



**NATIONAL PHARMACEUTICAL
REGULATORY DIVISION (a.k.a. NPRA)
MINISTRY OF HEALTH**

**MALAYSIAN VARIATION
GUIDELINE FOR BIOLOGICS
(MVGB)**

FIRST EDITION: JANUARY 2017

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1.0 INTRODUCTION

A biologic product will undergo various manufacturing process changes and updating to their product labeling throughout its lifetime. The changes will be inevitable and is often implemented in a constant manner. Reason of changes would include (but not limited to):

- a. To maintain the routine production (e.g replenishment of cell banks, seed lots, and reference standard)
- b. To improve the quality attributed or the efficiency of the product (e.g changes in manufacturing process, equipment of facility)
- c. To update product labeling information (e.g to add/edit indication and/or to improve the management of risk by adding a warning, limiting the target population, changing the dosage regimen and adding information on co-administration with other medicinal products)

Any changes made to the registered biologics may impact upon the quality, safety and efficacy of that product. Therefore, the National Pharmaceutical Regulatory Agency (NPRA) acting on behalf of the Drug Control Authority of Malaysia recognises the importance of this activity and hence is providing guidance (with the support of WHO assistance and guidance) for the industry. This guideline is based on the adaptation of WHO TRS 993 (2014) Annex 4: “Guidelines on Procedures and Data Requirement for Changes to Approved Vaccines”. However, modifications have been made taking into considerations of our current Malaysian Variation Guidelines (MVG) and also our current local requirements and policies based on the latest Drug Registration Guidance Document (DRGD).

2.0 SCOPE

This document provides guidance for manufacturers and the product registration holders (PRH) on the conditions and supporting documents for a variation application of registered biologic products. The Malaysian Variation Guidelines for Pharmaceutical Products (MVG) will still serve as a referral document in addition to this guideline. Although the original Annex 4 was published as guidance to vaccines, the general principles set out may also be applicable to other biologics. Therefore, the term ‘antigen’ being referred in this document will be synonymous to the term drug substance.

3.0 GENERAL CONSIDERATIONS

The type of categorisation will follow as per the Malaysian Variation Guideline for Pharmaceutical Products (MVG):

- a. **Major Variation (MaVB):** Variation to a registered product that may affect significantly and/or directly the aspects of quality, efficacy and safety and it does not fall within the definition of minor variation and new registration.
- b. **Minor Variation (MiVB-PA):** Variation to a registered products in terms of minimal changes with no or minimal impact on the aspects of efficacy, quality and safety.
- c. **Minor Variation (MiVB-N, “Do and Tell”):** Variation to a registered products in terms of administrative data and or/ changes with minimal/ no significant impact on the aspects of efficacy, quality and safety. If the notification fulfils the requirements (conditions and supporting documents) as per described under MiVB-N, product registration holder must notify NPRA and NPRA shall acknowledge receipt of a notification within 30 working days.

When procedures and timelines for certain consultations are not available within this guidance, the manufacturer or PRH should determine the classification of change based on a change-specific risk assessment using the principles and examples provided in this guidance.

If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change.

No change should be implemented before an approval is obtained unless otherwise stated in this guidance (exception is given for MiVB-N “Do and Tell”).

As of current, the practice of ‘Annual Reporting’ that is currently being applied by the other agencies will not be applicable here at this current time point.

4.0 PROCEDURES

All applications should be submitted via the QUEST 3+ system. For information on this system, kindly contact the NPRA helpdesk.

4.1 ADDITIONAL NOTES TO PRODUCT REGISTRATION HOLDER PRIOR TO SUBMISSION

4.1.1 NPRA reserves the right to re-categorize the application type, where deemed appropriate. Re-categorization may require the product registration holder to withdraw the original application and resubmit a new application according to the correct category.

4.1.2 Variation application should be submitted along with a declaration in the cover letter (attached in *Other Supporting Documents*) which is undersigned by the product registration holder declaring:

- There is no other change except for the proposed variation;
- The change will not adversely affect the quality, efficacy and safety of the product;
- All conditions for the variation concerned are fulfilled based on the best fit category;
- The required supporting documents as specified for the variation have been submitted; and

- The proposed change has been checked in reference to the currently approved data in the system.

4.1.3 In order to ensure smooth process of application, all PRH are advised to forward a cover letter of the intended variation application to the Head of Biologics Section, Centre for Product Registration. The cover letter should include the following:

- Proposed variation category
- Brief description of the proposed variation with justification
- Declaration that all of the conditions have been fulfilled based on the proposed category
- Approvals from NRA of country of origin/ reference agencies (if any)
- Current and proposed change of information affecting the dossier in tabulated format
- Declaration that there is no change except for the proposed change

4.1.4 Submission of revised draft of package insert and labelling is subject to current regulatory requirements as per latest Drug Registration Guidance Document (DRGD) and Circulars from NPRA.

4.1.5 NPRA reserves the right to request for additional information or material, as deemed appropriate, or to define conditions not specifically described in this document in order to allow for adequate assessment of the quality, safety and efficacy of a biologic product.

5.0 TIMELINES

| Reporting Categories | *Maximum Review Period |
|----------------------|------------------------|
| MiVB-N | 30 Working Days |
| MiVB-PA | 60 Working Days |
| MaVB | 90 Working Days |

*Note: Review Period will only begin once all supporting documents have been received.

6.0 FEES STRUCTURE

| Reporting Categories | Amount (RM)/ variation category |
|----------------------|---------------------------------|
| MiVB-N | - |
| MiVB-PA | 150 |
| MaVB | 300 |

Note: Fees Implementation will commence 1st July 2016 in accordance to circular reference (40)d/m.BPFK/PPP/01/03Jld.3 dated 31/12/2015 (http://portal.bpfk.gov.my/images/Circulars_Directive/Regulatory_Information/2016/160105_PEKELILING_MAKLUMAN_YURAN_2016.pdf)

SECTION 1: Changes to Antigen/ Drug Substance

A. General Information

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 1. Change in the name of antigen | | | |
| <i>Note: This change generally applies only to influenza vaccines (seasonal change)</i> | 1 | 1,2,3,9 | MiVB-PA1 |
| | 2 | 1-9 | MiVB-PA2 |
| Conditions: | | | |
| <ol style="list-style-type: none"> There is no change in the influenza strains for the formulation of an influenza vaccine according to the WHO recommendation for Influenza Vaccine Composition. There is a <u>change</u> in the influenza strains for the formulation of an influenza vaccine according to the WHO recommendation for Influenza Vaccine Composition | | | |
| Supporting data: | | | |
| <ol style="list-style-type: none"> Quality Overall Summary (QOS) for Drug substance. Current approved and proposed product labelling information (all labelling items). Information on the proposed nomenclature of the antigen and evidence that the proposed name for the antigen is recognized (for example, proof of acceptance by WHO). Information on the source of the seed viruses. Passage history until establishment of working seeds. Results of quality release test performed on working virus seeds (including identity confirmation). Specific validation data (including inactivation kinetics, splitting efficiency). Comparative batch analyses data (tabulated format) of the previous season batch and the proposed strains (for both drug substance and drug product) Stability data for both DS and DP produced in the previous season and a letter of undertaking to perform stability studies up to the proposed shelf-life of the product and to report of any out-of-specification result (with proposed action) or when requested. | | | |

