November 1995

11. FEEDBACK

Staff and customers may provide feedback about this document by emailing info@nmra.gov.lk

	NAME	**SIGNATURE**
Prepared by		

Reviewed By		
Recommended By		
Approved by		

Next Review Date	01/10/2022

APPENDIX I.

CONDITION (C) TO BE FULFILLED AND DOCUMENTS (D) TO BE SUBMITTED WITH VARIATION APPLICATIONS (FOR MEDICINE WITH CHEMICAL ENTITY ONLY)

1. MAJOR VARIATION (MaV)

MaV-1	**Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product**
C	1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Approved product labelling. 2. Proposed product labelling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4. Justifications for the changes proposed. 5. Approval letters from reference countries or country of origin which have approved the proposed indication or dosing regimen (where applicable). 6. Clinical expert reports and/or clinical trial reports (where applicable). 7. Clinical documents as per CTD (where applicable).
MaV-2	**Change of content of product labelling**
C	1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not a minor variation and not within the scope of MaV-1. 3. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI).
D	1. Approved product labelling. 2. Proposed product labelling, a clean and annotated version highlighting the changes made. 3. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes (where applicable). 4. Justifications for the changes proposed and supporting clinical documents when applicable.
MaV-3	**Addition or replacement of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. Specifications of drug substances remain unchanged. 2. For Change and/or addition of alternative manufacturer/site of drug substance where European Pharmacopoeial Certificate of Suitability (CEP) is available, please refer to MiV-PA4.

D	1. Complete CTD section S1-S7, or both the open and closed part of the Drug Master File (closed part may be provided directly by manufacturer) with the Letter of Access or equivalent audit document/certification from reference country which is deemed appropriate by the Drug Regulatory Authority. 2. Comparative tabulated format of the approved and proposed drug substance manufacture information (where applicable). 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. 4. A letter of commitment from marketing authorization holder 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 outside shelf-life specifications (with proposed action) or when requested.
MaV-4	**Addition or replacement of the manufacturing site of the drug product**
C	~~1. The manufacturer responsible for batch release or a site where only batch release takes place remains unchanged.~~ No change in the master formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, of FPP specification. 2. Approval of proposed manufacturing site by NMRA is a pre-requisite 3. The change does not concern a sterile FPP 4. Validation protocol is available and validation of the manufacturing process at the new site has been successfully carried out on at least three production-scale batches in accordance with the current protocol. 5. For addition or replacement of the company or party responsible for batch release, please refer to MiV-PA3. 6. If there are changes to the manufacturing process, MaV-9 is also applicable. ~~7. Approval of proposed manufacturing site by NMRA is a pre-requisite~~
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Proof that the proposed site is appropriately authorized for the pharmaceutical form concerned such as a valid Good Manufacturing Practice (GMP) certificate and~~/or~~ a Certificate of Pharmaceutical Product (CPP) which covers GMP certification. 3. Batch numbering system (where applicable). 4. In case of a contract manufacturer, letter of appointment and letter of acceptance for the proposed site to manufacture the product and stating the types of activity to be performed (where applicable). 5. Where applicable, for semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology. 6. Specification of drug substance. 7. Product formula and/or batch manufacturing formula. ~~8. Comparative dissolution profile data of at least one pilot/production batch of the drug product manufactured in the approved and proposed manufacturing site for oral solid dosage forms as per compendium and validated dissolution test method.~~ For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches. 9. Validation scheme and/or report of the manufacturing process at the proposed site should be provided upon submission. 10. Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable). 11. Release and shelf-life specifications of drug product. 12. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the approved site; batch analysis data on the next two full production batches should

	be available upon request or reported if outside specifications (with proposed action). ~~13. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action).~~ Stability data including six months accelerated study report and real time study report minimum for six months for three batches (excluding R & D batches) with commitment to completion of the study. 14. NMRA may grant Provisional Registration (PR) upon completion of the required conditions and documents required. ~~15. Justification for not submitting a new bioequivalence study (where applicable).~~
MaV-5	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product, please refer to MiV-PA36.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (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. Validation scheme and/or report on primary packaging processes at the proposed site should be provided upon submission. 5. Holding time studies testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-6	**Change of the specification of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available] and/or drug product** **a) Specification limits are widened** **b) Deletion of test parameter and limits**
C	1. Test procedures remain unchanged, 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; unless otherwise justified. 4. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	**(a) Specification limits are widened** 1. Revised specification of drug substance / drug product. 2. Comparative tabulated format of the approved and proposed specification of drug substance/drug product with changes highlighted. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of the drug substance/drug product for all tests in the proposed specification for two pilot or production scale batches. 4. Justification for change substantiated with scientific data to be provided. 5. Stability data as per new specifications. A report with proposed action should be submitted if any results fall outside shelf-life specifications. **(b) Deletion of test parameter and limits** All of the above documents except D5.
MaV-7	**Change of batch size of sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 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 three batches appropriate to the proposed batch size.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Validation scheme and/or report of the manufacturing process of the proposed batch size should be provided upon submission. 3. Release and shelf-life specifications of the drug product. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production batches 5. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-8	**Change of batch size of non-sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 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 three batches appropriate to the proposed batch size. 5. This is applicable to 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 approved batch size, please refer MiV-PA13.
D	1. 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 compendium and validated dissolution test method (where applicable). 2. Comparative tabulated format of approved and proposed batch manufacturing formula. 3. Validation scheme and/or report of the manufacturing process for the proposed batch size should be provided upon submission. 4. Release and shelf-life specifications of the drug product. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to approved and proposed batch sizes and letter of undertaking to submit batch analysis data on the next one full production batch. 6. Stability data of drug product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-9	**Major change in the manufacturing process for drug product**
C	1. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 2. The manufacturing site remains unchanged. If there is a change in manufacturing site, MaV-4 is also applicable. 3. For minor change of the manufacturing process for non-sterile product, please refer to MiV-PA20/MiV-N11.
D	1. Description of the proposed manufacturing process and technical justification for the change. 2. 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 compendium and validated dissolution test method. 3. Validation scheme and/or report of the proposed manufacturing process should be provided upon submission. 4. Copy of approved release and shelf-life specifications. Or, alternatively, copy of proposed release and shelf-life specifications that supports that the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product for a minimum of one production batch manufactured according to approved and proposed processes. 6. Stability data of drug product and report if any results fall outside shelf-life specifications (with proposed action).

	7. Justification for not submitting a new bioequivalence study (where applicable).
MaV-10	**Qualitative or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 2 and 3, Part III Components and Composition, SUPAC guideline)** **b) For modified release oral dosage forms** **c) For other critical dosage forms such as sterile preparations.**
C	1. Change will need to comply with the finished product specifications for example release and shelf-life specifications of the drug product remain unchanged, excluding product description except for update of product description with respect to appearance/odour/taste as a consequence of the change (where applicable). 2. Replacement of an excipient with a comparable excipient of the same functional characteristics. 3. The dissolution profile of the proposed product is comparable to that of the approved product. 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 three batches of the proposed product formula. 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-PA15.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A declaration that the proposed excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 3. Justification for the change must be given by appropriate development of pharmaceutics. 4. 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). 5. 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 compendium and validated dissolution test method (where applicable). 6. Revised batch manufacturing formula. 7. Validation scheme and/or report of the manufacturing process which is appropriate to the proposed change in product formula should be provided upon submission. 8. Revised CTD Section P3.1 to P3.4 (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). 11. Drug product release and shelf-life specifications. 12. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on at least two production (or one production batch and two pilot batches) according to approved and proposed product formula. 13. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action). 14. Justification for not submitting a new bioequivalence study (where applicable). 15. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).
MaV-11	**Quantitative change in coating of tablets and/or size of capsule shell for modified release oral dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the approved product. 2. The release and shelf-life specifications of the drug product remain unchanged except for the weight and/or size (where applicable). 3. For quantitative change in coating of tablets or weight and/or size of capsule shell for immediate release oral solid dosage forms, please refer to MiV-PA16.
D	1. Revised draft of product label incorporating the proposed change (where applicable).

