Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

PHILIPPINE VARIATION GUIDELINE FOR BIOLOGICAL PRODUCTS

Version 1.0
16 March 2023

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PURPOSE

This handbook was created to provide guidance specific to vaccine and biotherapeutic products.

PHILIPPINE VARIATION GUIDELINE FOR BIOLOGICAL PRODUCTS

I INTRODUCTION

Throughout the lifecycle of a biological product, the marketing authorization holder (MAH) is responsible for the product that is placed in the market and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the products to be manufactured and checked by means of generally accepted scientific methods. Such amendments have to be approved by the Food and Drug Administration (FDA) Philippines.

This Philippine Variation Guideline for Biological Products (PVGB) is based on the WHO Technical Report Series (TRS) incorporating country-specific requirements in accordance with the existing Philippine regulations. It is intended to provide supportive information on the requirements for submission of a variation application to implement a change to a biological product. Variation applications are categorized into major variation, minor variation (prior approval) and minor variation (notification). Updating of this guideline will be done whenever the related guidelines and regulations have been revised as deemed necessary.

II SCOPE OF THIS GUIDELINE

This Philippine Variation Guideline for Biological Products concerns the variation applications submitted by marketing authorization holders (MAH) for biological products.

III DEFINITION

III.a Major Variation (BMaV)

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

III.b Minor Variation (BMiV-PA)

Post-Approval Change to a registered biological product in terms of changes with no or minimal impact on the aspects of quality, safety, and efficacy.

III.c Minor Variation (BMiV-N)

Post-Approval Change to a registered biological product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of quality, safety, and efficacy.

IV PROCEDURE

Variation applications may be submitted any time within the validity of the Certificate of Product Registration (CPR) issued by FDA. Refer to FDA Circular No. 2023-___ *Application Process and Requirements for Post - Approval Changes of Biological Products Adopting the World Health Organization Guidelines for Changes to Approved Vaccines and Biotherapeutic Products* for a comprehensive guidance on the application process.

Once the variation application is considered approved or acknowledged, FDA shall issue the appropriate proof of authorization.

Type of Variation	Proof of Approval or Acknowledgement

Major Variation and Minor Variation – Prior Approval	Variation Certificate indicating the approved change/s
Minor Variation – Notification	Approval/acknowledgment through Document Tracking System (DTS)
Changes leading to new product registration	New CPR with new validity

V CHANGES LEADING TO A NEW PRODUCT REGISTRATION

The following changes shall lead to a new product registration leading to issuance of a new CPR:

a. Change/addition of new cell substrate/viral or bacterial seeds that are unrelated to the licensed master cell bank (MCB)/master seed lot (MSL) or pre-MCB/MSL material
b. Changes to the Active Pharmaceutical Ingredient (API)
    i. Change of an API to a different API including change in salt or isomer
    ii. Inclusion of an additional API to a single component or multicomponent product
    iii. Removal of an API from a multicomponent product
    iv. Change in the strength of one or more APIs
    v. Increase in overage
c. Changes in the dosage form
d. Changes in the route of administration (exception for parenteral route)
e. Change of drug product formulation which involves addition and/or removal of excipient
f. Changes to the adjuvant
    i. Change in adjuvant
    ii. Change in type/structure of a chemical adjuvant
    iii. Change in the type/component of a biological adjuvant
g. Addition of alternative drug product manufacturing site (e.g., bulk manufacturer, primary packager, secondary packager and batch release site) to the currently approved site for the same manufacturing activity
h. Addition of a new Container Closure System/presentation for a registered drug product, including its attached device or delivery system

VI OTHERS

ABBREVIATIONS/ACRONYMS

BMaV	=	Major Variation for Biological Products
BMiV-PA	=	Minor Variation – Prior Approval for Biological Products
BMiV-N	=	Minor Variation – Notification for Biological Products
B-OTH	=	Other changes not covered by the country-specific regulations

SECTION 1: CHANGES TO APPROVED VACCINES

I. 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 the antigen *Note: This change generally applies only to influenza vaccines.*	Refer to FDA Circular No. 2020-002		MaV-SC

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	7–10	1–4, 6–8	BMaV-1
	1–4, 7–10	2, 4–8	BMaV-2
b. Deletion of a manufacturing facility or manufacturer of an antigen intermediate, or antigen bulk	5, 6	9	BMiV-N1
c. Change of the name and/or address (for example: postal code, street name) of a manufacturer of the antigen/drug substance	11	1, 2	BMiV-N2

Conditions

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.
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).
7. Specifications of the antigen remain unchanged. If there are changes to the specification of the antigen, the applicant shall file for the applicable change/s. *See **changes 18** and **27**.*
8. If there is a change in the manufacturing site of the final product, the applicant shall file for the applicable change/s. *See **change 33**.*
9. If there are changes to the manufacturing process of the antigen, the applicant shall file for the applicable change/s. *See **changes 3** and **4**.*
10. If there is a change in scale of the antigen, the applicant shall file for the applicable change/s. *See **change 5**.*
11. The manufacturing site of the antigen remains unchanged.

Supporting data

1. Evidence that the facility is GMP compliant. For Change of the name and/or address of a manufacturer of the antigen (BMiV-N2), a valid GMP Certificate reflecting the proposed name and/or address of the manufacturer.

2. Updated information including name, address and responsibility of the manufacturer of the antigen (i.e., Section S2 of the ACTD/ICH CTD).
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 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.
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 3 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 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.
8. Updated post-approval stability protocol.
9. Reason for withdrawal/deletion.

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)	15, 16	1−7, 9, 11, 15	BMaV-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, 15, 16	1−6, 8, 10, 15	BMaV-4
c. A noncritical change with minimal 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	1−6, 9−11, 15, 16	1−4, 15	BMiV-PA1

or production scale; or duplication of a fermentation train)			
4. Change to the antigen 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)	15, 16	1, 2, 5–7, 9, 11, 12, 15	BMaV-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 reverse-phase HPLC)	2, 4, 15, 16	1, 2, 5–7, 10, 11, 15	BMaV-6
c. A noncritical change with minimal 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, 15, 16	1, 2, 15	BMiV-PA2
5. Change in scale of the manufacturing process:			
a. At the fermentation, viral propagation or cellular propagation stage	3–6, 11–13, 15, 16	2, 3, 5–7, 9, 11	BMaV-7
b. At the purification stage	1, 3, 5, 7, 15, 16	2, 5–7, 9, 11	BMaV-8
6. Change in supplier of raw materials of biological origin (for example, fetal calf serum, human serum albumin, trypsin)	17	4, 8, 12, 13	BMaV-9
	8, 17	4, 8	BMiV-PA3
7. Change in source of raw materials of biological origin	17	4, 7, 12, 13, 16	BMaV-10
	8, 17	4, 7, 16	BMiV-PA4
8. Introduction of reprocessing steps	14, 15	8, 10, 11, 14–15	BMaV-11

Conditions

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. If there are changes to the specification of the antigen, the applicant shall file for the applicable change/s. *See **changes 18** and **27**.*
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.
15. If there are changes to the specification of the antigen, the applicant shall file for the applicable change/s. *See **changes 18** and **27**.*
16. If there are changes to the in-process controls applied during the manufacture of antigen, the applicant shall file for the applicable change/s. *See **change 15**.*
17. If there are changes to the specification of the raw material, the applicant shall file for the applicable change/s. *See **change 14**.*

Supporting data

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.
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 if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
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 3 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 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.