B. Manufacture

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 2. Change to an antigen manufacturing facility: | | | |
| a. replacement or addition of the manufacturing facility for the antigen bulk, or any intermediate of the antigen | None | 1-4,6-8 | MaVB-1 |
| | 1-4 | 2,4-8 | MaVB-2 |
| b. deletion of a manufacturing facility or manufacturer of an antigen intermediate, or antigen bulk | 5,6 | None | MiVB-N1 |
| Conditions: | | | |
| <ol style="list-style-type: none"> 1. The new manufacturing facility/suite is an approved antigen manufacturing site. 2. Any changes to the manufacturing process and/or controls are considered minor with justification. 3. The new facility/suite is under the same quality assurance/quality control (QA/QC) oversight. 4. The proposed change does not involve additional containment requirements. 5. There should remain at least one site/manufacturer, as previously authorized, performing the same function as the one(s) to be deleted. 6. The deletion should not be due to critical deficiencies in manufacturing (such as recurrent deviations, recurrent out-of-specification events, environmental monitoring failures and so on). | | | |
| Supporting data: | | | |
| <ol style="list-style-type: none"> 1. Evidence that the facility is GMP compliant. 2. Name, address and responsibility of the proposed facility. 3. Process validation study reports. 4. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use. 5. Justification for the classification of any manufacturing process and/or control changes as | | | |

moderate or minor.

6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
7. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
8. Updated post-approval stability protocol.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|------------------|--------------------|
| 3.Change to the antigen fermentation, viral propagation or cellular propagation process: | | | |
| a. a critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, incorporation of disposable bioreactor technology) | None | 1-7, 9,11 | MaVB-3 |
| b. a change with moderate potential to have an impact on the quality of the antigen or final product (for example, extension of the in vitro cell age beyond validated parameters) | 2,4 | 1-6,8,10 | MaVB-4 |
| c. a noncritical change with minimum potential to have an impact on the quality of the antigen or final product (for example, a change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of detection of adventitious agents or production scale; or duplication of a fermentation train) | 1-6,9-11 | 1-4 | MiVB-PA3 |
| 4. Change to the purification process involving: | | | |
| a. a critical change (a change with high potential to have an impact on the quality of the antigen or final product)(for example, a change that could potentially have an impact on the viral clearance capacity of the process or the impurity profile of the antigen). | None | 1,2, 5-7,9,11,12 | MaVB-5 |
| b. a change with moderate potential to have an impact on the quality of the antigen or final product (for example, a change in the chemical separation method, such as from ion-exchange HPLC to reserve-phase HPLC) | 2,4 | 1,2,5-7, 10,11 | MaVB-6 |
| c. a noncritical change with minimum potential to have an impact on the quality of the antigen or final product (for example, addition of an in-line filtration step equivalent to the approved filtration step) | 1-5 | 1,2 | MiVB-N2 |
| 5. Change in the scale of manufacturing process: | | | |
| a. at the fermentation, viral propagation or cellular propagation stage | 3-6, 11-13 | 2,3,5-7,9,11 | MaVB-7 |
| b. at the purification stage | 1,3,5,7 | 2,5-7,9,11 | MaVB-8 |

| | | | |
|--|------|------------|---------|
| 6. Change in supplier of raw materials of biological origin (for example, fetal calf serum, human serum albumin, trypsin) | None | 4,8,12,13 | MaVB-9 |
| | 8 | 4,8 | MiVB-N3 |
| 7. Change in source of raw materials of biological origin | None | 4,7,12,13 | MaVB-10 |
| | 8 | 4,7 | MiVB-N4 |
| 8. Introduction of reprocessing steps | 14 | 8,10,11,14 | MaVB-11 |
| Conditions: | | | |
| <ol style="list-style-type: none"> 1. No change in the principle of the sterilization procedures of the antigen. 2. The change does not have an impact on the viral clearance data or the chemical nature of an inactivating agent. 3. No change in the antigen specification outside the approved limits. 4. No change in the impurity profile of the antigen outside the approved limits. 5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. 6. The change does not affect the purification process. 7. The change in scale is linear with respect to the proportionality of production parameters and materials. 8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials). 9. The new fermentation train is identical to the approved fermentation train(s). 10. No change in the approved in vitro cell age. 11. The change is not expected to have an impact on the quality, safety or efficacy of the final product. 12. No change in the proportionality of the raw materials (that is, the change in scale is linear). 13. The change in scale involves the use of the same bioreactor (that is, it does not involve the use of a larger bioreactor). 14. The need for reprocessing is not due to recurrent deviations from the validated process and the root cause triggering reprocessing is identified. | | | |
| Supporting data: | | | |
| <ol style="list-style-type: none"> 1. Justification for the classification of the change(s) as critical, moderate or noncritical as this relates to the impact on the quality of the antigen. 2. Flow diagram (including process and in-process controls) of the proposed manufacturing | | | |

process(es) and a brief narrative description of the proposed manufacturing process(es).

3. If the change results in an increase in the number of population doublings or subcultivations, information on the characterization and testing of the post-production cell bank for recombinant product, or of the antigen for non-recombinant product.
4. For antigens obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, and use and previous acceptance of the material).
5. Process validation study reports.
6. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and should be reported by the PRH if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

10. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least one (1) commercial-scale antigen batch produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the final product manufactured using the post-change antigen into the stability programme.
12. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk).
13. Information demonstrating comparability of the raw materials/reagents of both sources.
14. Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times and resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the antigen.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 9. Change to the cell banks: | | | |
| <i>Note: New cell substrates that are unrelated to the licensed master cell bank (MCB) or pre-MCB material generally require a new application for MA or licence application.</i> | | | |
| a. generation of a new MCB | 1 | 1,2,5,7-9 | MaVB-12 |
| b. generation of a new working cell bank (WCB) | None | 1,2 | MaVB-13 |
| | 2-4 | 1,2 | MiVB-PA4 |
| c. change in cell bank storage site | 7 | 10 | MiVB-N5 |
| 10. Change to the seed lots: | | | |
| <i>Note: New viral or bacterial seeds that are unrelated to the master seed lot (MSL) or pre-MSL material generally require a new application for MA or licence application.</i> | | | |
| a. generation of a new MSL | 1 | 1,5-9,11 | MaVB-14 |
| b. generation of a new working seed | 2,3 | 5-9,11 | MaVB-15 |
| | 2-4 | 5-6 | MiVB-PA5 |
| c. generation of a new WSL by extending the passage level of an existing WSL beyond an approved level | None | 5-7,11 | MaVB-16 |
| d. change in seed lot storage site | 7 | 10 | MiVB-N6 |

| | | | |
|---|------|-----|---------|
| 11. Change in the cell bank/seed lot testing/ storage site | 5,7 | 10 | MiVB-N7 |
| 12. Change in cell bank/ seed lot qualification protocol | None | 3,4 | MaVB-17 |
| | 6 | 4 | MiVB-N8 |

Conditions:

1. The new MCB is generated from a pre-approved MCB or WCB or the new MSL is generated from a pre-approved MSL or WSL.
2. The new cell bank/seed lot is generated from a pre-approved MCB/MSL.
3. The new cell bank/seed lot is at the pre-approved passage level.
4. The new cell bank/seed lot is released according to a pre-approved protocol/ process or as described in the original licence.
5. No changes have been made to the tests/acceptance criteria used for the release of the cell bank/seed lot.
6. The protocol is considered more stringent (that is, addition of new tests or narrowing of acceptance criteria).
7. No changes have been made to the storage conditions used for the cell bank/seed lot

Supporting data:

1. Qualification of the cell bank or seed lot according to guidelines considered acceptable by the NRA.
2. Information on the characterisation and testing of the MCB/WCB, and cells from the end-of-production passage or post-production passage of the change to the cell bank/seed lot qualification protocol.
3. Justification of the change to the cell bank/seed lot qualification protocol.
4. Updated cell bank/seed lot qualification protocol.
5. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.