	2. A declaration that the change does not interfere with the drug product release and shelf-life specifications test method. 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 compendium and validated dissolution test method (where applicable). 4. Approved and proposed product and batch manufacturing formula. 5. Revised release and shelf-life specifications of the drug product. 6. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action). 7. Justification for not submitting a new bioequivalence study (where applicable).
MaV-12	**Change in primary packaging material for sterile product a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of primary packaging material**
C	1. Release and shelf-life specifications of the drug product remain unchanged. 2. For change in the primary packaging material for non-sterile drug product, please refer to MiV-PA28.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Appropriate scientific data on proposed packaging (comparative data on permeability, e.g. moisture, O_2, CO_2). 3. Proof must be provided that no interaction between the content and the packaging material occurs (where applicable). 4. Validation scheme and/or report of the manufacturing and sterilization process which is appropriate to the proposed change in primary packaging material should be provided upon submission. 5. Comparative tabulated format of specifications of the approved and proposed primary packaging material. 6. Revised CTD Sections P3 and/or P7 (where applicable). 7. Stability data as per for the drug product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-13	**Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product**
C	1. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. The packaging material remains unchanged. 3. Release and shelf-life specifications of the drug product are not affected, except pack size/fill volume specification. 4. Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile drug product, please refer to MiV-PA30.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Validation data of the manufacturing process, sterilization and container closure system (where applicable). 4. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action).
MaV-14	**Inclusion or replacement of the solvent/diluent for the drug product**
C	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-PA18. 3. For change of shelf-life and/or storage condition of the drug product after first opening and/or after dilution/reconstitution, please also refer to MaV-15/MiV-PA34 and/or MaV-16/MiV-PA35 (where applicable).
D	1. Revised drafts of the package insert and labelling incorporating the proposed

	variation. 2. Documentary evidence to certify the manufacturing site of diluents/solvents complies with current applicable GMP standards (where applicable). 3. Batch numbering system (where applicable). 4. A letter of authorization from product owner to authorize the manufacturing site to manufacture and package the solvent/diluent (where applicable). 5. A declaration from the marketing authorization holder that the release and shelf-life specifications of drug product are not affected. 6. In addition to section P for the solvent/diluent and reconstitution stability data, section S is also required (where applicable).
MaV-15	**Extension of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	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-PA34.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change (where applicable). 3. A letter of commitment from product owner or marketing authorization holder 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 at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution Results of microbiological testing should be included (where appropriate).
MaV-16	**Change of storage conditions of the drug product (Lowering from the approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	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-PA35.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long term stability studies covering the duration of approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution Results of microbiological testing should be included (where appropriate).
MaV-17	**Major change in the manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. No adverse change in qualitative and/or quantitative impurity profile which would require further qualifications in safety studies. 2. The synthetic route is different. Refer to MiV-PA7 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. Physicochemical characteristics and other relevant properties of drug substance remain unchanged. 5. Stability performance of drug substance remain unchanged. 6. If there are changes to the specification of drug substance, MiV-PA8 is also applicable.
D	1. Relevant CTD section S1-S7, or both the open and closed part of the Drug Master File (closed part may be provided directly by manufacturer) with the Letter of Access or equivalent audit document/certification from reference country which is deemed appropriate by the Drug Regulatory Authority. 2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. A letter of declaration from marketing authorization 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. 5. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed (where applicable). 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed process. 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product will be started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the approved and proposed processes.

2. MINOR VARIATION REQUIRING APPROVAL (MIV_1 - PA)

MIV_1- PA1	**Change of drug product name**
C	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 proposed name does not (i) suggest greater safety or efficacy than supported by clinical data (ii) imply a therapeutic use (iii) imply superiority over another similar product and (iv) imply the presence of substance(s) not present in the product.
D	1. Revised draft package insert and labelling incorporating the proposed variation. 2. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 3. Official letter from product owner or marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 4. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the change of drug product name. 5. Trademark certificate (where applicable).
MIV_1- PA2	**Change of product labelling (in accordance to country specific labelling requirement)** Includes: a) Change of the layout/artwork without altering meaning. b) Addition/deletion/replacement of pictures, diagrams, bar code, 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. f) Change of distributor's details.
C	1. Product labelling refers to Package Insert (PI), Patient Information Leaflet (PIL), unit carton label, inner label and/or blister strips. 2. The change is not a MaV and does not contain promotional information. For major change in product labelling, please refer to MaV-2.
D	1. Approved product labelling. 2. Proposed product labelling, a clean and annotated version highlighting the changes made. 3. Letter of declaration from the marketing authorization holder stating that no other changes on the label except for the intended change. 4. Relevant document/reference to support the changes (where applicable).
MIV_1. PA3	**Addition or replacement of the company or party responsible for batch release**
C	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	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. 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. 3. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable).
MIV_1. PA4	**Addition or replacement of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]**
C	1. Specifications of drug substances remain unchanged. 2. For change and/or addition of alternative manufacturer/site of drug substance where CEP is not available, please refer to MaV-3.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by the European Directorate for the Quality of medicines (EDQM). 2. A letter of commitment from marketing authorization holder 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 outside shelf-life specifications (with proposed action) or when requested. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed manufacturing sites. 4. If the re-test period is not stated in the CEP, long term and accelerated stability data up to the proposed re-test period on two pilot batches of the drug substance manufactured from the proposed manufacturing sites should be provided.
MIV_1. PA5	**Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	1. The change does not affect the reproducibility of the process. 2. Specifications of drug substance remain unchanged. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. A letter of declaration from marketing authorized holder that the specifications of drug substance have not changed and the reproducibility of the process has not been affected 2. Certificate of analysis and/or batch analysis data with specification and results (in a comparative tabulated format) on a minimum of one production or pilot

	batch manufactured to both the approved and proposed batch sizes. Batch analysis data on the next two full production batches should be available on request or reported if outside specification (with proposed action). 3. Amended relevant CTD Section S (where applicable).
MIV_1. PA6	**Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	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. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. 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. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of two production batches of the drug substance for all tests in the proposed specification (where applicable).
MIV_1. PA7	**Minor change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]**
C	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 remain unchanged). Refer to MaV-17 if 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	1. Drug Master File (DMF), or relevant updated drug substance (DS) section or equivalent/audit document. 2. Comparative tabulated format of the approved and proposed processes with changes highlighted (where available). 3. For sterile drug substance, process validation report (where applicable). 4. A letter of declaration from marketing authorization 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. 5. A letter of declaration from the marketing authorization holder stating that the specifications of the drug substance have not changed. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for two batches of the drug substance. 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two batches (pilot/production scale) manufactured with the drug substance according to the approved and proposed processes.
MIV_1. PA8	**Change of the specification of drug substance** **a) Specification limits are tightened**

	b) Addition of new test parameter and limits
	1. This is only applicable for drug substances which are non-compendial and generic drug substances without European Pharmacopoeial Certificate of Suitability (CEP) 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified. 3. Test procedures remain unchanged, or changes in the test procedure are minor. 4. For (b) - applicable to non-compendial method only. 5. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12. 6. For widening of specification limits and deletion of test parameter and limits of drug substance, please refer to MaV-6.
D	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed specification of drug substance with changes highlighted. 3. Comparative batch analysis data of the drug substance for all tests in the proposed specification for two pilot or production scale batches. **(b) Addition of new test parameter and limits** In addition to the above documents, 4. Description of any new analytical method and summary of the validation data.
MIV_1. PA9	**Change of the test procedure of non-compendial drug substance**
C	1. Results of method validation show proposed test procedure to be at least equivalent to the approved procedure. 2. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. Description of the proposed test procedure with a summary of change(s) from the approved test procedure. 2. Appropriate verification/validation data of the proposed test procedure. 3. Specification of the drug substance. 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for at least two pilot batches of the drug substance from the approved and proposed test procedure.
MIV_1. PA10	**Change of shelf-life or re-test period for drug substance**
C	1. The stability studies must show compliance with specification. 2. There is no change in storage condition. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. Specifications of the drug substance. 2. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the proposed shelf-life or retest period.
MIV_1. PA11	**Change of storage condition for drug substance**
C	1. The stability studies must show compliance with specification. 2. There is no change in shelf-life/re-test period. 3. For change of specification of drug substance where a CEP is available, please refer to MiV-PA12.
D	1. Specifications of the drug substance. 2. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the proposed storage condition.
MIV_1. PA12	**Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance**