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 3 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 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.
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.
15. Comparative tabulated format of the description of the current and proposed manufacturing processes, including in-process controls, with changes highlighted.
16. Comparative tabulated format of the information on the current and proposed sources of the raw material (for example, animal species, country of origin).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
9. Change to the cell banks: *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 license application.*			
a. Generation of a new MCB	1	1, 2, 5, 7–9	BMaV-12
b. Generation of a new working cell bank (WCB)	None	1, 2	BMaV-13
	2–4	1, 2	BMiV-PA5
c. Change in cell bank storage site	7	10	BMiV-N3
10. Change to the seed lots: *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 license application.*			
a. Generation of a new MSL	1	1, 5–9, 11	BMaV-14
b. Generation of a new working seed lot (WSL)	2, 3	5–9, 11	BMaV-15
	2–4	5-6	BMiV-PA6
c. Generation of a new WSL by extending the passage level of an existing WSL beyond an approved level	None	5–7, 11	BMaV-16
d. Change in seed lot storage site	7	10	BMiV-N4
11. Change in cell bank/seed lot testing/storage site	5, 7	10	BMiV-N5
12. Change in cell bank/seed lot qualification protocol	None	3, 4	BMaV-17
	6	4	BMiV-PA7
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 license. 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 and the transport conditions of the cell bank/seed lot has been validated.
Supporting data 1. Qualification of the cell bank or seed lot according to guidelines considered acceptable. 2. Information on the characterization and testing of the MCB/WCB, and cells from the end-of-production passage or post-production passage. 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. 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 3 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 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. 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	1, 2	1−6	BMaV-18
b. Introduction of new equipment with the same operating principles but different product contact material	1, 2	1, 3−6	BMaV-19
c. Introduction of new equipment with different operating principles but the same product contact material	1, 2	1−3, 5, 6	BMaV-20
d. Replacement of equipment with equivalent equipment (including filter)	1, 2	1, 5−7	BMiV-PA8
Conditions 1. If there are changes to the specification of the antigen, the applicant shall file for the applicable change/s. *See **changes 18** and **27**.* 2. If there are changes to the in-process controls applied during the manufacture of antigen, the applicant shall file for the applicable change/s. *See **change 15**.*			
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 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 or deletion of test parameter and 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, 13	BMaV-21
b. Raw materials/intermediates: Narrowing of the approved specification limits or addition of test parameter and limits for starting materials/intermediates	1−4	1, 3−7, 13	BMiV-PA9
c. Raw materials/intermediates: Change of a test procedure for starting materials/intermediates	4, 7	1, 3−7, 13	BMiV-PA10
d. Raw materials/intermediates: Change of specifications and/or test procedure following the updates in the compendium	13	1, 3, 13, 15	BMiV-N6

15. Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen, involving:			
a. Narrowing of in-process limits	3, 5, 8, 9, 12	2, 6, 14	BMiV-PA11
b. Addition of new in-process test and limits	4, 5, 10, 11, 12	2−6, 8, 10, 14	BMiV-PA12
c. Deletion of a non-significant in‑process test	4−6, 12	2, 6, 9, 14	BMiV-PA13
d. Widening of the approved in‑process limits	12	2−6, 8, 10, 11, 14	BMaV-22
	3−5, 12	2, 6, 8, 10, 11, 14	BMiV-PA14
e. Deletion of an in-process test which may have a significant effect on the overall quality of the antigen	12	2, 6, 8, 10, 14	BMaV-23
f. Addition or replacement of an in‑process test as a result of a safety or quality issue	12	2−6, 8, 10, 14	BMaV-24
16. Change in in-process controls testing site	3−5, 7, 8	12	BMiV-N7

Conditions

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. the applicant shall file for the applicable change/s. *See **changes 18** and **27**.*
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. If there are changes to the in-process controls applied during the manufacture of antigen, the applicant shall file for the applicable change/s. *See **change 15**.*
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).
12. Release and shelf-life specifications of the antigen remain unchanged. If there are changes to the specification of the antigen, the applicant shall file for the applicable change/s. *See **changes 18** and **27**.*
13. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.

Supporting data

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 if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
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.
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 3 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 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.
12. Evidence that the new company/facility is GMP compliant.
13. Comparative tabulated format of the current and revised specifications and/or test procedures of the raw material/intermediate with changes highlighted.
14. Comparative tabulated format of description of the current and proposed test procedures/in-process controls with changes highlighted.
15. Copy of the official monograph of the updated compendium.

C. Control of the 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 of the antigen, involving:			
a. Transfer of the QC testing activities for a non-pharmacopoeial assay to a new company not approved in the current MA or licence	1−3	1−2	BMiV-PA15
b. Transfer of the QC testing activities for a pharmacopoeial assay to a new company not approved in the current MA or licence	1	1−2	BMiV-PA16
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. 3. Transfer within a site approved in the current MA for the performance of other tests.			

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 a test	None	1, 5, 8, 9	BMaV-25
b. Addition of a test	1−3	1−3, 5, 9	BMiV-PA17
c. Replacement of an analytical procedure	None	1−5, 9	BMaV-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, 9	BMaV-27
e. Minor changes to an approved analytical procedure	4−7	1, 4, 5, 9	BMiV-PA18
f. Change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure	4, 7	1−3, 9	BMiV-PA19
g. Widening of an acceptance criterion	None	1, 5, 8, 9	BMaV-28
h. Narrowing of an acceptance criterion	1, 8, 9	1, 9	BMiV-PA20
i. Change of specifications and/or test procedure following the updates in the compendium	10	1, 9, 10	BMiV-N8

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 limits/acceptance criteria outside the approved limits for the approved assays.
3. The addition of the test is not intended to monitor new impurity species.
4. No change in the acceptance criteria outside the approved limits.
5. 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.
6. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
7. The change does not concern potency testing.
8. 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).
9. The analytical procedure remains the same, or changes to the analytical procedure are minor.
10. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.

Supporting data
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. 9. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the antigen with changes highlighted. 10. Copy of the official monograph of the updated compendium.

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	BMiV-PA21
20. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	BMiV-PA22
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	BMiV-PA23
22. Change to reference standard qualification protocol	None	3, 4	BMiV-PA24
23. Extension of reference standard shelf-life	2	5	BMiV-PA25
Conditions 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 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	BMaV-29
	1	1, 3, 5	BMiV-PA26
Conditions 1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.			
Supporting data 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 3 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 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.
5. Comparative table of pre- and post-change specifications.

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, 4	BMiV-PA27
b. Addition of a test	3	1−3, 4	BMiV-PA28
c. Replacement of an analytical procedure	6, 7	1−3, 4	BMiV-PA29
d. Minor changes to an analytical procedure	4−7	1−3, 4	BMiV-PA30
e. Widening of an acceptance criterion	None	1, 2, 4	BMiV-PA31
f. Narrowing of an acceptance criterion	8	1, 4	BMiV-PA32

Conditions

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

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.
4. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the primary container closure system with changes highlighted.