6. Quality control test results as quantitative data in tabular format for the new seed lot.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the antigen derived from the new cell bank/seed lot. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
8. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
9. Updated post-approval stability protocol.
10. Evidence that the new company/facility is GMP compliant.
11. Revised information on the quality and controls of critical starting materials (for example, specific pathogen-free eggs and chickens) used in the generation of the new WSL, where applicable.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 13. Change in equipment used in the antigen manufacturing process, such as: a. introduction of new equipment with different operating principles and different product contact material | None | 1-6 | MaVB-18 |
| b. introduction of new equipment with the same operating principles but different product contact material | None | 1,3-6 | MaVB-19 |
| c. introduction of new equipment with different operating principles but the same product contact material | None | 1-3, 5, 6 | MaVB-20 |
| d. replacement of equipment with equivalent equipment (including filter) | None | 1, 5-7 | MiVB-N9 |

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|---|
| |
| Conditions: None |
| |
| Supporting data: 1. Information on the in-process control testing. 2. Process validation study reports. 3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the antigen produced with the approved and proposed product contact equipment/ material. Batch data on the next two full-production batches should be made available on request and reported by the PRH if outside specification (with proposed action). 4. Information on leachables and extractables. 5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment. 6. Information demonstrating requalification of the equipment or requalification of the change. 7. Rationale for regarding the equipment as similar/comparable, as applicable. |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 14. Change in specification for the materials, involving: | | | |
| a. raw materials/ intermediates: widening of the approved specification limits for starting materials/ intermediates, which may have a significant effect on the overall quality of the antigen and/ or final product and are not changes to the cell banks or seed lots | None | 1, 3-6, 8, 11 | MaVB-21 |
| b. raw materials/ intermediates: narrowing of the approved specification limits for starting materials/ intermediates | 1-4 | 1,3-7 | MiVB-PA6 |
| 15. Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen involving: | | | |
| a. narrowing of the in-process limits | 3,5,8,9 | 2,6 | MiVB-PA7 |
| b. addition of new in-process test and limits | 4,5,10,11 | 2-6,8,10 | MiVB-PA8 |
| c. deletion of a non-significant in-process test | 4-6 | 2,6,9 | MiVB-N10 |
| | None | 2-6,8,10,11 | MaVB-22 |
| d. widening of the approved in-process limits | 3-5 | 2,6,8,10,11 | MiVB-PA9 |
| e. deletion of an in-process test which may have been | None | 2,6,8,10 | MaVB-23 |

| | | | |
|---|---------|----------|----------|
| significant effect on the overall quality of the antigen | | | |
| f. addition or replacement of an in-process test as a result of a safety or quality issue | None | 2-6,8,10 | MaVB-24 |
| 16. Change in in-process controls testing site | 3-5,7-8 | 12 | MiVB-N11 |
| <p>Conditions:</p> <ol style="list-style-type: none"> 1. The change in specification for the materials is within the approved limits. 2. The grade of the materials is the same or is of higher quality, where appropriate. 3. No change in the antigen specification outside the approved limits. 4. No change in the impurity profile of the antigen outside the approved limits. 5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. 6. The test does not concern a critical attribute (for example, content, impurity, any critical physical characteristics or microbial purity). 7. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable. 8. No change in the in-process controls outside the approved limits. 9. The test procedure remains the same, or changes in the test procedure are minor. 10. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 11. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods). | | | |
| <p>Supporting data:</p> <ol style="list-style-type: none"> 1. Revised information on the quality and controls of the materials (for example, raw materials, starting materials, solvents, reagents and catalysts) used in the manufacture of the post-change antigen. 2. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen. 3. Updated antigen specification, if changed. 4. Copies or summaries of analytical procedures, if new analytical procedures are used. 5. Validation study reports, if new analytical procedures are used. 6. Comparative table or description, where applicable, of pre- and post-change in-process tests/limits. | | | |

7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the PRH if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three(3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
9. Justification/risk assessment showing that the attribute is non-significant.
10. Justification for the new in-process test and limits.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/ hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/ or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
12. Evidence that the new company/facility is GMP compliant.

C. Control of Antigen/ Drug Substance

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 17. Change affecting the quality control (QC) (release and stability) testing site of the antigen, involving: <i>Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections</i> | | | |
| a. transfer of the QC activities for a non-pharmacopoeial assay to a new company or to a different facility within the same company | 1,2 | 1,2 | MiVB-PA10 |
| b. transfer of the QC activities for a pharmacopoeial assay to a new company not approved in the current MA or license | 1 | 1,2 | MiVB-PA11 |
| Conditions 1. The transferred QC test is not a potency assay (for example, the test may be a bioassay such as an endotoxin assay or sterility assay). 2. No changes to the test method. | | | |
| Supporting Data 1. Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant. | | | |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 18. Change in the specification used to release the antigen, involving: | | | |
| a. deletion of test | None | 1,5,8 | MaVB-25 |
| b. addition of test | 1,3 | 1-3,5 | MiVB-N12 |
| c. replacement of an analytical procedure | None | 1-5 | MaVB-26 |
| d. change in animal species/ strains for a test (for example, new species/ strains, animals of different age, new supplier where genotype of the animal cannot be confirmed) | None | 6,7 | MaVB-27 |

| | | | |
|--|-------|-------|-----------|
| e. minor changes to an approved analytical procedure | 2,4-6 | 1,4,5 | MiVB-PA12 |
| f. change from an in-house analytical procedure to a recognized compendia/ pharmacopoeial analytical procedure | 2,6 | 1-3 | MiVB-N13 |
| g. widening of an acceptance criterion | None | 1,5,8 | MaVB-28 |
| h. narrowing of an acceptance criteria | 1,7,8 | 1 | MiVB-N14 |

Conditions

1. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity or change in total impurity limits).
2. No change in the acceptance criteria outside the approved limits.
3. The addition of the test is not intended to monitor new impurity species.
4. The method of analysis is the same and is based on the same analytical technique or principle (for example, a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
6. The change does not concern potency testing.
7. Acceptance criteria for residuals are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
8. The analytical procedure remains the same, or changes to the analytical procedure are minor.

Supporting documents

1. Updated antigen specification.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Validation reports, if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification for deletion of the test or for the proposed antigen specification (for example, tests, acceptance criteria or analytical procedures).
6. Data demonstrating that the change in animals/strains give results comparable to those obtained using the approved animals/strains.