C	None
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. If this change is due to drug substance specification change, a declaration from the applicant that the relevant stability studies of the drug product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 3. Specifications of drug substance (where applicable). 4. Certificate of analysis and/or results of batch analysis data (in a comparative tabulated format) from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP (where applicable). 5. Additional data to address any relevant parameter(s) not addressed in the CEP such as stability data (S7), if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc.), if applicable. * If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc.), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.
MIV_1. PA13	**Change of batch size of non-sterile drug product**
C	1. The change does not affect consistency of production. 2. The product formulation remains unchanged. 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 three batches at the proposed batch size. 4. Release and shelf-life specifications of drug product remain unchanged. 5. This is applicable to change of batch size up to 10-fold compared to the approved batch size. 6. For change of batch size for sterile products, please refer to MaV-7 and for change of batch size more than 10-fold compared to the approved batch size, please refer MaV-8.
D	1. Comparative tabulated format of approved and proposed batch manufacturing formula. 2. Validation scheme and/or report of the manufacturing process which is appropriate to the proposed batch size should be provided upon submission. 3. Revised CTD Section P3.1-3.4 (where applicable). 4. Release and shelf-life specifications of the drug product. 5. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one production batch manufactured according to approved and proposed batch sizes and letter of undertaking to submit batch analysis data on the next one full production batch. 6. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action).
MIV_1. PA14	**Reduction or removal of overage**
C	1. Changes of approved manufacturing overages of drug substance only. 2. Release and shelf-life specifications of drug product remain unchanged.
D	1. Justification for the change. 2. Comparative tabulated format of approved and proposed batch manufacturing formula. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for two batches of the finished product. 4. Stability data drug product and report if any results fall outside shelf-life specifications (with proposed action).
MIV_1. PA15	**Qualitative and/or quantitative change of excipient** **a) For immediate release oral dosage forms (as per Level 1, Part III Components and Composition, SUPAC guideline)**

	b) For other non-critical dosage forms e.g. oral liquid, external preparation.
C	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 three batches of the proposed product formula. 4. Release and shelf-life specifications of the 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-10.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A declaration that the proposed excipient does not interfere with the drug product release and shelf-life specifications test method (where applicable). 3. Justification for the change must be given by appropriate development of pharmaceutics. 4. 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). 5. 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 compendium and validated dissolution test method (where applicable). 6. Revised batch manufacturing formula. 7. Validation scheme and/or report of the manufacturing which is appropriate to the proposed change in product formula should be provided upon submission (where applicable). 8. Revised CTD Section P3.1-3.4 (where applicable). 9. Specifications of the proposed excipient. 10. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). 11. Release and shelf-life specifications. 12. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production (or one production batch and two pilot batches) according to approved and proposed product formula. 13. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action). 14. Justification for not submitting a new bioequivalence study (where applicable). 15. For quantitative and qualitative changes in preservative, results of Preservative Effectiveness Test (PET) at lowest specified preservative level (where applicable).
MIV_1- PA16	**Quantitative change in coating of tablets and/or size of capsule shell for immediate release oral solid dosage form**
C	1. The dissolution profile of the proposed product is comparable to that of the approved product. 2. The product release and shelf-life specifications of the 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-11.
D	1. Revised draft of product label incorporating the proposed change (where applicable). 2. A declaration from marketing authorization holder that the change does not

	interfere with the drug product release and shelf-life specifications test method. 3. Comparative tabulated format of approved and proposed product and batch manufacturing formula. 4. 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 compendium and validated dissolution test method (where applicable). 5. Revised release and shelf-life specifications of the drug product. 6. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action). Except for the change in weight and/or size of capsule shell, a letter of declaration from the applicant that the relevant stability studies of the drug product have been started will suffice. 7. Justification for not submitting a new bioequivalence study (where applicable).
MIV_1- PA17	**Change of the colouring agent/flavouring agent/capsule shell colour of the product**
C	i. Same functional characteristics, no change in dissolution profile for solid oral dosage forms. i. The proposed colouring agents /flavouring agents/capsule shell must not have been rejected for pharmaceutical use. i. The release and shelf-life specifications of the 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). v. If there is a change to the source of capsule shell, MiV-PA23 is also applicable.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A declaration that the proposed colouring agent/flavouring agent/capsule shell colour does not interfere with the drug product release and shelf-life specifications test method. 3. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 4. Revised product formulation and batch manufacturing formula. 5. Qualitative and quantitative information of the approved and proposed colouring agent/flavouring agent/capsule shell colour in a comparative table. 6. For proposed excipients made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (BSE)-free certificate issued from relevant authority of the issuing country and/or documentary evidence from the supplier (where applicable). 7. Revised release and shelf-life specifications of the drug product. 8. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action). 9. Certificate of Analysis of proposed colouring agent/flavouring agent/capsule shell (where applicable).
MIV_1- PA18	**Deletion of the solvent/diluent for the drug product**
C	1. The proposed change does not result in any change in the dosage form, regimen, indication, method of administration of the product.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the deletion of the solvent/diluent, including a statement regarding alternative means to obtain the solvent/diluent. 3. Amended relevant CTD Section P (where applicable).
MIV_1- PA19	**Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)**
C	1. Release and shelf-life specifications of drug product remain unchanged. 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.
D	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. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product of at least two production/pilot batches.
MIV_1- PA20	**Minor change of the manufacturing process for non-sterile product**
C	1. The manufacturing site remains unchanged. 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-9/MiV-N11.
D	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 compendium and validated dissolution test method (where applicable). 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. For semi solid and suspension products, validation scheme and/or report of the manufacturing process should be provided upon submission. 5. Copy of approved release and shelf-life specifications. Or, alternately, copy of revised release and shelf-life specifications that supports that the proposed process must lead to an identical or better product regarding all aspects of quality, safety and efficacy. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) of drug product on a minimum of one batch manufactured to both the approved and the proposed process; batch analysis data on the next two full production batches should be made available upon request. 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action). 8. Justification for not submitting a new bioequivalence study (where applicable).
MIV_1- PA21	**Change of specifications of non compendial excipient** **a) Specification limits are tightened/widened** **b) Addition/replacement/deletion of test parameter and limits**
C	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. For compendial excipients, please refer to MiV-N9.
D	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 specification of the excipient with changes highlighted. 3. Certificate of analysis of the excipient for all tests in the proposed specification.