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	BMaV-30
	1−5	1, 2, 5	BMiV-PA33
b. Reduction	None	1−5	BMaV-31
	6	2−4	BMiV-PA34
Conditions 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. *Note: Problems arising during manufacturing or stability concerns should be reported for evaluation.*			
Supporting data 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, interim stability testing results and a commitment to notify 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 or stability commitment, such as deletion of a test parameter or limit, replacement of an analytical procedure, widening of specification limits, or change in storage temperature	None	1−7	BMaV-32
	1	1, 2, 4−7	BMiV-PA35
b. Addition of time point(s) into the post-approval stability protocol	None	4, 6	BMiV-PA36
c. Addition of test(s) into the post-approval stability protocol or tightening of specification limits	2	1, 2, 4, 6, 7	BMiV-PA37
d. Deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	BMiV-PA38

e. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 6	BMiV-PA39
f. Change to the post-approval stability protocol, such as change in specifications and/or test procedures following the updates in the compendium	4	4, 7, 8	BMiV-N9
Conditions 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. 4. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.			
Supporting data 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 for the change to the post-approval stability protocol. 7. Comparative tabulated format of the currently approved and proposed stability protocols or stability commitments with changes highlighted. 8. Copy of the official monograph of the updated compendium.			

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	BMaV-33
	1, 2	1−3	BMiV-PA40
Conditions 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.			
Supporting data 1. Proposed storage conditions and shelf-life. 2. Updated post-approval stability protocol and stability commitment. 3. Justification of the change in the labelled storage conditions/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).			

II. CHANGES TO THE FINAL PRODUCT

G. Description and Composition of the Final Product

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 (for example, lyophilised powder to liquid)	New registration application		
b. Change in the formulation (for example, addition or removal of an excipient)	New registration application		
c. Change in the formulation (for example, qualitative or quantitative change of excipient, or new diluents for lyophilized product) *Note: Change in 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 MA or licensure.*	1	1−10	BMaV-34
d. Change in fill volume (that is, same concentration, different volume)	1, 2	1, 5, 7, 10	BMaV-35
e. Change of presentation (for example, from pre-filled syringe to vial)	1	1, 3, 5, 7−10	BMaV-36
f. 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)	1	1, 3, 5, 7−11	BMaV-37
Conditions 1. Change will need to comply with the finished product specifications, for example release and shelf-life specifications of the drug product remain unchanged, except for the update of product description with respect to presentation/appearance/fill volume as a consequence of the change (where applicable). If there are changes to the specification of the final product, the applicant shall file for the applicable change/s. *See **changes 46** and **58**.* 2. The packaging material remains unchanged.			

Supporting data

1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).
2. Characterization data demonstrating that the conformation and immunogenicity of the antigen is comparable in the formulation.
3. Comparative tabulated format of the currently approved and proposed packaging presentations/primary packaging materials/diluents or product formulations with calculated changes highlighted (state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable).
4. Discussion of the components of the final product, as appropriate (for example, choice of excipients, compatibility of antigen and excipients, leachates or compatibility with new container closure system, as appropriate).
5. Information on the batch formula, manufacturing process and process controls, control of critical steps and intermediates, and process validation study reports.
6. Control of excipients, if new excipients are proposed (for example, specification).
7. 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.
8. Information on the container closure system and leachables and extractables, if any of the components have changed (for example, description, materials of construction and summary of specification).
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 3 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 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.
10. Supporting clinical data or a justification for why such studies are not needed.
11. Amended relevant ACTD/ICH CTD section/s.

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.*

- *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	BMiV-PA41
	1−3	5	BMiV-PA42
b. Change in manufacture of a chemical/synthetic adjuvant	None	3−5, 10, 11, 14	BMiV-PA43
c. Change in specification of a chemical/synthetic adjuvant (including tests and/or the analytical procedures)	None	7−11, 14	BMiV-PA44
	1, 3	7−9, 14	BMiV-PA45
31. Change involving a biological adjuvant:			
a. Change in supplier of a biological adjuvant	None	1−7, 10−13	BMaV-38
b. Change in manufacture of a biological adjuvant	None	1−7, 10−14	BMaV-39
	4	1−7, 10−12, 14	BMiV-PA46
c. Change in specification of a biological adjuvant (including tests and/or the analytical procedures)	None	6−10, 14	BMiV-PA47
	1, 3	7−8, 14	BMiV-PA48

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).
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 3 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 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.
12. Supporting nonclinical and clinical data, if applicable.
13. Evidence that the facility is GMP compliant.
14. Comparative tabulated format of the currently approved and proposed manufacturing processes/specifications and/or test procedures of the adjuvant with changes highlighted.

I. Description and Composition of the Final Product: Change to a Diluent

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 diluent, involving: *Note: Inclusion or replacement of the diluent for the drug product, refer to BMaV-34.*			
a. Change in manufacturing process	None	1−4, 7	BMiV-PA49
b. Replacement of the source of a diluent	None	1−6, 9	BMiV-PA50
c. Addition to the source of a diluent	None	1−6, 8, 9	BMiV-PA51
d. Change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5, 6	BMiV-PA52
d. Addition of a diluent filling line	1−3	1, 3, 5, 7	BMiV-PA53
e. Addition of a diluent into an approved filling line	1, 2	1, 3, 5	BMiV-PA54
f. Deletion of a diluent	None	10	BMiV-N10
Conditions 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 a 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 addition of the diluent filling line is in an approved filling facility.			
Supporting data 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 diluent.			

5. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned.
6. Comparative tabulated format of information on the currently registered and proposed production facilities (such as name, address and responsibilities).
7. Comparative tabulated format of the description of the current and proposed manufacturing processes or lines, including in-process controls, with changes highlighted.
8. Amended relevant ACTD/ICH CTD section/s.
9. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).
10. Reason for withdrawal/deletion.

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 and primary packaging)	None	1−7, 11	BMaV-40
	1−5	1−3, 5−8, 11	BMaV-41
b. Addition of a manufacturing facility for the final product (including formulation/filling and primary packaging)	None	1−7, 9, 11	BMaV-42
	1−5	1−3, 5−9, 11	BMaV-43
c. Replacement of a secondary packaging facility, a labelling/storage facility or a distribution facility	2, 3	1−3, 11	BMiV-PA55
d. Addition of a secondary packaging facility, a labelling/storage facility or a distribution facility	2, 3	1−3, 9, 11	BMiV-PA56
e. Replacement of the company or party responsible for batch release	9	1, 2, 11, 12	BMiV-PA57
f. Addition of the company or party responsible for batch release	9	1, 2, 9, 11, 12	BMiV-PA58
g. Deletion of a final product manufacturing facility/packager/batch releaser	6	10, 11	BMiV-N11
h. Change of the name or address (for example: postal code, street name) of the manufacturer/packager of drug product or company responsible for batch release	7, 8	2, 11, 13	BMiV-N12
i. Change of product owner	7, 10	11, 14−16	BMiV-N13

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
2. If there is/are changes in the composition, manufacturing process, and/or final product specification, the applicant shall file for the applicable change/s. *See* ***changes 29, 30, 31, 34****,* ***46****, and* ***58****.*
3. If there is/are changes in the container/closure system and storage conditions, the applicant shall file for the applicable change/s. *See* ***changes 52, 53,*** *and* ***59.****.*
4. The same validated manufacturing process is used.
5. 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.

6. There should remain at least one site/manufacturer/batch releaser, as previously authorized, performing the same function as the one(s) to be deleted.
7. The manufacturing/packaging/batch release site remains unchanged.
8. Not applicable in case it involves change in ownership of the manufacturer.
9. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed.
10. This shall cover imported drug products only. For locally manufactured drug products, refer to the conditions and requirements stipulated in **BMiV-N41**.