7. Copies of relevant certificate of fitness for use (for example, veterinary certificate).
8. Declaration/evidence that consistency of quality and of the production process is maintained.

D. Reference Standards or Materials

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 19. Qualification of a new reference standard against a new primary international standard | None | 1,2 | MiVB-PA13 |
| 20. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard | None | 1,2 | MiVB-PA14 |
| 21. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard) | 1 | 1,2 | MiVB-N15 |
| 22. Change to reference standard qualification protocol | None | 3,4 | MiVB-PA15 |
| 23. Extension of reference standard shelf-life | 2 | 5 | MiVB-PA16 |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. Qualification of the new reference standard is according to an approved protocol. 2. The extension of the shelf-life is according to an approved protocol. | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Justification for the change in reference standard. 2. Information demonstrating qualification of the proposed reference standards or materials (for example, source, characterization, certificate of analysis and comparability data). 3. Justification of the change to the reference standard qualification protocol. 4. Updated reference standard qualification protocol. 5. Summary of stability testing and results to support the extension of reference standard shelf-life. | | | |
| | | | |

E. Container Closure System

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 24. Change in the primary container closure system(s) for the storage and shipment of the antigen | None | 1,2,4,5 | MaVB-29 |
| | 1 | 1,3,5 | MiVB-PA17 |
| | | | |
| <p>Conditions</p> <ol style="list-style-type: none"> 1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties. | | | |
| <p>Supporting Data</p> <ol style="list-style-type: none"> 1. Information on the proposed container closure system (for example, description, composition, materials of construction of primary packaging components and specification). 2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing). 3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (for example, results of transportation or interaction studies, and extractable/leachable studies). 4. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA. 5. Comparative table of pre- and post-change specifications. | | | |

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| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 25. Change in the specification of the primary container closure system for the antigen, involving: | | | |
| a. deletion of a test | 1,2 | 1,2 | MiVB-N16 |
| b. addition of a test | 3 | 1-3 | MiVB-N17 |
| c. replacement of an analytical procedure | 6,7 | 1-3 | MiVB-N18 |
| d. minor changes to an analytical procedure | 4-7 | 1-3 | MiVB-N19 |
| e. widening of an acceptance criterion | 3 | 1,2 | MiVB-PA18 |
| f. narrowing of an acceptance criterion | 8 | 1 | MiVB-N20 |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement. 2. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the antigen. 3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. 4. There is no change in the acceptance criteria outside the approved limits. 5. The new analytical procedure is of the same type. 6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure. 7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. 8. The change is within the range of approved acceptance criteria or has been made to reflect a new pharmacopoeial monograph specification for the container closure component. | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Updated copy of the proposed specification for the primary container closure system. 2. Rationale for the change in specification for a primary container closure system. 3. Description of the analytical procedure and, if applicable, validation data. | | | |

F. Stability

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 26. Change in the shelf-life/ hold time for the antigen or for a stored intermediate of the antigen, involving: | | | |
| a. extension | None | 1-5 | MaVB-30 |
| b. reduction | 1-5 | 1,2,5 | MiVB-PA19 |
| | None | 1-5 | MaVB-31 |
| | 6 | 2-4 | MiVB-N21 |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. No changes to the container closure system in direct contact with the antigen with the potential of impact on the antigen, or to the recommended storage conditions of the antigen. 2. The approved shelf-life is at least 24 months. 3. Full long-term stability data are available covering the proposed shelf-life and are based on stability data generated on at least three (3) commercial-scale batches. 4. Stability data were generated in accordance with the approved stability protocol. 5. Significant changes were not observed in the stability data. 6. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns. <p><i>Note: Problems arising during manufacturing or stability concerns should be reported for evaluation.</i></p> | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Summary of stability testing and results (for example, studies conducted, protocols used and results obtained). 2. Proposed storage conditions and shelf-life, as appropriate. 3. Updated post-approval stability protocol and stability commitment. 4. Justification of the change to the post-approval stability protocol or stability commitment. 5. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches). For intermediates, | | | |

data to show that the extension of shelf-life has no negative impact on the quality of the antigen. Under special circumstances and with prior agreement of the NRA, interim stability testing results and a commitment to notify the NRA of any failures in the ongoing long-term stability studies may be provided.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 27. Change in the post-approval stability protocol of the antigen, involving: | | | |
| a. significant change to the post-approval stability protocol for stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature | None | 1-6 | MaVB-32 |
| | 1 | 1,2,4-6 | MiVB-PA20 |
| b. addition of time point(s) into the post-approval stability protocol | None | 4,6 | MiVB-PA21 |
| c. addition of test(s) into the post approval stability protocol | 2 | 1,2,4,6 | MiVB-PA22 |
| d. deletion of time point(s) from the post approval stability protocol beyond the approved shelf-life | None | 4,6 | MiVB-PA23 |
| e. deletion of time point(s) from the post- approval stability protocol within the approved shelf-life | 3 | 4,6 | MiVB-PA24 |
| | | | |
| <p>Conditions</p> <ol style="list-style-type: none"> 1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. 2. The addition of test(s) is not due to stability concerns or to the identification of new impurities. 3. The approved antigen shelf-life is at least 24 months. | | | |
| <p>Supporting Data</p> <ol style="list-style-type: none"> 1. Copies or summaries of analytical procedures, if new analytical procedures are used. 2. Validation study reports, if new analytical procedures are used. 3. Proposed storage conditions and/or shelf-life, as appropriate. 4. Updated post-approval stability protocol and stability commitment. 5. If applicable, stability testing results to support the change to the post-approval stability protocol or | | | |

| |
|--|
| <p>stability commitment (for example, data showing greater reliability of the alternative test).</p> <p>6. Justification for the change to the post-approval stability protocol.</p> |
| |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 28. Change in the storage conditions for the antigen, involving: | | | |
| a. addition or change of storage condition for the antigen (for example, widening or narrowing of a temperature criterion) | None | 1-4 | MaVB-33 |
| | 1,2 | 1-3 | MiVB-PA25 |
| | | | |
| <p>Conditions</p> <ol style="list-style-type: none"> 1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. 2. The change consists in the narrowing of a temperature criterion within the approved ranges. | | | |
| <p>Supporting Data</p> <ol style="list-style-type: none"> 1. Proposed storage conditions and shelf-life. 2. Updated post-approval stability protocol and stability commitment. 3. Justification of the change in the labeled storage condition/ cautionary statement. 4. Results of stability testing (that is, full real-time/ real temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches) | | | |