MIV_1. PA22	**Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure**
C	1. Appropriate method validation studies have been performed. 2. Results of method validation show proposed test procedure to be at least equivalent to the approved procedure. 3. There have been no changes of the total impurity limits. 4. Only applicable to the approved test parameters. 5. No new unqualified impurities are detected. 6. This applies for non-compendial excipient. For compendial excipients, please refer to MiV-N9.
D	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_1. PA23	**Change in the source of empty hard capsule**
C	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 finished product release and shelf-life specifications remain unchanged
D	1. A letter of declaration from the manufacturer or the marketing authorization holder of the material that it is purely of vegetable, animal or synthetic origin. 2. Technical specifications and composition of the empty hard capsule of the proposed source. 3. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate or Bovine Spongiform Encephalopathy (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 two sources for oral solid dosage as per as per compendium and validated dissolution test method (where applicable). 6. Certificate of Analysis of the empty hard capsule of the proposed source. 7. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action).
MIV_1. PA24	**Change of release and shelf-life specifications of the drug product** **a) Specification limits are tightened** **b) Addition of new test parameter and limits**
C	1. Applicable to non-compendial method. 2. The change should not be the result of unexpected events arising during manufacture or because of stability concerns; unless otherwise justified. 3. The test methods remain unchanged or changes in the test methods are minor. 4. If there are changes to the test procedure, MiV-PA27 is also applicable. 5. For widening of specification limits and deletion of test parameter and limits of drug product, please refer to MaV-6.
D	**(a) Specification limits are tightened** 1. Technical justification for the change. 2. Comparative tabulated format of the approved and proposed release and shelf-life specifications of the drug product with changes highlighted. 3. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the drug product for all tests in the proposed specification of at least two batches. **(b) Addition of new test parameter and limits** In addition to the above documents: 1. Description of any new method and summary of analytical validation data for

	non-compendial method. 2. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action). (where applicable).
MIV_1- PA25	**Change of imprints, bossing or other markings on tablets or printing on capsules including addition or change of inks used for product marking**
C	**(a) Except score/break-line** 1. Proposed markings do not cause confusion with other registered products. 2. Any ink proposed must comply to relevant pharmaceutical legislation or of food grade and not a listed banned substance. 3. Release and shelf-life specifications of the drug product remain unchanged except for appearance. **(b) On score/break-line** In addition to the above conditions, 4. Score/break-line is not meant for cosmetic purpose. 5. Applicable to addition or removal of score/break-line.
D	**(a) Except score/break-line** 1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A letter of commitment from product owner or marketing authorization holder to inform users of the relevant change (where applicable). 3. Details and specifications of the proposed inks (where applicable). 4. Detailed drawing or written description of the approved and proposed imprint/bossing/markings. 5. Certificate of analysis of ink/printing material (pharmaceutical grade and of food grade) (where applicable). 6. Release and shelf-life specifications of the drug product with the proposed product description. **(b) On score/break-line** In addition to the above documents, 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. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the drug product of two production/pilot scale batches.
MIV_1- PA26	**Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass** **a) Immediate release oral solid dosage form, suppositories and pessaries** **b) Other than immediate release oral solid dosage forms, suppositories and pessaries.**
C	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 the drug product remain unchanged except for dimension and/or shape.
D	**(a) Immediate release oral solid dosage form, suppositories and pessaries** 1. Revised drafts of the package insert and labelling incorporating the proposed variation (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 compendium and validated dissolution test method (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 the drug product with proposed

	dimension and/or shape. **(b) Other than immediate release oral solid dosage forms, suppositories and pessaries** In addition to the above condition, 6. Justification for not submitting a new bioequivalence study (where applicable).
MIV_1. PA27	**Change in the test procedure of the drug product (including replacement or addition of a test procedure)**
C	1. Drug product specifications are not adversely affected unless the specifications are tightened. 2. Results of method verification/validation show proposed 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.
D	1. Justification for the proposed change. 2. Comparative tabulated format of the approved and proposed release and shelf-life specifications 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. 5. Certificate of analysis and/or batch analysis (in a comparative tabulated format) of the finished product of two production batches when made available.
MIV_1. PA28	**Change in primary packaging material for non-sterile product** **a) Qualitative and quantitative composition and/or** **b) Type of container and/or** **c) Inclusion of primary packaging material**
C	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 change in the primary packaging material for sterile drug product, please refer to MaV-12.
D	1. Revised drafts of the package insert incorporating the proposed variation (where applicable). 2. Justification for the change in packaging material and appropriate scientific studies on the proposed packaging. 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 CTD Sections P3 and/or P7 (where applicable). 6. Stability data for the drug product and report if any results fall outside shelf-life specifications (with proposed action).
MIV_1. PA29	**Addition or replacement of a manufacturer for secondary packaging**
C	None
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. 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. 3. Official letter from product owner authorizing the proposed manufacturer or packager to perform secondary packaging (where applicable).
MIV_1. PA30	**Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product**

C	1. The change only concerns the same packaging type and material. 2. The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. Change in the dimension of the primary packaging (where applicable). 4. Release and shelf-life specifications of the drug product remain unchanged. 5. For change of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product, please refer to MaV-13.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Justification for the proposed pack size. 3. Revised CTD Sections P3 and/or P7 (where applicable). 4. A declaration from the marketing authorization holder that the relevant stability studies of the drug product have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).
MIV_1. PA31	**Change of outer carton pack sizes for a drug product**
C	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	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Letter of declaration from the marketing authorization holder stating that no other changes except for the change of outer carton pack sizes for a drug product.
MIV_1. PA32	**Change in any part of the (primary) packaging material not in contact with the finished product formulation such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)**
C	1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
D	1. Amendment of the relevant section(s) of the dossier (presented in the ~~A~~CTD format), including revised product labelling as appropriate.
MIV_1. PA33	**Addition or replacement of measuring device for oral liquid dosage forms and other dosage form**
C	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	1. Revised draft of the package insert and labelling incorporating the proposed variation (where applicable). 2. Description of the device (including a drawing; where applicable). 3. The composition of the device material. Where applicable the materials should comply with the pharmacopoeia. 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.
MIV_1. PA34	**Reduction of shelf-life of the drug product** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	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-15.

D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change (where applicable). 3. A letter of commitment from product owner or marketing authorization holder 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 at least two pilot/production scale batches of the product in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution Results of appropriate microbiological testing should be included (where appropriate).
MIV_1- PA35	**Change of storage conditions of the drug product (Increasing from the approved storage condition)** **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**
C	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-16. 4. General precautionary statements on storage conditions in product labelling may be included but should not be used to conceal stability problems.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Technical justification for the proposed change. 3. Results of appropriate long term stability studies covering the duration of approved shelf-life (at proposed storage condition) of at least two pilot/production scale batches of the product and in the authorized packaging material a) as a package for sale and/or b) after first opening and/or c) after the dilution/reconstitution Results of microbiological testing should be included (where appropriate). 4. Data on photosensitivity and/or moisture sensitivity test on drug product (where applicable).
MIV_1- PA36	**Addition or replacement of alternative site for primary packaging (direct contact with drug product) for non-sterile product**
C	1. No other changes except for the addition or replacement of alternative site for primary packaging (direct contact with drug product). 2. For addition or replacement of alternative site for primary packaging (direct contact with drug product) for sterile product, please refer to MaV-5.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (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. 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 testing of bulk pack during storage and transportation between the bulk production site to primary packager (where applicable). 6. A letter of commitment from marketing authorization holder to conduct long

	term and accelerated stability studies for the drug product packed at the proposed site, and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
MIV_1- PA37	**Addition or replacement of the company or party responsible for quality control testing site (where applicable)**
C	1. Only applicable for quality control testing site. 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	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 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 (where applicable).