Supporting data

1. Comparative tabulated format of information on the currently registered and proposed production facilities (such as name, address and responsibilities) involved in the manufacture of the drug product including bulk, packaging and release.
2. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned. In the case of **BMiV-N12**, a valid FDA-issued GMP Certificate reflecting the proposed name and/or address of the manufacturer.
3. 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 3 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 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.
8. Rationale for considering the proposed formulation/filling facility as equivalent.
9. Amended relevant ACTD/ICH CTD section/s.
10. Reason for withdrawal/deletion.
11. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).
12. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable).
13. Official letter from product owner authorizing the manufacturer with proposed name/address to manufacture/release the drug product.
14. Declaration on the transfer of ownership between the currently approved and the proposed product owner.
15. Official letter from the proposed product owner declaring the change and authorizing the local license holder to be responsible for the product license.

16. If the proposed product owner is not the manufacturer of the drug product, an official letter by the proposed product owner authorizing the manufacturer to manufacture the drug product on its behalf, and letter of acceptance from the manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product.

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	BMaV-44
b. Addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, and lyophilizer)	None	1−8	BMaV-45
	5	2, 7−9	BMiV-PA59
c. Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	1−4	1, 4	BMiV-PA60
d. Addition of a new step (for example, filtration)	3	1−6	BMaV-46

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).
6. If there are changes to the specification of the final product, the applicant shall file for the applicable change/s. *See **changes 46** and **58***.
7. If there are changes to the in-process controls applied during the manufacture of drug product, the applicant shall file for the applicable change/s. *See **change 35***.

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 3 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 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.
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 tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:			
a. Narrowing of in-process limits	1–3, 7	1, 5, 11	BMiV-PA61
b. Addition of new in-process test and limits	1–3, 8, 9	1−6, 8, 11	BMiV-PA62
c. Deletion of a non-significant in‑process test	1−4	1, 5, 7, 11	BMiV-PA63
d. Widening of the approved in‑process limits	1	1−6, 8, 9, 11	BMaV-47
	1−3	1, 5, 6, 8, 9, 11	BMiV-PA64
e. Deletion of an in-process test which may have a significant effect on the overall quality of the final product	1	1, 5, 6, 8, 11	BMaV-48
f. Addition or replacement of an in‑process test as a result of a safety or quality issue	1	1−6, 8, 11	BMaV-49
36. Change in in-process controls testing site	1−3, 5, 6	10	BMiV-N14

Conditions
1. No change in final product specification outside the approved limits. If there are changes to the specification of the final product, the applicant shall file for the applicable change/s. *See **changes 46** and **58**.*
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 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 physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)

Supporting data
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 tests.

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.
7. Justification/risk assessment showing that the attribute is non-significant.
8. Justification for the new in-process test and limits.
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 3 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 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.
10. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned.
11. Comparative tabulated format of description of the current and proposed test procedures/in-process controls with changes highlighted.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
37. Change in the specification used to release the excipient, involving: *Note: This change excludes adjuvants. See adjuvant-specific changes for details (**changes 30** and **31**).*			
a. Deletion of a test	5, 8	1, 3, 4	BMiV-PA65
b. Addition of a test	4	1−4	BMiV-PA66
c. Replacement of an analytical procedure	1−3	1, 2, 4	BMiV-PA67
d. Minor changes to an approved analytical procedure	None	1, 2, 4	BMiV-PA68
e. Change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1, 2, 4	BMiV-PA69
f. Widening of an acceptance criterion	None	1, 3, 4	BMiV-PA70
g. Narrowing of an acceptance criterion	3, 4, 6, 7	1, 4	BMiV-PA71
h. Change of specifications and/or test procedure following the updates in the compendium	9	1, 4, 5	BMiV-N15

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect the new 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 a 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. 9. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.
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). 4. Comparative tabulated format of the current and revised specifications and/or test procedures of the excipient with changes highlighted. 5. Copy of the official monograph of the updated compendium.

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	7	2−7, 11	BMaV-50
39. Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source	7	1, 3, 5, 6, 11	BMiV-PA72
40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5−7	2−7, 11	BMiV-PA73
41. Change in manufacture of a biological excipient *Note: This change excludes biological adjuvants; see adjuvant-specific changes above for details (**changes 30** and **31**).*	7	2−7	BMaV-51
	2, 7	2−7	BMiV-PA74
	1, 2, 7	2−7	BMiV-PA75
42. Change in supplier for a plasma-derived excipient (for example, human serum albumin)	7	3−8	BMaV-52
	3, 4, 7	5, 6, 9	BMiV-PA76
43. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient) *Note: This change excludes adjuvants; see adjuvant-specific changes above for details (**changes 30** and **31**).*	7	2, 3, 5−7	BMiV-PA77
	1, 5−7	3	BMiV-PA78
44. Change in excipient testing site	1, 7	10	BMiV-N16
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. 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. 7. If there are changes to the specification of the excipient, the applicant shall file for the applicable change/s. *See* ***change 37.***
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 3 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 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. 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. 11. Comparative tabulated format of the information on the current and proposed sources of the excipient (for example, animal species, country of origin).

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:			
a. Transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company or to a different site within the same company	2	1−3	BMiV-PA79

b. Transfer of the QC testing activities for a pharmacopoeial assay to a new company	1, 2	1−3	BMiV-PA80
c. Addition or replacement of the company or party responsible for quality control/stability testing (different from the batch release site)	2	1−3	BMiV-N17
Conditions 1. The transferred QC test is not a potency assay or a bioassay. 2. The manufacturer of the final product remains unchanged. If there are changes to the manufacturer of the final product, the applicant shall file for the applicable change/s. *See **change 33.***			
Supporting data 1. Information demonstrating technology transfer qualification. 2. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned.			

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, diluent for reconstitution of lyophilized vaccines), replacing the sterility test with process parametric release	None	1, 2, 6, 8, 10, 12	BMaV-53
b. Deletion of a test	None	2, 9, 10, 12	BMaV-54
c. Addition of a test	1, 2, 9	2−4, 8, 12	BMiV-PA81
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, 12	BMaV-55
e. Replacement of an analytical procedure	None	2−4, 7, 8, 12	BMaV-56
f. Minor changes to an approved analytical procedure	3–6	3, 8, 12	BMiV-PA82
g. Change from an in-house analytical procedure to a recognized compendial analytical procedure	3, 6	2−4, 12	BMiV-PA83
h. Widening of an acceptance criterion	None	2, 8, 10, 12	BMaV-57
i. Narrowing of an acceptance criterion	7−10	2, 12	BMiV-PA84
j. Change of specifications and/or test procedure following the updates in the compendium	11	2, 12–14	BMiV-N18
Conditions 1. No change in the limits/acceptance criteria outside the approved limits for the approved assays. 2. The additional test is not intended to monitor new impurity species. 3. No change in the acceptance criteria outside the approved limits. 4. 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. The change is within the range of approved acceptance criteria.			

8. 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). 9. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, or impurity content outside of the approved limits). 10. The analytical procedure remains the same, or changes to the analytical procedure are minor. 11. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.
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). 12. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the drug product with changes highlighted. 13. For change in test procedure, appropriate verification data of the proposed test procedure. 14. Copy of the official monograph of the updated compendium.