7.0 REFERENCES

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(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4_Q__R1_.pdf, accessed 14 December 2014).
2. M4Q Implementation Working Group. Questions & Answers (R1) (Current version, 17 July 2003). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2003
(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4_Quality_Questions_Answers_R1.pdf, accessed 14 December 2014).
3. Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: forty-second report. Geneva: World Health Organization; 1992: Annex 1 (WHO Technical Report Series, No. 822; http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf?ua=1, accessed 2 December 2014).
4. Guidelines on stability evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: fifty-seventh report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 962; http://whqlibdoc.who.int/trs/WHO_TRS_962_eng.pdf?ua=1, accessed 2 December 2014).
5. WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva: World Health Organization; 2003 (WHO/BCT/QSD/2003.01; <http://www.who.int/biologicals/publications/en/whotse2003.pdf>, accessed 30 November 2014).
6. Malaysian Variation Guideline for Pharmaceutical Products 2013.
[http://bpfk.moh.gov.my/images/Guidelines_Central/Guidelines_on_Regulatory/Malaysia%20Variation%20Guideline%20for%20Pharmaceutical%20Products%202013_edition%201\(April%202013\)%20080513%20\(1\).pdf](http://bpfk.moh.gov.my/images/Guidelines_Central/Guidelines_on_Regulatory/Malaysia%20Variation%20Guideline%20for%20Pharmaceutical%20Products%202013_edition%201(April%202013)%20080513%20(1).pdf)

SECTION 2: Changes to the Final Product

G. Description and composition of the final product

Note: Changes in dosage form and/or presentation may, in some cases, necessitate the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|---|-----------------|--------------------|
| 29. Change in the description or composition of the final product, involving: | | | |
| a. addition of a dosage form or change in the formulation (for example, lyophilised powder to liquid, change in the amount of excipient or new diluents for lyophilised product) <i>Note: Change in the formulation does not include changes in antigen(s) or adjuvants. A change in antigen(s) or adjuvant(s) requires the filing of a new application for licensure. PRH are encouraged to contact the NRA for further guidance.</i> | New registration application | | |
| b. change in fill volume (that is. same concentration, different volume) | None | 1-4 | MaVB-34 |
| | 1,2 | 1,3,4 | MaVB-35 |
| | 1-3 | 3,4 | MiVB-PA26 |
| c. addition of a new presentation (for example, addition of a new pre-filled syringe where the approved presentation is a vial for a vaccine in a liquid dosage form) | New registration application as line extension. | | |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. No changes classified as major in the manufacturing process to accommodate the new fill volume. 2. No change in the dose recommended. 3. Narrowing of fill volume while maintaining the lower limit of extractable volume. | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Revised final product labeling information (as applicable). 2. Information on the batch formula, manufacturing process and process controls, control of critical steps and intermediates, and process validation study reports. 3. Information on specification, analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three (3) consecutive commercial-scale batches should be provided). Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified. 4. Supporting clinical data or a justification for why such studies are not needed. | | | |

H. Description and composition of the final product: change to an adjuvant

Note:

- ■ Change in type/structure of a chemical adjuvant, in the type of a biological adjuvant or in a component of a biological adjuvant may necessitate the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.
- ■ For additional guidance on the required supporting data for quality changes for chemical and biological adjuvants, see recommendations for other changes to the final product, such as changes to facilities, equipment, manufacturing process, quality control, shelf-life, and so on, as applicable.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 30. Change involving an approved chemical/ synthetic adjuvant: | | | |
| a. change in supplier of a chemical/ synthetic adjuvant | None | 4,5,10,11 | MaVB-36 |
| | 1-3 | 5 | MiVB-N22 |
| b. change in manufacture of a chemical/ synthetic adjuvant | None | 3-5,10,11 | MiVB-PA27 |
| c. change in specification of a chemical/ synthetic adjuvant (including test and/ or the analytical procedure) | None | 7-11 | MiVB-PA28 |
| | 1,3 | 7-9 | MiVB-N23 |
| 31. Change involving a biological adjuvant: | | | |
| a. change in supplier of a biological adjuvant | None | 1-7, 10-13 | MaVB-37 |
| b. change in manufacture of a biological adjuvant | None | 1-7, 10-12 | MaVB-38 |
| | 4 | 1-7, 10-12 | MiVB-PA29 |
| c. change in specification of a biological adjuvant (including test and/ or the analytical procedure) | None | 6-10 | MiVB-PA30 |
| | 1,3 | 7-8 | MiVB-N24 |
| Conditions | | | |
| 1. The specification of the adjuvant is equal to or narrower than the approved limits (that is, narrowing of acceptance criterion). | | | |
| 2. The adjuvant is an aluminium salt. | | | |
| 3. The change in specification consists of the addition of a new test or of a minor change to an | | | |

analytical procedure.

4. There is no change in the manufacturer and/or supplier of the adjuvant.

Supporting Data

1. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, BSE/TSE risk) (5).
2. Information on the quality and controls of the materials (for example, raw materials, starting materials) used in the manufacture of the proposed adjuvant.
3. Flow diagram of the proposed manufacturing process(es), a brief narrative description of the proposed manufacturing process(es), and information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.
4. Process validation study reports (for example, for manufacture of the adjuvant) unless otherwise justified.
5. Description of the general properties, including stability, characteristic features and characterization data of the adjuvant, as appropriate.
6. Comparability of the pre- and post-change adjuvant with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the adjuvant, existing relevant nonclinical and clinical data, and aspects of vaccine use.
7. Updated copy of the proposed specification for the adjuvant (and updated analytical procedures if applicable).
8. Copies or summaries of analytical procedures, if new analytical procedures are used.
9. Validation study reports, if new analytical procedures are used.
10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the final product with the pre-change (approved) and post-change (proposed) adjuvant, as applicable. Comparative test results for the approved adjuvant do not need to be generated concurrently; relevant historical testing results are acceptable.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies.

Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

12. Supporting nonclinical and clinical data, if applicable.

13. Evidence that the facility is GMP compliant.

I. Description and composition of the final product: Change to a Diluents

Note: Changes to diluents containing adjuvants and/or antigens are considered final products and as such the corresponding changes to final product (not diluent) should be applied.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 32. Change to the diluents, involving: | | | |
| a. Change in manufacturing process | None | 1-5 | MiVB-PA31 |
| | 1,3 | 1-4 | MiVB-N25 |
| b. replacement of or addition to the source of a diluent | None | 1-5 | MiVB-PA32 |
| | 1-3 | 1-3 | MiVB-N26 |
| c. change in facility used to manufacture a diluent (same company) | 1,2 | 1,3,5 | MiVB-N27 |
| d. addition of a diluent filling line | 1,2,4 | 1,3,5 | MiVB-N28 |
| e. addition of a diluent into an approved filling line | 1,2 | 1,3,5 | MiVB-N29 |
| f. deletion of a diluents | 1,2 | 1,3,5 | MiVB-N30 |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. The diluent is water for injection or a salt solution (including buffered salt solutions)- that is, it does not include an ingredient with a functional activity (such as preservative) and there is no change to its composition. 2. After reconstitution, there is no change in the final product specification outside the approved limits. 3. The proposed diluent is commercially available in the NRA country/ jurisdiction. 4. The addition of the diluent filling line is in an approved filling facility. | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es). 2. Updated copy of the proposed specification for the diluent. 3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the approved and proposed diluent. Comparative test results for the approved diluent do not need to be generated concurrently; relevant historical testing results are acceptable. 4. Updated stability data on the product reconstituted with the new diluents. 5. Evidence that the facility is GMP compliant. | | | |