3. MINOR VARIATION REQUIRING NOTIFICATION (MIV_1 - N)

MIV_1 - N1	**Change in name and/or address (for example: postal code, street name) of the marketing authorization holder** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The name change refers to the renaming of a company or organization. 2. The change does not include transfer of marketing authorization to another company. 3. For change on the part of marketing authorization holder in product labelling only. Please refer to MaV-2 and MiV-PA2 if other parts are involved.
D	1. Revised draft package insert and labelling incorporating the proposed variation (where applicable). 2. Letter by the product owner authorizing the proposed name of marketing authorization holder to hold the product license. 3. Official document from the relevant authority confirming the change with the proposed name and/or address.
MIV_1 - N2	**Change of product owner**
C	The marketing authorization holder remains unchanged. The manufacturing site remains unchanged.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Updated CPP (where applicable) 3. Declaration on the transfer of ownership between the approved and proposed product owner. 4. Official letter from the proposed product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 5. 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. a. 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 efficacy, quality and safety aspect of the drug product.
MIV_1 - N3	**Change in ownership of manufacturer** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary

C	1. The manufacturing site remains unchanged. 2. No other changes except for the change in ownership of manufacturer.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Letter of justification on the transfer of ownership such as a valid GMP certificate. 3. Official letter stating the transfer of ownership to the proposed manufacturer (where applicable). 4. 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. 5. In case of a contract manufacturer, letter of acceptance from the proposed manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product.
MIV_1 - N4	**Change of the name or address (for example: postal code, street name) of the manufacturer of drug product** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturing site remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug product. 3. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A valid GMP certificate, CPP which covers the GMP certification or official document from relevant authority confirming the proposed name and/or address. 3. Official letter from product owner authorizing the manufacturer with proposed name/address to manufacture the drug product.
MIV_1 - N5	**Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release** [Note: The Drug Regulatory Authority reserves the right to re-categorize this variation as MiV-PA, if deemed necessary]
C	1. The manufacturer of the drug product remains unchanged. 2. The batch release site remains unchanged. 3. Not applicable to the case in which it involves change in ownership of the manufacturer. For change in ownership of manufacturer, please refer MiV-N3.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. A valid GMP certificate CPP which covers the GMP certification or official document from relevant authority confirming the proposed name or address (where applicable). 3. Official letter from product owner authorizing company/manufacturer with proposed name/address responsible for batch release. 4. A declaration from the marketing authorization holder that the change does not involve change of batch release site.
MIV_1 - N6	**Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance**
C	1. The manufacturing site of the drug substance remains unchanged. 2. No other changes except for the change of the name and/or address of a manufacturer of the drug substance.
D	1. Updated information of the manufacturer of the drug substance. 2. Official document/evidence where applicable.
MIV_1 - N7	**Withdrawal/deletion of the alternative manufacturer(s) (for drug substance and/or drug product and/or packager)**

C	1. An alternative manufacturer is registered.
D	1. Reason for withdrawal/deletion.
MIV_1 - N8	**Renewal of European Pharmacopoeial Certificate of Suitability (CEP)**
C	1. Only applicable if the renewal of CEP does not involve any variation.
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM.
MIV_1 - N9	**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**
C	3. Applicable to compendial specifications and/or test procedure only. 4. Change is made exclusively to comply with an update of the relevant monograph of the compendium.
D	1. Tabulation of the approved and proposed release and/or shelf-life/re-test specifications and/or test procedure of the drug product with changes highlighted. 2. Batch analysis data (in comparative tabulated format) of the drug product for all tests in the proposed specification of at least two batches and/or certificate of analysis of excipient and/or drug substance. 3. Revised release and/or shelf-life/re-test specifications. 4. For change in test procedure, appropriate verification data of the proposed test procedure (where applicable).
MIV_1 - N10	**Deletion of pack size for a product**
C	1. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labelling. 2. For addition of pack size for sterile and non-sterile products, please refer to MaV-13 and MiV-PA30 respectively. For change in the outer carton pack size, please refer to MiV-PA31.
D	1. Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). 2. Reason for deletion.
MIV_1 - N11	**Minor change in the manufacturing process of an immediate release solid oral dosage form, semi-solid or oral solutions**
C	1. The change, as per Level 1, Part VI Manufacturing, SUPAC Guideline. 2. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 3. The manufacturing principle including the single manufacturing steps remain unchanged, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process. 4. The approved process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls. 5. The specifications of the finished product or intermediates are unchanged. 6. The proposed process must lead to an identical product regarding all aspects of quality, safety and efficacy. 7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or production scale batch and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
D	1. Amendment of the relevant section(s) of the dossier, as appropriate, including a direct comparison of the approved process and the proposed process.

	2. For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method. 3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). 4. Justification for not submitting a new bioequivalence study (where applicable). 5. Copy of approved release and shelf life specifications. 6. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the approved and the proposed process. Batch analysis data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action). 7. A declaration from the marketing authorization holder that the relevant stability studies of the drug product will be started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).

APPENDIX. II

EXAMPLES OF DOCUMENTARY REQUIREMENT OF VARIATION APPLICATIONS FOR BIOLOGICALS / BIOTECH PRODUCTS

I. MAJOR VARIATION (MaV)

MaV-1 VARIATION OF PRODUCT INFORMATION AFFECTING SAFETY AND NOT REQUIRING CLINICAL DATA	
V-1.1 Change of Product Information affecting the safety aspect.	**D :** A. Administrative document, Product Information, and Label : Product Information. B. Clinical document • Justification and/or other supporting documents in accordance with the proposed changes. • Periodic safety update report/PSUR (if necessary). **C.** Other references.

MaV-2 VARIATION RELATED TO DRUG SUBSTANCE and/or FORMULA AFFECTING EFFICACY AND SAFETY ASPECT REQUIRING CLINICAL DATA	
MaV-2.1 Replacement of Master Cell Bank (MCB)/Master Seed Lot (MSL).	**D :** A. Quality document 1. Source, history and passage number of the new master cell/seed with documentation of all raw material of human or animal origin used for the entire culture history. 2. Result of all identity testing, including cytogenetic characteristics that could be used to identify the cells. 3. Information of characterization and testing of MCB/Working Cell Bank (WCB) and cell from final production or post-production stage. 4. Results of all available adventitious agent testing on the donor and the new master cells. 5. Growth and expression characteristic if the cell substrate is used to produce a recombinant protein. This includes evaluating the copy number and stability of introduced nucleic acids and the quantity and quality of express protein up to a passage level beyond the anticipated production cycle time. 6. Qualification of cell bank or seed lot based onthe prevailing standards. 7. Validated cell stability under the freezing and storage conditions using cell recovery or viability data. 8. For viral master seed, all document related manipulation of the viral phenotype, such as attenuation of virulence or genetic re- assortment or recombinant. This includes the determination of the nucleic acid sequences and sourcing of the biological starting material. 9. Sterility tests, mycoplasmas and adventitious viruses test data (if appropriate). 10. Comparability of approved and proposed Drug Substance with respect to physicochemical characterization, biological activity and impurity profile. 11. Batch analysis data (in a tabular format) of at least three batches of Drug Substance derived from the current and new cell/seed lots. 12. Result of appropriate stability study of at least three batches manufactured using the new cell/seed lot as per the relevant guidelines; and a statement letter declaring the willingness to continue the stability study until the approved shelf-life, if necessary, and report to the NMRA if any results fall outside of the specifications (with proposed action) or if required by the NMRA. 13. Commitment to submit the stability study in accordance with the proposed change. B. Clinical Document 1. Clinical overview or justification document of variation. 2. List of documents supporting the proposed changes. 3. Available tabular listing of all clinical studies for the proposed changes. 4. Clinical study reports (as stated in the tabular listing of all clinical studies).