L. Reference Standards or Materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
47. Qualification of a reference standard against a new primary international standard	None	1, 2	BMiV-PA85
48. Change of the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	BMiV-PA86
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	BMiV-PA87
50. Change to the reference standard qualification protocol	None	3, 4	BMiV-PA88
51. Extension of the shelf-life of the reference standard	2	5	BMiV-PA89

Conditions 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 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. Modification of a container closure system: *Note:* ▪ *The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation; refer to **BMaV-37**.*			
a. Change in primary container closure system (for example, new coating, adhesive, stopper or type of glass)	None	1−8	BMaV-58
	4	1, 3, 7, 8	BMiV-PA90
	1−3	1, 3, 8	BMiV-PA91
b. Change in any part of the packaging material not directly in contact with the finished product formulation such as change in the bossing (from direct printing to use of sticker) on the labeling materials, inclusion/deletion of an aluminum pouch, and inclusion/deletion of blister pack enclosing the primary packaging of a drug product	5	1, 3, 6, 8	BMiV-PA92
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, 8	BMaV-59
54. Deletion of a container closure system	None	1	BMiV-N19
Conditions 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). 4. The modified part is not in contact with the drug product. 5. For the change in the bossing on the labeling materials, the layout and information on the labels remain unchanged. Otherwise, refer to ***change 137*** (whichever is applicable) for the change in the labeling of the drug product.			
Supporting data 1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).			

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 3 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 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.
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).
8. Comparative tabulated format of descriptions and specifications of the current and proposed packaging materials, including illustrations.

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	1, 2	1, 2	BMiV-PA93
b. Deletion of a supplier	None	3	BMiV-N20
Conditions 1. 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. 2. No change in the specification of the container closure component outside the approved limits. If there are changes to the specification of the container closure, the applicant shall file for the applicable change/s. *See* ***change 56***.			
Supporting data 1. Letter from the MA holder certifying that there are no changes to the container closure system. 2. Certificate of analysis for the container provided by the new supplier and comparison with the certificate of analysis for the approved container. 3. Reason for withdrawal/deletion.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category

56. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving:			
a. Deletion of a test	1, 2	1, 2, 4	BMiV-PA94
b. Addition of a test	3	1, 2, 4	BMiV-PA95
c. Replacement of an analytical procedure	6, 7	1−3, 4	BMiV-PA96
d. Minor changes to an analytical procedure	4−7	1−4	BMiV-PA97
e. Widening of an acceptance criterion	None	1, 2, 4	BMiV-PA98
f. Narrowing of an acceptance criterion	8	1, 4	BMiV-PA99
Conditions 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 final product. 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 new pharmacopoeial monograph specifications for the container closure component.			
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. 4. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the container closure with changes highlighted.			

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	BMaV-60
b. Reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1−5	BMiV-PA100
Conditions None			
Supporting data 1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable). 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 to the post-approval stability protocol or stability commitment, such as deletion of a test parameter or limit, replacement/deletion of an analytical procedure, widening of specification limits, or change in storage temperature	None	1−6	BMaV-61
b. Addition of time point(s) into the post-approval stability protocol	None	4, 6	BMiV-PA101
c. Addition of test(s) into the post-approval stability protocol or tightening of specification limits	1	4, 6	BMiV-PA102
d. Deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	BMiV-PA103
e. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 6	BMiV-PA104
f. Replacement of the sterility testing by the container/closure system integrity testing	None	1, 2, 4, 6	BMaV-62
	3	4, 6	BMiV-PA105
g. Change to the post-approval stability protocol, such as change in specifications and/or test procedures following the updates in the compendium	4	4, 7−9	BMiV-N21
Conditions 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. 4. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.			
Supporting data 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. 7. Comparative tabulated format of the currently approved and proposed stability protocols or stability commitments with changes highlighted. 8. For change in test procedure, appropriate verification data of the proposed test procedure. 9. Copy of the official monograph of the updated compendium.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
59. Change in the labelled storage conditions for the final product or the diluted or reconstituted vaccine, involving:			
a. Addition or change of storage condition(s) for the final product, or for diluted or reconstituted vaccine (for example, widening or narrowing of a temperature criterion, or addition of or change to controlled temperature chain conditions)	None	1−4, 6	BMiV-PA106
b. Addition of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 5	BMiV-PA107
c. Deletion of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 6	BMiV-PA108
Conditions None			
Supporting data 1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where 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.			

SECTION 2: BIOTHERAPEUTIC PRODUCTS

III. CHANGES TO THE DRUG SUBSTANCE

O. Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
60. Change to a drug substance manufacturing facility:			
a. Replacement or addition of a manufacturing facility for the bulk drug substance or any intermediate	7–10	1–4, 6–8	BMaV-63
	1–3, 7–10	1–8	BMaV-64
b. Conversion of a drug substance manufacturing facility from single-product to multi-product	4	9, 10	BMaV-65
c. Deletion of a manufacturing facility or manufacturer of an intermediate drug substance, or bulk	5, 6	11	BMiV-N22
d. Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance	11	1, 2	BMiV-N23

Conditions

1. The proposed facility is an approved drug substance facility for biotherapeutics.
2. Any changes to the manufacturing process and/or controls are considered minor (for example, duplication of product line).
3. The new facility/suite is under the same quality assurance/quality control 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 (for example, recurrent out-of-specification events, environmental monitoring failures, etc.).
7. Specifications of the drug substance remain unchanged. If there are changes to the specification of the drug substance, the applicant shall file for the applicable change/s. *See **changes 78, 79, 81** and **92**.*
8. If there is a change in the manufacturing site of the drug product, the applicant shall file for the applicable change/s. *See **change 97**.*
9. If there are changes to the manufacturing process, the applicant shall file for the applicable change/s. *See **changes 65** and **66**.*
10. If there is a change in scale of the drug substance, the applicant shall file for the applicable change/s. *See **change 67**.*
11. The manufacturing site of the drug substance remains unchanged.

Supporting data

1. Evidence of GMP compliance of the facility. For Change of the name and/or address of a manufacturer of the antigen (BMiV-N23), a valid GMP Certificate reflecting the proposed name and/or address of the manufacturer.
2. Updated information including name, address and responsibility of the manufacturer of the drug substance (i.e., Section S2 of the ACTD/ICH CTD).
3. Summary of the process validation studies and results.
4. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may be required if quality data alone

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 the knowledge of the product, existing relevant nonclinical and clinical data, and aspects of their use.

5. Justification for the classification of any manufacturing process and/or control changes as minor.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/holdtime of the drug substance under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, use of smaller-scale batches and/or use of fewer than three batches of drug substance for stability testing may be acceptable where justified.
8. Updated post-approval stability protocol.
9. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If no revisions, the manufacturer should state that no changes were made to the change-over procedures.
10. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.
11. Reason for withdrawal/deletion.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
61. Change to the cell banks: *Note: New cell substrates that are unrelated to the licensed master cell bank (MCB) or pre-MCB material may require a new application for marketing authorization or license application.*			
a. Adaptation of an MCB into a new culture medium	None	1, 2, 5–8, 10	BMaV-66
b. Generation of a new MCB	1	1, 2, 5–8	BMaV-67
c. Generation of a new working cell bank (WCB)	2–4	1, 2	BMiV-PA109
62. Change in the cell bank manufacturing site	None	1, 2, 9	BMaV-68
63. Change in the cell bank testing/storage site	5, 7	9	BMiV-N24
64. Change in the cell bank qualification protocol	None	3, 4	BMaV-69
	6	4	BMiV-PA110
Conditions 1. The new MCB is generated from the original clone or from a pre-approved MCB and is grown in the same culture medium. 2. The new cell bank is generated from a pre-approved MCB. 3. The new cell bank is at the pre-approved passage level.			