J. Manufacture

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 33. Change involving a final product manufacturer/ manufacturing facility, such as: | | | |
| a. replacement of a manufacturing facility for the final product (including formulation/ filling) | Refer MVG | | MaV-5 (CoS) |
| b. replacement of a manufacturing facility for the final product (for primary packaging) | Refer MVG | | MaV-6 |
| c. addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging) | 1-6 | 1-8 | MaVB-39 |
| d. replacement or addition of a secondary packaging facility, a labeling/ storage facility or a distribution facility | 2,3 | 1-3 | MiVB-PA33 |
| e. deletion of a final product manufacturing facility | None | None | MiVB-N31 |
| | | | |
| <p>Conditions</p> <ol style="list-style-type: none"> The proposed facility is an approved formulation/filling facility (for the same company/PRH). There is no change in the composition, manufacturing process and final product specification. There is no change in the container/closure system and storage conditions. The same validated manufacturing process is used. The newly introduced product is in the same family of product(s) or therapeutic classification as the products already approved at the site, and also uses the same filling process/equipment. There is no change in the current final batch releaser. | | | |
| <p>Supporting Data</p> <ol style="list-style-type: none"> Name, address and responsibility of the proposed production facility involved in manufacturing and testing. Evidence that the facility is GMP compliant. Confirmation that the manufacturing process description of the final product has not changed as | | | |

- a result of the submission (other than the change in facility), or revised description of the manufacturing process.
4. Comparative description of the manufacturing process if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
 5. Process validation study reports. The data should include transport between sites, if relevant.
 6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
 7. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
 8. Rationale for considering the proposed formulation/filling facility as equivalent.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 34. Change in the final product manufacturing process, such as: | | | |
| a. scale-up of the manufacturing process at the formulation/ filling stage | 1-4 | 1-6 | MaVB-40 |
| b. addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, and lyophilizer); see change 13 above | None | 1-8 | MaVB-41 |
| | 5 | 2, 7-9 | MiVB-PA34 |
| c. addition of a new scale bracketed by the approved scales or scale-down the manufacturing process | 1-4 | 1,4 | MiVB-PA35 |
| d. addition of a new step (for example, filtration) | 3 | 1-6 | MaVB-42 |
| Conditions | | | |
| 1. The proposed scale uses similar/ comparable equipment to the approved equipment. Note: Change in | | | |

equipment size is not considered as using similar/ comparable equipment.

2. Any changes to the manufacturing process and/ or to the in-process controls are only those necessitated by the change in batch size (for example, the same formulation, controls and SOPs are utilized)
3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the final product.
5. Replacement of equipment with equivalent equipment; the change is considered “like for like” (that is, in terms of product contact material, equipment size and operating principles).

Supporting Data

1. Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
2. Information on the in-process control testing, as applicable.
3. Process validation study reports (for example, media fills), as appropriate.
4. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
5. Comparative pre- and post-change test results for the manufacturer’s characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
6. Information on leachables and extractables, as applicable.
7. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
8. Information demonstrating requalification of the equipment or requalification of the change.
9. Rationale for regarding the equipment as similar/comparable, as applicable.

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 35. Change in the controls (in process test and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as: | | | |
| a. narrowing of in-process limits | 2,3,7 | 1,5 | MiVB-PA36 |
| b. addition of new in-process test and limits | 2,3,8,9 | 1-6, 8 | MiVB-PA37 |
| c. deletion of a non-significant in-process test | 2-4 | 1,5,7 | MiVB-N32 |
| d. widening of the approved in-process limits | None | 1-6, 8,9 | MaVB-43 |
| | 1-3 | 1,5,6,8,9 | MaVB-44 |
| e. deletion of an in-process test which may have a significant effect on the overall quality of the final product | None | 1,5,6,8 | MaVB-45 |
| f. addition or replacement of an in-process test as a result of a safety or quality issue | None | 1-6,8 | MaVB-46 |
| 36. Change in in-process controls testing site | 1-3,5,6 | 10 | MiVB-N33 |
| <p>Conditions</p> <ol style="list-style-type: none"> 1. No change in the final product specification outside the approved limits. 2. No change in the impurity profile of the final product outside the approved limits. 3. The change is not necessitated by recurring events arising during the manufacture or because of stability concerns. 4. The test does not concern a critical attribute (for example, content, impurities, any critical physical characteristics or microbial purity). 5. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable. 6. No change in the in-process control limits outside the approved limits. 7. The test procedure remains the same, or changes in the test procedure are minor. 8. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 9. The new test method is not a biological/ immunological/ immunochemical or physiochemical method or a method using biological reagent (does not include standard pharmacopoeial microbiological methods). | | | |
| <p>Supporting Data</p> <ol style="list-style-type: none"> 1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen. 2. Updated final product specification if changed. 3. Copies or summaries of analytical procedures, if new analytical procedures are used. 4. Validation study reports, if new analytical procedures are used. 5. Comparative table or description, where applicable, of current and proposed in-process test. | | | |

| |
|---|
| <p>6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product (certificates of analysis should be provided.) Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable.</p> <p>7. Justification/ risk assessment showing that the attribute is non-significant.</p> <p>8. Justification for the new in-process test and limits.</p> <p>9. Comparative pre and post change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale final product batches produced with the proposed changes under real-time/ real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/ holding time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by NRA.</p> <p>10. Evidence that the new company/ facility is GMP compliant.</p> |
| |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| <p>37. Change in the specification used to release the excipient, involving:</p> <p><i>Note: This change excludes adjuvants.</i></p> | | | |
| a. deletion of a test | 5,8 | 1,3 | MiVB-N34 |
| b. addition of a test | 4 | 1-3 | MiVB-N35 |
| c. replacement of an analytical procedure | 1-3 | 1,2 | MiVB-N36 |
| d. minor changes to an approved analytical procedure | None | 1,2 | MiVB-PA38 |
| e. change from an in-house analytical procedure to a recognized compendia analytical procedure | None | 1,2 | MiVB-N37 |
| f. widening of an acceptance criterion | None | 1,3 | MiVB-PA39 |
| g. narrowing of an acceptance criterion | 3,4,6,7 | 1 | MiVB-N38 |
| <p>Conditions</p> <p>1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.</p> <p>2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.</p> <p>3. The change is within the range of approved acceptance criteria or has been made to reflect the new</p> | | | |

pharmacopoeial monograph specification for the excipient.

4. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for Class 3 residual solvent or pharmacopoeial requirements).
5. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
6. The analytical procedure remains the same, or changes in the test procedure are minor.
7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity or change in total impurity limits).
8. An alternative test analytical procedure is already authorized for the specification attribute/test and this procedure has not been added through a minor change submission.

Supporting Data

1. Updated excipient specification.
2. Where an in-house analytical procedure is used and a recognized compendial standard is claimed, results of an equivalency study between the in-house and compendial methods.
3. Justification of the proposed excipient specification (for example, demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the final product).