	5. Periodic safety update report/PSUR up to the recent period (if necessary). 6. Other references (if necessary).
MaV-2.2 Critical change to fermentation process (a change with high potential to have an impact on the quality of the Drug Substance or Finished Product) – <u>Only for Recombinant Products</u>	**D :** Quality document 1. Flow diagram (including process and in- process controls (IPC)) and a brief narrative description of the proposed manufacturing process. 2. If the change results in an increase in thenumber of population doublings or sub- cultivations, information on the characterization and testing of the post- production cell bank for recombinant product, or of the antigen for non-recombinant product. 3. If obtained from animal, the information of the animal origin and the Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) free certificate should be provided. 4. Process validation report 5. Comparability of pre- and post change with respect to physicochemical properties, biology property, purity, impurities and contaminants. 6. Nonclinical and/or clinical studies, if quality data are insufficient to establish comparability. 7. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance.

	8. Comparison of long-term Drug Substance stability testing results, at least for three commercial-scale batches of Drug Substance manufactured with the proposed change (at least for three months of testing unless otherwise justified). 9. Commitment to continue the long-term Drug Substance Stability Study.
MaV-2.3 Critical change to the purification process of Drug Substance with high potential to have an impact on the viral clearance capacity of the process or the purity profile of the Drug Substance.	**D :** A. Quality Document 1. Flow diagram (including process and In-process control (IPC) and a brief narrative description of the proposed manufacturing process 2. Process validation reports. 3. Comparative study of the pre- and post- change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 4. Nonclinical and/or clinical studies, if quality data are insufficient to establish comparability. 5. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance. 6. Comparison of long-term stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 7. Commitment to continue long-term Drug Substance stability study. 8. Information assessing the risk with respect to potential contamination with adventitious agent (for example, impact on viral clearance studies and BSE/TSE risk).
MaV-3 VARIATION RELATED TO QUALITY OF DRUG SUBSTANCE	
MaV-3.1 Change of Working Cell Bank (WCB) or new Working Seed Lot (WSL) Note : 1. New cell bank or seed lot is obtained from the approved MCB/MSL. 2. New cell bank is in the approved passage level.	**D :** A. Administrative Document, Product Information and Label Revised information related to quality and control of critical raw materials (e.g. specific pathogen-free egg and chickens) used in the new generation of the proposed WCB. Updated Quality Document 1. Qualification of cell bank or seed lot. 2. Information on the characterization and testing of the WCB and cells from the post- production passage. 3. Comparative study of the pre- and post-change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 4. Nonclinical and/or clinical studies, if quality data are insufficient to establish comparability. 5. Quality control testing results in the form of quantitative data in a tabular format for the proposed new cell bank. 6. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance. 7. Comparison of long-term Drug Substance stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 8. Commitment to continue the long term Drug Substance Stability Study.
V-3.2 Replacement	**D :**

and/oraddition of manufacturing facility for the Drug Substance or intermediates of the Drug Substance	Quality document 1. Validation reports of Drug Substance manufacturing process. 2. Comparability study of the pre- and post- change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 3. Nonclinical and/or clinical studies, if quality data are insufficient to establish comparability. 4. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance. 5. Comparison of long-term Drug Substance stability testing results, at least for three commercial-scale batches of Drug Substance manufactured with the proposed change (at least for three months of testing unless otherwise justified). 6. Commitment to continue long-term Drug Substance stability study.
V-3.3 Replacement and/or addition of manufacturer/source of raw materials of biological origin.	A. Quality document 1. BSE/TSE certificate (if using materials that are at risk of transmitting BSE/TSE) or information and evidence that the material does not pose a potential BSE/TSE risk. 2. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance. 3. Information assessing the risk with respect to potential contamination with adventitious agents. 4. Information demonstrating comparability of the raw materials/reagents of both sources.
MaV-3.4 Production-scale change to fermentation, viral or cellular propagation stage	**D :** A. Quality Document 1. Flow diagram (including process and IPC) and abrief narrative description of the proposed manufacturing process. 2. Information of characterization and testing of the post-production cell bank for recombinant product, or of the antigen for non-recombinant product if the change results in an increase in the number of population doublings or sub-cultivations. 3. Process validation reports. 4. Comparability of the pre- and post-change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 5. If quality data are insufficient to establish comparability, nonclinical and/or clinical studies should be submitted. 6. Comparison of IPC and release testing results for at least three consecutive commercial scale batches of the pre-and post-change Drug Substance.
MaV-3.5 Change in the scale of manufacturing process at the purification stage.	**D :** A. Quality document 1. Flow diagram (including process and IPC) and a narrative description of the proposed manufacturing process.

	2. Process validation reports. 3. Comparability of the pre- and post-change with respect to physicochemical properties, biological activity, purity, impurities and contaminants. 4. Nonclinical and/or clinical studies, if quality data are insufficient to establish comparability. 5. Comparison of IPC and release testing results for at least three consecutive commercial scale batches of the pre-and post-change Drug Substance 6. Comparison of long-term stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 7. Commitment to continue long-term Drug Substance stability study.
MaV-3.6 Widening of the approved in-process limits for manufacture of the Drug Substance	**D :** A. Quality document 1. Scientific and/or historical data to support reason/justification of the proposed change. 2. Information of IPC at critical stage and intermediates of the Drug Substance. 3. Copy or summary of the analytical procedure, if new analytical procedure is used. 4. Validation study reports, if new analytical procedure is used. 5. Comparison of pre- and post-change IPCs or specifications. 6. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance. 7. Justification for the new in-process tests and limits. 8. Comparison of long-term Drug Substance stability testing results, at least for three commercial-scale batches of Drug Substance manufactured with the proposed change (at for three months of testing unless otherwise justified). 9. Commitment to continue long-term Drug Substance stability study. 10. Comparative table of changes in specification of the Drug Substance (if necessary).
V-3.7 Deletion of an in-process test which may have a significant effect on the overall quality of the Drug Substance.	**D :** A. Quality document 1. Scientific and/or historical data to support reason/justification of the proposed change. 2. Information of IPC at critical stage and intermediates of the Drug Substance. 3. Comparison of pre- and post-change IPCs or specifications. 4. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance
MaV-3.8 Addition or replacement of an in-process test as a result of a safety or quality issue.	**D :** A. Quality document 1. Scientific and/or historical data to support reason/justification of the proposed change. 2. Information of IPC at critical stage and intermediates of the Drug Substance. 3. Copy or summary of the analytical procedure, if new analytical procedure is used.

	4. Validation study reports, if new analytical procedure is used. 5. Comparison of pre- and post-change IPCs or specification 6. Comparison of IPC and release testing results for at least three consecutive commercial- scale batches of the pre-and post-change Drug Substance. 7. Comparative table of changes in specification of the Drug Substance (if necessary).
MaV-3.9 Change in animal species/strain for a release test of Drug Substance (for example, new species/strains,a nimals of different ages,and/or new supplier where genotype of the animal cannot be confirmed).	**D :** **A.** Quality document 1. Data demonstrating that the proposed change in animals/strains gives results comparable to those obtained using the approved animals. 2. Certificate of fitness for use of the animals in the test.
MaV-3.10 Deletion of Drug Substance release testing parameters	**D :** A. Quality document 1. Specification of the proposed Drug Substance. 2. Scientific and/or historical data to support reason/justification of the proposed change. 3. Evidence that quality and manufacturing process is consistently maintained
MaV-3.11 Widening of acceptance criteria for Drug Substance release	**D :** A. Quality document 1. Scientific and/or historical data to support reason/justification of the proposed change. 2. Specification of the proposed Drug Substance. 3. Evidence that quality and manufacturing process is consistently maintained
MaV-3.12 Change in the shelf-life specification of the Drug Substance	**D :** A. Quality document 1. Scientific and/or historical data to support reason/justification of the proposed change. 2. Comparison between the approved release and/or shelf-life specification and the proposed one with the marked-change. 3. The stability of the Drug substance is at least three commercial-scale batches with the proposed specification and commitment to continue the stability study until the shelf life
MaV-3.13 Change of testing procedure in the process control, and release and stability of the Drug Substance	**D :** A. Quality document 1. Description of the proposed testing method. 2. Study reports of the proposed testing procedure validation 3. Comparative testing result of the approved and proposed testing procedures.