4. The new cell bank is released according to a pre-approved protocol/process or as described in the original license. 5. No changes have been made to the tests/acceptance criteria used for the release of the cell bank. 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, and the transport conditions of the cell bank have been validated.
Supporting data 1. Qualification of the cell bank. 2. Information on the characterization and testing of the MCB/WCB, and cells from the end-of production passage or post-production passage. 3. Justification of the change to the cell bank qualification protocol. 4. Updated cell bank qualification protocol. 5. Comparability of the pre-change and post-change drug substance 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 product, existing relevant nonclinical and clinical data, and aspects of its use. 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 consecutive commercial-scale batches of the drug substance derived from the new cell bank. Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified. 7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold time of the drug substance under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified. 8. Updated post-approval stability protocol. 9. Evidence that the new company/facility is GMP-compliant. 10. Supporting nonclinical and clinical data or a request for a waiver of in vivo studies with justification.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
65. Change to the fermentation or cell culture process:			
a. A critical change (a change with high potential to have an impact on the quality of the drug substance or drug product; for example,	14, 15	1–7, 9, 11, 15	BMaV-70

incorporation of disposable bioreactor technology)			
b. A change with moderate potential to have an impact on the quality of the drug substance or drug product (for example, extension of the in vitro cell age beyond validated parameters)	1, 3, 14, 15	1–6, 8, 10, 15	BMaV-71
c. A noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product, such as: • 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; • duplication of a fermentation train; or • addition of similar/comparable bioreactors	1–5, 7–10, 14, 15	1, 2, 4, 8, 15	BMiV-PA111
66. Change to the purification process, involving the following:			
a. A critical change (a change with high potential to have an impact on the quality of the drug substance or drug 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 drug substance)	14, 15	1, 2, 5–7, 9, 11, 12, 15	BMaV-72
b. A change with moderate potential to have an impact on the quality of the drug substance or drug product (for example, a change in the chemical separation method, such as ion-exchange HPLC1 to reversed-phase HPLC)	1, 3, 14, 15	1, 2, 5–7, 10–12, 15	BMaV-73
c. A noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product (for example, addition of an in-line filtration step equivalent to the approved filtration step)	1–4, 14, 15	1, 2, 15	BMiV-PA112
67. Change in scale of the manufacturing process:			
a. At the cell culture stage	3, 9–11, 14, 15	2, 3, 5–7, 9, 11	BMaV-74
b. At the purification stage	1, 2, 4, 6, 14, 15	2, 5–7, 9, 11	BMaV-75
68. Introduction of reprocessing steps	12–14	8, 10, 11, 13, 15	BMiV-PA113
69. Addition of a new holding step or change in the parameters of an approved holding step	14	5, 14, 15	BMaV-76

Conditions

1. The change does not have an impact on the viral clearance data or the chemical nature of an inactivating agent.
2. There is no change in the drug substance specification outside the approved limits. If there are changes to the specification of the drug substance, the applicant shall file for the applicable change/s. *See **changes 78**, **79**, **81** and **92**.*
3. There is no change in the drug substance impurity profile outside the approved limits.
4. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
5. The change does not affect the purification process.

6. The change in scale is linear with respect to the proportionality of production parameters and materials.
7. The new fermentation train is identical to the approved fermentation train(s).
8. There is no change in the approved in vitro cell age.
9. The change is not expected to have an impact on the quality, safety or efficacy of the final product.
10. There is no change in the proportionality of the raw materials (that is, the change in scale is linear).
11. The change in scale involves the use of the same bioreactor (that is, it does not involve the use of a larger bioreactor).
12. The need for reprocessing is not due to recurrent deviations from the validated process, and the root cause triggering reprocessing is identified.
13. The proposed reprocessing steps have been shown to have no impact on product quality.
14. If there are changes to the specification of the drug substance, the applicant shall file for the applicable change/s. *See **changes 78, 79, 81** and **92**.*
15. If there are changes to the in-process controls applied during the manufacture of drug substance, the applicant shall file for the applicable change/s. *See **change 74.***

Supporting data

1. Justification for the classification of the change(s) as critical, moderate or noncritical in terms of its impact on the quality of the drug substance.
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 postproduction cell bank for recombinant product or of the drug substance for nonrecombinant product.
4. For drug substance 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, use and previous acceptance of the material).
5. Process validation results.
6. Comparability of the pre-change and post-change drug substance 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 product, existing relevant nonclinical and clinical data, and aspects of its 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 consecutive commercial-scale batches of the pre-change and post-change drug substance. 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, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative prechange 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 marketing authorization holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and.

9. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months and one batch of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative prechange test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified.
10. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes with at least one commercial-scale drug substance 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 batches on the stability programme are acceptable. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report 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.
11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the drug product manufactured using the postchange drug substance 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. Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times, resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the drug substance.
14. Demonstration that the new or revised holding step has no negative impact on the quality of the drug substance (data from one commercial-scale or scientifically justified representative drug substance batch should be provided).
15. Comparative tabulated format of the description of the current and proposed manufacturing processes, including in-process controls, with changes highlighted.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
70. Change in equipment used in the drug substance manufacturing process, involving the following: *Note: New bioreactor technology (for example, a change from stainless steel bioreactor to disposable bioreactor) is excluded from this table and should be filed according to* ***BMaV-70****.*			
a. Introduction of new equipment with different operating principles and different product contact material	6, 7	1, 3–5	BMaV-77
b. Introduction of new equipment with the same operating principles but different product contact material	3, 4, 6, 7	1, 4, 5	BMiV-PA114

c. Introduction of new equipment with different operating principles but the same product contact material	6, 7	1–3, 5	BMaV-78
	4, 6, 7	1, 2, 5	BMiV-PA115
d. Replacement of product contact equipment with equivalent equipment	6, 7	3	BMiV-PA116
e. Change of product-contact equipment from dedicated to shared	1, 2, 6, 7	1, 6	BMiV-PA117
f. Relocation of major equipment to another room in the same facility/suite/ premises	2, 4–7	7	BMiV-PA118
Conditions 1. The site is approved as a multi-product facility. 2. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures. 3. The manufacturing process is not impacted by the change in product-contact equipment. 4. The change has no impact on product quality. 5. Re-qualification of the equipment follows the original qualification protocol. 6. If there are changes to the specification of drug substance, the applicant shall file for the applicable change/s. *See **changes 78, 79, 81** and **92**.* 7. If there are changes to the in-process controls applied during the manufacture of drug substance, the applicant shall file for the applicable change/s. *See **change 74.***			
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 commercial-scale batch of the drug substance 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 marketing authorization holder 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 describing the change-over procedures for the shared product-contact equipment. 7. Justification for the proposed change.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
71. Change in specification for the materials, involving the following:			
a. Narrowing of the approved specification limits or addition of test parameter and limits for starting materials/intermediates	1–4	1–3, 5, 11	BMiV-PA119
b. Widening of the approved specification limits or deletion of test parameter and limits for starting materials/intermediates	None	1–3, 5, 7, 11	BMaV-79
	3–7	3–6, 11	BMiV-PA120
c. Change of a test procedure for starting materials/intermediates	4	1–3, 5, 11	BMiV-PA121
d. Change of specifications and/or test procedure of the raw materials/intermediates, following the updates in the compendium	9	1, 2, 11, 12	BMiV-N25
72. Change in supplier of raw materials of biological origin (for example, fetal calf serum, insulin, trypsin)	None	4, 6, 9, 10	BMaV-80
	8	4, 6	BMiV-PA122

73. Change in source of raw materials of biological origin (for example, bovine trypsin to porcine trypsin)	None	4, 7, 9, 10, 13	BMaV-81
	8	4, 7, 13	BMiV-PA123

Conditions

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. There is no change in the drug substance specification outside the approved limits. If there are changes to the specification of the drug substance, the applicant shall file for the applicable change/s. *See **changes 78, 79, 81** and **92**.*
4. There is no change in the impurity profile of the drug substance outside the approved limits.
5. The change has no significant effect on the overall quality of the drug substance and/or drug product and there are no changes to the cell banks.
6. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
7. The test does not concern a critical attribute (for example, content, impurity, any critical physical characteristics or microbial purity).
8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).
9. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.