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 38. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk | None | 2-7 | MaVB-47 |
| 39. Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source | None | 1,3,5,6 | MaVB-48 |
| 40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source | 5,6 | 2-7 | MiVB-N39 |
| 41. Change in manufacture of a biological excipient <i>Note: This change excludes biological adjuvants; see adjuvant-specific changes above for details</i> | None | 2-7 | MaVB-49 |
| | 2 | 2-7 | MiVB-PA40 |
| | 1,2 | 2-7 | MiVB-N40 |
| 42. Change in supplier for a plasma-derived excipient (for example, human serum albumin) | None | 3-8 | MaVB-50 |
| | 3,4 | 5,6,9 | MiVB-PA41 |
| 43. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient) <i>Note: This change excludes adjuvants; see adjuvant-specific changes above for details</i> | None | 2,3,5-7 | MiVB-PA42 |
| | 1,5,6 | 3 | MiVB-N41 |
| 44. Change in excipient testing site | 1 | 10 | MiVB-N42 |

Conditions

1. No change in the specification of the excipient or final product outside the approved limits.
2. The change does not concern a human plasma-derived excipient.
3. The human plasma-derived excipient from the new supplier is an approved medicinal product and no manufacturing changes were made by the supplier of the new excipient since its last approval in the country/jurisdiction of the NRA.
4. The excipient does not influence the structure/conformation of the active ingredient.
5. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material.
6. Any new excipient does not require the assessment of viral safety data.

Supporting Data

1. Declaration from the manufacturer of the excipient that the excipient is entirely of vegetable or synthetic origin.
2. Details of the source of the excipient (for example, animal species, country of origin) and the steps undertaken during processing to minimize the risk of TSE exposure.
3. Information demonstrating comparability in terms of physicochemical properties, and the impurity profile of the proposed excipient compared to the approved excipient.
4. 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.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial-scale batches of the proposed excipient.
6. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
7. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, or BSE/TSE risk) including viral safety

documentation where necessary.

8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
9. Letter from the supplier certifying that no changes were made to the plasma-derived excipient compared to the currently approved corresponding medicinal product.
10. Evidence that the new company/facility is GMP compliant.

K. Control of the Final Product

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 45. Change affecting the QC testing of the final product (release and stability), involving: <i>Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections</i> | | | |
| a. transfer of the QC testing activities for a non-pharmacoeial assay (in-house) to a new company or to a different site within the same company | None | 1,2 | MaVB-52 |
| b. transfer of the QC testing activities for a pharmacoeial assay to a new company | 1 | 1,2 | MiVB-N43 |
| Conditions 1. The transferred QC test is not a potency assay or a bioassay. | | | |
| Supporting Data 1. Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant. | | | |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|----------------------------|-----------------|--------------------|
| 46. Change in the specification used to release the final product, involving: | | | |
| a. for products or components subject to terminal sterilization by heat (for example, diluents for reconstitution of lyophilized vaccines), replacing the sterility test with process parametric release | None | 1,2,6,8,10 | MaVB-52 |
| b. deletion of a test | None | 2,9,10 | MaVB-53 |
| c. addition of a test | 2,8 | 2-4,8 | MiVB-N44 |
| d. change in animal species/ strains for a test (for example, new species/strains, animals of different ages, and/or new supplier where genotype of the animal cannot be confirmed) | None | 5,11 | MaVB-54 |
| e. replacement of an analytical procedure | None | 2-4,7,8 | MaVB-55 |
| f. minor changes to an approved analytical procedure | 1,3-5 | 3,8 | MiVB-PA43 |
| g. change from an in-house analytical procedure to a | 1,5 | 2-4 | MiVB-PA44 |

| | | | |
|--|------|--------|----------|
| recognized compendial analytical procedure | | | |
| h. widening of an acceptance criteria | None | 2,8,10 | MaVB-56 |
| i. narrowing of an acceptance criteria | 6-9 | 2 | MiVB-N45 |

Conditions

1. No change in the acceptance criteria outside the approved limits.
2. The additional test is not intended to monitor new impurity species.
3. The method of analysis is the same (for example, a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
6. The change does not concern potency testing.
7. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
8. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, or impurity content outside of the approved limits).
9. The analytical procedure remains the same, or changes to the analytical procedure are minor.

Supporting Data

1. Process validation study reports on the proposed final product.
2. Updated copy of the proposed final product specification.
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Validation study reports, if new analytical procedures are used.
5. Data demonstrating that the change in animals gives results comparable to those obtained using the approved animals.
6. Description of the batches and summary of results as quantitative data for a sufficient number of batches to support the process parametric release.
7. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial-scale batches of the final product.
8. Justification for the change to the analytical procedure (for example, demonstration of the suitability of the analytical procedure in monitoring the final product, including the degradation products) or for the change to the specification (for example, demonstration of the suitability of the revised acceptance criterion in controlling the final product).
9. Justification for the deletion of the test (for example, demonstration of the suitability of

the revised specification in controlling the final product).

10. Declaration/evidence that consistency of quality and of the production process is maintained.

11. Copies of relevant certificates of fitness for use (for example, veterinary certificate).

L. Reference Standards or Materials

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 47. Qualification of a new reference standard against a new primary international standard | None | 1,2 | MiVB-PA45 |
| 48. Change of the reference standard from in-house (no relationship with international standard) to pharmacopial or international standard | None | 1,2 | MiVB-PA46 |
| 49. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard) | 1 | 2 | MiVB-N46 |
| 50. Change to the reference standard qualification protocol | None | 3,4 | MiVB-PA47 |
| 51. Extension of the shelf life of the reference standard | 2 | 5 | MiVB-PA48 |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. The qualification of a new standard is carried out in accordance with an approved protocol. 2. The extension of the shelf-life of the reference standard is carried out in accordance with an approved protocol. | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Revised product labelling to reflect the change in reference standard (as applicable). 2. Qualification data of the proposed reference standards or materials (for example, source, characterization and certificate of analysis). 3. Justification of the change to the reference standard qualification protocol. 4. Updated reference standard qualification protocol. 5. Summary of stability testing and results or retest data to support the extension of the reference standard shelf-life. | | | |
| | | | |

M. Container Closure System

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|--|-----------------|--------------------|
| 52 a. Modification of a primary container closure system (for example, new coating, adhesive, stopper or type of glass) | None | 1-7 | MaVB-57 |
| | 1-3 | 3 | MiVB-PA49 |
| b. addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) | New registration application as line extension | | |
| 53. Change from a reusable container to a disposable container with no changes in product contact material (for example, change from reusable pen to disposable pen) | None | 1,3,6 | MaVB-58 |
| 54. Deletion of a container closure system <i>Note: The NRA should be notified of the deletion of a container closure system, and product labeling information should be updated, as appropriate</i> | None | 1 | MiVB-N47 |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. No change in the type of container closure or materials of construction. 2. No change in the shape or dimensions of the container closure. 3. The change is made only to improve the quality of the container and does not modify the product contact material (for example, increased thickness of the glass vial without changing interior dimensions). | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Revised product labelling information, as appropriate. 2. For sterile products, process validation study reports, or providing equivalency rationale. For a secondary functional container closure system, validation testing report. 3. Information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary/secondary packaging components, performance specification). 4. Results demonstrating protection against leakage, no leaching of undesirable substance and compatibility with the product, and results from the toxicity and biological reactivity tests. 5. Summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre- | | | |

change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.

6. Comparative pre- and post-change test results for the manufacturer’s characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do

not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 6 months testing unless otherwise justified.

Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

7. Information demonstrating the suitability of the proposed container/closure system with respect to its relevant properties (for example, results from last media fills; results of transportation and/or interaction studies demonstrating the preservation of protein integrity and maintenance of sterility for sterile products; results of maintenance of sterility in multidose containers and results of user testing).