MaV-3.14 Change in the container-closure system of the Drug Substance	**D :** A. Quality document 1. Information regarding construction material and design feature of the proposed packaging system. 2. Study reports of compatibility, leaching materials, leak test, etc. demonstrating the compatibility of the proposed container- closure system to be used. 3. Validation reports of the manufacturing process using the proposed container-closure system (if necessary). 4. Drug Substance release and shelf-life specification. 5. Result of the stability study for at least three batches of Drug Substance manufactured using the proposed container-closure system in accordance with the relevant stability guideline and a statement letter declaring the willingness to continue the stability study until the approved shelf-life, if necessary, and report to the NMRA if any results fall outside of the specifications (with proposed action) or if required by the NMRA.
MaV-3.15 Inclusion of new, updated or amended Plasma Master File (PMF)	**D :** A. Administrative document 1. GMP Certificate of the plasma collecting and processing facilities and/or declaration of GMP compliant from the plasma collecting and processing facility in case of update/change of plasma source. B. Quality Document 1. Drug substance release and shelf-life specification 2. Drug release and shelf-life specification. 3. Comparative batch analysis data (in a tabular format) of at least batches manufactured using the approved and new source of plasma. 4. Result of appropriate stability study of at least three batches manufactured using the new source of PMF and/or new source of plasma, as per the relevant guidelines. 5. Adventitious Agents Safety Evaluation reports, if necessary. 6. Expert statement outlining the changes to the new PMF or document containing evaluation of potential effects of the change of PMF on the Drug, including specific risk assessment. 7. For new/amended PMF, it should be enclosed with: a. new/new version of PMF; b. Plasma specification and analytical data of plasma pool batch; c. Annual EMA recertification letter and, if any, recertified report of assessment results; d. Letter of Access issued by PMF holder to the product owner; Information in section 2.3.S.2.3 covering: • Source and pooling of plasma • Characterization of donation. • Epidemiologic data regarding blood transmissible infections. • Selection/exclusion criteria • Plasma quality and safety • Storage and transportation condition of plasma • Plasma specification and analytical data of plasma pool batch.
MaV-4 VARIATION RELATED TO QUALITY OF DRUG PRODUCT	

MaV-4.1 Scale-up of manufacturing process at the formulation / filling stage	**D :** A.Quality document 1. Description of the proposed manufacturing process, if different from the approved process and information of IPC at critical stage and intermediates of the Finished Product proposed. 2. Information of IPC test, as proposed. 3. Study report of process validation (e.g. media fill), as proposed. 4. Comparison of release testing results for at least three consecutive commercial-scale batches of the pre-and post-change Drug. 5. Comparison of long-term Drug stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 6. Commitment to continue the long-term stability study to support shelf-life/hold-time in normal storage condition and report to the NMRA if there is any failure during the performance of the long-term stability study. 7. Information of leachables and extractables, as proposed
MaV-4.2 Change of Excipient of Biological Product	**D :** A. Quality document 1. Comparative table of the approved and proposed batch Formula and per dosage unit of the Drug. 2. Justification for the change should be provided in the form of appropriate pharmaceutical development (including stability aspect and preservation with antimicrobials, if appropriate). 3. Information demonstrating comparability of approved and proposed Excipient with respect to physicochemical characterization and impurity profile. 4. For Excipient which is at risk of transmitting TSE, submit the followings if required: • Certificate of Suitability for the Excipient. • Documented evidences showing that the TSE risk has been evaluated. 5. Comparative table of the approved and proposed Drug release and shelf-life specification. 6. Batch analysis data (in a comparative tabular format) for at least three batches of Drug manufactured using the approved and proposed formulation. 7. Result of the stability study for at least three batches of Drug manufactured using the proposed formula in accordance with the relevant stability guideline and a statement letter declaring the willingness to continue the stability study until the approved shelf-life, if necessary, and report to the NMRA if any results fall outside of the specifications (with proposed action) or if required by the NMRA.
MaV-4.3 Change in the Drug Product manufacturing process at the same site of manufacturer.	**D :** A. Quality document 1. Report and summary of the proposed process validation . 2. Drug release and shelf-life specification. 3. Batch analysis data (in a comparative tabular format) for at least three batches of Drug manufactured using the approved and proposed process.

	4. Result of the stability study for at least three batches of Drug manufactured using the proposed manufacturing process in accordance with the relevant stability guideline and a statement letter declaring the willingness to continue the stability study until the approved shelf-life, if necessary, and report to the NMRA if any results fall outside of the specifications (with proposed action) or if required by the NMRA. 5. A statement letter declaring that : a. there is no change in the qualitative and quantitative impurity profile or physicochemical characteristics; b. the change does not result in a negative change to the process reproducibility; c. the change is not due to any unexpected event during the manufacturing process or because of stability concerns. d. the Drug specification remains unchanged.
MaV-4.4 Change to the specification of drug release and shelf life	**D :** A. Quality document 1. Justification of change and scientific and/or historical data to support reason/justification of the proposed change. 2. Comparison between the approved and the proposed Drug release and/or shelf-life specification with the change being marked 3. Drug batch analysis for all tests in the proposed specification (at least three batches). 4. For any change to the stability-indicating parameters in the specification: • result of the appropriate stability study for at least three batches of Drug tested in the proposed specification in accordance with the relevant stability guideline; and • a statement letter declaring the willingness to continue the stability study until the approved shelf-life, if necessary, and report to the NMRA if any results fall outside of the specifications (with proposed action) or when required by the NMRA.
MaV-4.5 Widening of the approved in-process limits in the Drug Product manufacturing process.	**D :** A. Quality document 1. Information of the proposed manufacturing process control at critical stage and intermediates of the antigen. 2. Updated specification of Finished Drug, if changed. 3. Copy or summary of the analytical procedure, if new analytical procedure is used. 4. Validation study reports, if analytical procedure is used. 5. Comparative table or description of the approved and proposed limits, according to the change. 6. Comparison of batch analysis data for at least three consecutive commercial-scale batches of the pre-and post-change of Drug Product. 7. Justification for new in-process tests and limits. 8. Comparison of long-term Drug stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified).
MaV-4.6 Change to the testing procedure of the excipient of Drug Product	**D :** A. Quality document 1. Description of the proposed testing method. 2. Validation study report of the proposed testing procedure.