Supporting data

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 drug substance.
2. Updated drug substance specification, if changed.
3. Copies or summaries of analytical procedures if new analytical procedures are used.
4. For drug substance 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, use and previous acceptance of the material).
5. Comparative table or description, where applicable, of pre-change and postchange in-process tests/limits.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative prechange 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 marketing authorization holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for three consecutive commercial-scale batches of the pre-change and post-change drug substance. 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, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
8. Justification/risk assessment showing that the attribute is non-significant.
9. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk).
10. Information demonstrating suitability of the auxiliary materials/reagents of both sources through the comparability of the drug substance.

11. Comparative tabulated format of the current and revised specifications and/or test procedures of the raw material/intermediate with changes highlighted.
12. Copy of the official monograph of the updated compendium.
13. Comparative tabulated format of the information on the current and proposed sources of the raw material (for example, animal species, country of origin).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
74. Change to in-process tests and/or acceptance criteria applied during manufacture of the drug substance, involving the following:			
a. Narrowing of approved in-process limits	1, 3, 6, 7	1, 4, 10	BMiV-PA124
b. Addition of new in-process test and limits	1–3, 6	1–5, 8, 10	BMiV-PA125
c. Deletion of a non-significant in-process test	1–4, 6	1, 4, 7, 10	BMiV-PA126
d. Widening of the approved in-process limits	None	1–4, 6, 8, 10	BMaV-82
	1–4	1, 4, 5, 8, 10	BMiV-PA127
e. Deletion of an in-process test which may have a significant effect on the overall quality of the drug substance	None	1, 4, 6, 8, 10	BMaV-83
f. Addition or replacement of an in-process test as a result of a safety or quality issue	1	1–4, 6, 8, 10	BMaV-84
75. Change in the in-process controls testing site	1–3, 5, 6	9	BMiV-N26

Conditions

1. No change in the drug substance specification outside the approved limits. If there are changes to the specification of the drug substance, the applicant shall file for the applicable change/s. *See **changes 78**, **79**, **81** and **92**.*
2. No change in the impurity profile of the drug substance outside the approved limits.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. The test does not concern a critical attribute (for example, content, impurity, 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 approved in-process controls outside the approved limits.
7. The test procedure remains the same, or changes in the test procedure are minor.

Supporting data

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
2. Updated drug substance specification, if changed.
3. Copies or summaries of analytical procedures if new analytical procedures are used.
4. Comparative table or description, where applicable, of pre-change and post-change in-process tests/limits.
5. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. 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 marketing authorization holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for three consecutive commercial-scale batches of the pre-

change and post-change drug substance. 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, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified. 7. Justification/risk assessment showing that the attribute is non-significant. 8. Justification for the new in-process test and limits. 9. Evidence that the new company/facility is GMP-compliant. 10. Comparative tabulated format of description of the current and proposed test procedures/in-process controls with changes highlighted.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
76. Change in the approved design space, involving the following:			
a. Establishment of a new design space	None	1	BMaV-85
b. Expansion of the approved design space	None	1	BMaV-86
c. Reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space)	1	1	BMiV-PA128
Conditions 1. The reduction in design space is not necessitated by recurring problems arising during manufacture.			
Supporting data 1. Manufacturing development data to support the establishment of, or changes to, the design space.			

P. Control of the Drug Substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting Category
77. Change affecting the quality control (release and stability) testing of the drug substance, involving the following:			
a. Transfer of the quality control testing activities for a non-pharmacopoeial assay to a new company not approved in the current marketing authorization or licence, or to a different site within the same company	None	1–3	BMaV-87
	1–3	1–3	BMiV-PA129
b. Transfer of the quality control testing activities for a pharmacopoeial assay to a new company not approved in the current marketing authorization or licence	None	1–3	BMaV-88
	1	1–3	BMiV-PA130
Conditions 1. The transferred quality control test is not a potency assay or bioassay. 2. No changes are made to the test method. 3. The transfer is within a facility approved in the current marketing authorization for the performance of other tests.			
Supporting data 1. Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay. 2. Evidence that the new company/facility is GMP-compliant.			

3. Comparative tabulated format of information on the currently registered and proposed production facilities (such as name, address and responsibilities) involved in the manufacture of the drug substance.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
78. Change in the standard/monograph (that is, specifications and/or test procedures) claimed for the drug substance, involving the following:			
a. A change from a pharmacopoeial standard/monograph to an in-house standard	None	1–6	BMaV-89
b. A change from an in-house standard to a pharmacopoeial standard/monograph or from one pharmacopoeial standard/monograph to a different pharmacopoeial standard/monograph	1–4	1–3, 6, 7	BMiV-PA131
79. Change in the specifications and/or test procedures for the drug substance in order to comply with an updated pharmacopoeial standard/monograph	1, 2	1, 2, 6, 7	BMIV-N27
Conditions 1. The change is made exclusively in order to comply with a pharmacopoeial monograph. 2. There is no change in drug substance specifications outside the approved ranges. If there are other changes to the specification of drug substance, the applicant shall file for the applicable change/s. See ***changes 78, 79, 81*** and ***92***. 3. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph. 4. There are no deletions or changes to any analytical procedures, except to comply with a pharmacopoeial standard/monograph.			
Supporting data 1. Revised drug product labelling information, as applicable. 2. Updated copy of the proposed drug substance specifications. 3. Where an in-house analytical procedure is used and a pharmacopoeial standard/ monograph is claimed, results of an equivalency study between the in-house and pharmacopoeial methods. 4. Copies or summaries of validation reports if new analytical procedures are used. 5. Justification of specifications and/or test procedure with data. 6. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the drug substance with changes highlighted. 7. Copy of the official monograph containing the proposed specification and/or test procedure.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
80. Changes in the control strategy of the drug substance, involving the following:			
a. Change from end-product testing to upstream controls for some test(s) (for example, real-time release testing, process analytical technology)	None	1–3, 5	BMaV-90
b. Addition of a new critical quality attribute in the control strategy	None	1–5	BMaV-91
c. Deletion of a critical quality attribute from the control strategy	None	1, 5	BMaV-92
Conditions None			
Supporting data			

1. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
2. Updated copy of the proposed drug substance specifications.
3. Copies or summaries of analytical procedures if new analytical procedures are used.
4. Copies or summaries of validation reports if new analytical procedures are used to monitor the new CQA at release.
5. Justification and supporting data for each proposed change to the control strategy.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
81. Change in the specification/analytical procedure used to release the drug substance, involving the following:			
a. Deletion of a test	8	1, 5–7	BMaV-93
b. Addition of a test	1–3, 8	1–3, 5, 7	BMiV-PA132
c. Replacement of an analytical procedure	8	1–5, 7	BMaV-94
	5, 6, 8	1, 4, 5, 7	BMiV-PA133
d. Changes to an approved analytical procedure	8	1–5, 7	BMaV-95
	2, 4–6, 8	1, 4, 5, 7	BMiV-PA134
e. Change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure	None	1–5, 7	BMiV-PA135
	2, 6	1–3, 7	BMiV-PA136
f. Widening of an approved acceptance criterion	8	1, 5–7	BMaV-96
g. Narrowing of an approved acceptance criterion	1, 4, 7, 8	1, 7	BMiV-PA137

Conditions

1. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits).
2. There is no change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability.
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, 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 improves performance parameters of the method.
6. The change does not concern potency-testing.
7. Acceptance criteria for residual solvent are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
8. For changes in the standard/monograph (specifications and/or test procedures) claimed for the drug substance, or change of specifications of the drug substance following the updates in the compendium, see ***changes 78,*** and ***79***.