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 55. Change in the supplier for a primary container closure component, involving: | | | |
| a. replacement or addition of a supplier <i>Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data such as change 52 above</i> | 1,2 | 1-3 | MiVB-N48 |
| b. deletion of a supplier | None | None | MiVB-N49 |
| | | | |
| Conditions <ol style="list-style-type: none"> No change in the type of container closure, materials of construction, shape and dimensions, or in the sterilization process for a sterile container closure component. No change in the specification of the container closure component outside the approved limits. | | | |
| Supporting Data <ol style="list-style-type: none"> Information on the supplier and make of the proposed container closure system (for example, certificate of analysis, description, materials of construction of primary packaging components, specification). Letter from the PRH certifying that there are no changes to the container closure system. | | | |

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|---|
| 3. Certificate of analysis for the container provided by the new supplier and comparison with the certificate of analysis for the approved container. |
| |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 56. Change in the specification used to release a primary container closure component, involving: | | | |
| a. deletion of a test | 1,2 | 1,2 | MiVB-PA50 |
| b. addition of a test | 3 | 1,2 | MiVB-N50 |
| c. replacement of an analytical procedure | 6,7 | 1-3 | MiVB-PA51 |
| d. minor changes to an analytical procedure | 4-7 | 1-3 | MiVB-PA52 |
| e. widening of an acceptance criterion | None | 1,2 | MiVB-PA53 |
| f. narrowing of an acceptance criterion | 8 | 1 | MiVB-N51 |

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|---|
| <p>Conditions</p> <ol style="list-style-type: none"> The deleted test has been demonstrated to be redundant or is no longer a pharmacopoeial requirement. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the final product. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. There is no change in the acceptance criteria outside the approved limits. The new analytical procedure is of the same type. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the container closure component. |
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Supporting Data

1. Updated copy of the proposed specification for the primary or functional secondary container closure component.
2. Rationale for the change in specification for a primary container closure component.
3. Description of the analytical procedure and, if applicable, validation data.

N. Stability

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 57. Change in the shelf life of the final product, involving: | | | |
| a. extension (includes extension of shelf-life of the final product as packaged for sale, and hold-time after opening and after dilution or reconstitution) | None | 1-5 | MaVB-59 |
| b. reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution) | None | 1-5 | MiVB-PA54 |
| Conditions None | | | |
| Supporting Data 1. Updated product labelling information, as appropriate. 2. Proposed storage conditions and shelf-life, as appropriate. 3. Updated post-approval stability protocol. 4. Justification of the change to the post-approval stability protocol or stability commitment. 5. Results of stability testing under real-time/real-temperature conditions covering the proposed shelf-life generated on at least three (3) commercial-scale batches. | | | |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 58. Change in the post-approval stability protocol of the final product, involving: | | | |
| a. major change of the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature | None | 1-6 | MaVB-60 |
| b. addition of time point(s) into the post-approval stability protocol | None | 4,6 | MiVB-PA55 |
| c. addition of test(s) into the post-approval stability protocol | 1 | 4,6 | MiVB-PA56 |

| | | | |
|---|------|---------|-----------|
| d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf life | None | 4,6 | MiVB-PA57 |
| e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life | 2 | 4,6 | MiVB-PA58 |
| f. replacement of the sterility testing by the container/closure system integrity testing | None | 1,2,4,6 | MaVB-61 |
| | 3 | 4,6 | MiVB-PA59 |
| Conditions | | | |
| <ol style="list-style-type: none"> 1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities. 2. The approved shelf-life of the final product is at least 24 months. 3. The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application. | | | |
| Supporting Data | | | |
| <ol style="list-style-type: none"> 1. Copies or summaries of analytical procedures, if new analytical procedures are used. 2. Validation study reports, if new analytical procedures are used. 3. Proposed storage conditions and or shelf-life, as appropriate. 4. Updated post-approval stability protocol and stability commitment. 5. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (for example, data showing greater reliability of the alternative test). 6. Justification of the change to the post-approval stability protocol or stability commitment. | | | |

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 59. Change in the labeled storage conditions for the final product or the diluted or reconstituted product, involving: | | | |
| a. addition or change of storage condition(s) for the final product, or for diluted or reconstituted product (for example, widening or narrowing of a temperature criterion, or addition of a change to controlled temperature chain conditions) | None | 1-4,6 | MiVB-PA60 |
| b. addition of a cautionary statement (for example, “Do not freeze”) | None | 1,2,4,5 | MaVB-62 |

| | | | |
|--|------|---------|---------|
| c. deletion of a cautionary statement (for example, “Do not freeze”) | None | 1,2,4,6 | MaVB-63 |
| | | | |
| Conditions None | | | |
| Supporting Data <ol style="list-style-type: none"> 1. Revised product labelling information, as applicable. 2. Proposed storage conditions and shelf-life. 3. Updated post-approval stability protocol and stability commitment. 4. Justification of the change in the labelled storage conditions/cautionary statement. 5. Results of stability testing under appropriate stability conditions covering the proposed shelf-life, generated on one (1) commercial-scale batch unless otherwise justified. 6. Results of stability testing under appropriate conditions covering the proposed shelf-life, generated on at least three (3) commercial-scale batches unless otherwise justified. | | | |
| | | | |

O. Others

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|--|----------------------------|-----------------|--------------------|
| 60. Inclusion of a new, updated or amended Plasma Master File in the approved dossier of a product involving: | | | |
| a. Updating/ amending of Plasma Master File | None | 1,2,3,4 | MiVB-PA61 |
| | | | |
| Conditions None | | | |
| Supporting Data <ol style="list-style-type: none"> 1. Declaration that the PMF Certificate and Evaluation Report are fully applicable for the authorised product, PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the PRH (where the PRH is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation that has been approved. 2. PMF certificate and evaluation report. 3. An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished products including product specific risk assessments. 4. Tabular listing outlining the “present” and “proposed” PMF changes in the dossier. | | | |
| | | | |

8.0 REFERENCES

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2. M4Q Implementation Working Group. Questions & Answers (R1) (Current version, 17 July 2003). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2003
(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4_Quality_Questions_Answers_R1.pdf, accessed 14 December 2014).
3. Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: forty-second report. Geneva: World Health Organization; 1992: Annex 1 (WHO Technical Report Series, No. 822;
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http://whqlibdoc.who.int/trs/WHO_TRS_962_eng.pdf?ua=1, accessed 2 December 2014).
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6. Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.
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7. Malaysian Variation Guideline for Pharmaceutical Products 2013.
([http://bpfk.moh.gov.my/images/Guidelines_Central/Guidelines_on_Regulatory/Malaysia%20Variation%20Guideline%20for%20Pharmaceutical%20Products%202013_edition%201\(April%202013\)%20080513%20\(1\).pdf](http://bpfk.moh.gov.my/images/Guidelines_Central/Guidelines_on_Regulatory/Malaysia%20Variation%20Guideline%20for%20Pharmaceutical%20Products%202013_edition%201(April%202013)%20080513%20(1).pdf))
8. Post Notice of Compliance (NOC) Changes- Quality Guidance
(http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-final-eng.pdf, accessed 18 August 2016)