	3. Result of comparative tests between the approved and the proposed testing procedures. 4. Specification of Excipient.
MaV-4.7 Change to the manufacturing of biological excipient (excluding Biological Adjuvant)	**D :** A.Quality document 1. Detailed information regarding source of Excipient (e.g. animal species, country of origin) and the steps undertaken during the processing to minimize the risk of TSE exposure. 2. Comparison in terms of physicochemical properties, and the impurity profile of the proposed Excipient compared to the approved Excipient. 3. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed Excipient. 4. Comparison of batch analysis data for at least three consecutive commercial-scale batches of the pre-and post-change Excipient. 5. Comparison of long-term Drug stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 6. Commitment to continue long-term Drug stability study. 7. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) including the viral safety documentation as required.
MaV-4.8 Change in manufacturer of plasma-derived excipient	**D :** A. Quality Document 1. Comparison in terms of physicochemical properties, and impurity profile of the proposed excipient compared to the approved excipient 2. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed Excipient. 3. Comparison of batch analysis data for at least three consecutive commercial-scale batches of the pre-and post-change Excipient. 4. Comparison of long-term Drug stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 5. Commitment to continue long-term Drug stability study. 6. Information assessing the risk with respect to potential contamination with adventitious agents. 7. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
MaV-4.9 Change to the testing procedure of the process control in the Drug manufacturing process.	**D :** Quality document 1. Description of the proposed testing method. 2. Validation study report of the proposed testing procedure 3. Result of comparative tests between the approved and the proposed testing procedures
MaV-4.10 Changes to the testing procedure of the Drug related to its release/stability study	**D :** A. Quality document 1. Drug release and shelf-life specification. 2. Description of the proposed testing method.

	3. Validation study report of the proposed testing procedure. 4. Result of comparative tests between the approved and the proposed testing procedures.
MaV-4.11 Changes to the Drug's container closure system	**D :** A. Quality document 1. Information regarding construction material and design feature of the proposed container- closure system. 2. Study reports of compatibility, leaching materials, leak test, etc. demonstrating the compatibility of the proposed container- closure system.. 3. Validation reports of the manufacturing process using the proposed container-closure system (if necessary). 4. Drug release and shelf-life specification 5. Comparison of long-term Drug stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 6. Commitment to continue long-term Drug stability study.
MaV-4.12 Change to the container-closure system for diluents	**D :** Quality document 1. Information regarding construction material and design feature of the proposed container- closure system. 2. Study reports of compatibility, leaching materials, leak test, etc. demonstrating the compatibility of the proposed container-closure system. 3. Validation reports of the manufacturing process using the proposed container-closure system (if necessary). 4. Diluent release and shelf-life specification. 5. Results of appropriate stability studies for at three batches of diluent manufactured using the proposed container-closure system in accordance with relevant stability studies.

II. MINOR VARIATION PA (MiV-PA)

-PA 1 VARIATION RELATED TO QUALITY OF DRUG SUBSTANCE	
V-PA 1.1 Minor change to the manufacturing process of Drug Substance.	A. Quality document 1. Justification for change. 2. Justification for the category of change related to its impact on the quality of antigen. 3. Summary of change to the process in connection with the approved process in a tabular format. 4. Flow diagram (including process and IPC) and a narrative description of the proposed manufacturing process. 5. BSE/TSE certificate (if using materials that are at risk of transmitting BSE/TSE) such as ruminant origin, or information and evidence that the material does not pose a potential BSE/TSE risk. 6. Process change validation (if necessary). 7. For change to manufacturing process of the Drug Substance, comparability of the Drug Substance with respect to physicochemical properties, biological activity and impurities profile. 8. Batch analysis data (in a comparative tabular format) for at least three batches manufactured using the approved and proposed process. 9. The stability study uses at least three batches of Drug Substance (pilot-

	or production-scale) in accordance with the relevant stability guideline or commitment to conduct appropriate stability study and report to the NMRA if any results fall outside of the specifications or if required by the NMRA. 10. Commitment to submit the Drug Stability Study Report in accordance with the proposed change.
V-PA 1.2 Addition or replacement of equipment in the manufacturing process of the Drug (e.g. formulation tank, filter housing, filling line and head, and lyophilizer).	A.Quality document 1. Description of manufacturing process, if different from the approved process and information on monitoring of the proposed manufacturing process at critical stage and intermediates of Finished Product. 2. IPC testing information, as proposed. 3. Process validation study report, as proposed. 4. Batch analysis data (in table) for at least three batches of pre- and post-change Drug. 5. Comparison of long-term Drug stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 6. Commitment to continue long-term Drug stability study. 7. Information of leachables and extractables, as proposed. 8. Information of new equipment and comparison of similarities and differences between the approved and proposed operational principle and specification.
-PA 1.3 Addition or change of testing site of the Drug Substance including testing for stability study and process control.	A. Quality document 1. Summary of testing validation study at the new testing site. 2. Data of testing result of at least three batches tested at the approved and the proposed site. 3. Information and specification of the reference standard. 4. In particular for change of stability testing site, report of stability test at new testing site.
V-PA 1.4 Addition or change of storage condition of the Drug Substance (e.g. widening or narrowing of temperature criteria)	A. Quality document 1. The proposed storage condition and shelf-life. 2. Result of stability test (in the form of complete long-term stability data during the proposed shelf-life for at least three commercial-scale batches).
-PA 2 VARIATION RELATED TO QUALITY OF DRUG PRODUCT	
-PA 2.1 Minor change to the drug manufacturing process	A. Quality document 1. Summary of process change related to the approved process in a tabular format. 2. Justification for the change. 3. Process change validation (if necessary). 4. Batch analysis data (in a comparative tabular format) for at least three batches manufactured using the approved and proposed processes. 5. The stability study for at least three batches Drug Substance (pilot- or production-scale) in accordance with the relevant stability guideline or commitment to conduct the appropriate stability study and report to the NMRA if any results fall outside of the specifications or if required

	by the NMRA
-PA 2.2 Addition of new stage/s in the Drug Manufacturing process	A. Quality document 1. Description of the proposed manufacturing process, if different from the approved process and information of manufacturing process monitoring at critical stage and intermediates of the Finished Product proposed. 2. Information of IPC test, as proposed. 3. Study report of process validation (e.g. media fill), as proposed. 4. Comparison of release testing results for at least three consecutive commercial-scale batches of the pre-and post-change Drug. 5. Comparison of long-term Drug stability testing results, at least for three commercial-scale batches manufactured with the proposed change (at least for three months of testing unless otherwise justified). 6. Information of leachables and extractables, as proposed
V-PA 2.3 Addition or replacement of in-process test due to safety or quality	A. Quality document 1. Justification for the change and scientific and/or historical data to support the proposed change. 2. Information of manufacturing process monitoring at critical steps and intermediates of antigen proposed. 3. Analytical procedure, if new analytical procedure is used. 4. Validation study reports, if analytical procedure is used. 5. Comparative table or description of the approved and proposed limits, according to the change. 6. Comparison of release test results for at least three consecutive commercial-scale batches of the pre-and post-change Drug.

III. MINOR VARIATION NOTIFICATION (MiV-N)

-N 1 VARIATION RELATED TO QUALITY OF DRUG SUBSTANCE	
MiV-N 1.1 Manufacture of new WCB **Note** : 1. New cell bank is obtained from the pre-approved MCB/MSL. 2. New cell bank is in the same passage level of that previously approved. 3. New cell bank is released based on the protocol /process previously approved	A. Quality document 1. Qualification of cell bank or seed lot based on the procedure approved by the National Agency of Drug and Food Control. 2. Information of characterization and tests of MCB/WCB and cell from end of production or post-production passage.
-N 1.2 Change of seed lot: new generation of WSL. **:** 1. New seed lot obtained from the pre-approved	A. Quality document 1. Comparability of the approved and proposed Drug Substance with respect to physicochemical characterization, biological

MSL. 2. New seed lot is in the same passage level of that previously approved. 3. New seed lot is released based on the protocol / process previously approved or as described in the original license	activity and impurity profile. 2. Quality control testing results in the form of quantitative data in a tabular format for the proposed new seed lot. 3. Commitment to submit the stability study of the Drug Substance manufactured using the proposed seed and report to the NMRA if any results fall outside of the specifications or if required by the NMRA

References

1. WHO Guideline on Procedures and Data Requirements for Changes to Approved Biotherapeutic Products, 2017
2. Annex 4 WHO TRS 993, Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines, 2015