Supporting data

1. Updated drug substance specifications.
2. Copies or summaries of analytical procedures if new analytical procedures are used.
3. Validation/qualification results if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification for the proposed drug substance specification (for example, tests, acceptance criteria or analytical procedures).
6. Documented evidence that consistency of quality is maintained.
7. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the drug substance with changes highlighted.

Q. Reference Standards or Materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
82. Replacement of a primary reference standard	None	1, 2	BMaV-97
83. Change of the reference standard from pharmacopoeial or international standard to in-house (no relationship with international standard)	None	1, 2	BMaV-98
84. Change of the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	3	1, 2	BMiV-PA138
85. Qualification of a new batch of reference standard against the approved reference standard (including qualification of a new batch of a secondary reference standard against the approved primary standard)	1	1, 2	BMiV-PA139
86. Change to reference standard qualification protocol	None	3, 4	BMiV-PA140
87. Extension of the reference standard shelf-life or re-test period	2	5	BMiV-PA141
Conditions 1. Qualification of the new reference standard is in accordance with an approved protocol. 2. The extension of the shelf-life of the reference standard is in accordance with an approved protocol. 3. The reference standard is used for a physicochemical test.			
Supporting data 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, 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.			

R. Drug Substance Container Closure System

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
88. Change in the primary container closure system(s) for the storage and shipment of the drug substance	None	1, 2, 4, 5	BMaV-99
	1	1, 3, 5	BMiV-PA142
Conditions 1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (including results of transportation or compatibility studies, if appropriate).			
Supporting data			

1. Updated dossier sections describing information on the proposed container closure system (for example, description, composition, materials of construction of primary packaging components, specifications).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing) and compliance with pharmacopoeial standards, if applicable.
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 compatibility studies, and extractable/leachable studies).
4. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating parameters with commercial-scale drug substance material using several container batches (for example, three different batches) produced with the proposed changes and stored under accelerated and/ or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three container batches for stability testing may be acceptable where justified.
5. Comparative table of pre-change and post-change specifications of the container closure system.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
89. Change in the supplier for a primary container closure, involving the following:			
a. Replacement or addition of a supplier	None	1–4	BMaV-100
	1, 2	1	BMiV-PA143
b. Deletion of a supplier	None	1, 5	BMiV-PA144

Conditions

1. There is no change in the type of container closure, the materials of construction or the sterilization process for a sterile container closure component.
2. There is no change in the specifications of the container closure component outside the approved ranges. If there are changes to the specification of the container closure, the applicant shall file for the applicable change/s. *See* ***change 90***.

Supporting data

1. Comparative tabulated format of information on the currently registered and proposed supplier for a primary container closure.
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3. Information on the proposed container closure system (for example, description, materials of construction of primary packaging components, specifications).
4. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative prechange test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified.

5. Reason for withdrawal/deletion.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
90. Change in the specification/analytical procedure of the primary container closure system for the drug substance, involving the following:			
a. Deletion of a test	1, 2	1, 2, 4	BMiV-PA145
b. Addition of a test	3	1–4	BMiV-PA146
c. Replacement of an analytical procedure	6, 7	1–4	BMiV-PA147
d. Minor changes to an analytical procedure	4–7	1–4	BMiV-PA148
e. Widening of an acceptance criterion	None	1, 2, 4	BMiV-PA149
f. Narrowing of an acceptance criterion	8	1, 4	BMiV-PA150
Conditions 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 and does not result in a potential impact on the performance of the drug substance. 3. The change is not necessitated by unexpected recurring events arising during manufacture of the primary container closure system 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 or sensitivity. 8. The change is within the range of approved acceptance criteria.			
Supporting data 1. Updated copy of the proposed specification for the primary container closure system. 2. Rationale for the change. 3. Description of the analytical procedure and, if applicable, validation data. 4. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the primary container closure system with changes highlighted.			

S. Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
91. Change in the shelf-life of the drug substance or for a stored intermediate of the drug substance, involving the following:			
a. Extension	None	1–5	BMaV-101
	1–4	1, 2, 5	BMiV-PA151
b. Reduction	None	1–5	BMaV-102
	5	2–4	BMiV-PA152
Conditions 1. There are no changes to the container closure system in direct contact with the drug substance with the potential of impact on the drug substance, or to the recommended storage conditions of the drug substance. 2. Full long-term stability data are available covering the proposed shelf-life and are based on stability data generated on at least three commercial-scale batches. 3. Stability data were generated in accordance with the approved stability protocol.			

4. Significant changes were not observed in the stability data. 5. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns *(Note: Problems arising during manufacturing or stability concerns should be reported for evaluation).*
Supporting data 1. Summary of stability testing and results (for example, studies conducted, protocols used, results obtained). 2. Proposed storage conditions and shelf-life, as appropriate. 3. Updated post-approval stability protocol and stability commitment. 4. Justification for 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 stability testing of at least three commercial-scale batches unless otherwise justified). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the drug substance. Under special circumstances, interim stability-testing results and a commitment to report any failures in the ongoing long-term stability studies may be provided. In such cases, the extrapolation of shelf-life should be made in accordance with ICH Q1E guidelines.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
92. Change in the post-approval stability protocol of the drug substance, involving:			
a. Substantial change to the post-approval stability protocol or stability commitment, such as deletion of a test parameter or limit, replacement of an analytical procedure, widening of specification limits, or change in storage temperature	None	1–6	BMaV-103
	1	1, 2, 4–6	BMiV-PA153
b. Addition of a test or limit into the post-approval stability protocol or tightening of specification limits	2	1, 2, 4–6	BMiV-PA154
c. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 5	BMiV-PA155
d. Change to the post-approval stability protocol, such as change in specifications and/or test procedures following the updates in the compendium	4	4, 6, 7	BMiV-N28
Conditions 1. In the case of 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. Deletion of time point(s) is made in accordance with relevant guidelines. 4. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.			
Supporting data 1. Copies or summaries of analytical procedures if new analytical procedures are used. 2. Validation results if new analytical procedures are used. 3. Proposed storage conditions and/or shelf-life, as appropriate. 4. Updated post-approval stability protocol including justification for the changes, 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 to show greater reliability of the alternative test).			

6. Comparative tabulated format of the currently approved and proposed stability protocols or stability commitments with changes highlighted. 7. Copy of the official monograph of the updated compendium.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
93. Change in the storage conditions for the drug substance, involving the following:			
a. Addition or change to storage conditions for the drug substance (for example, widening or narrowing of a temperature criterion)	None	1–4	BMaV-104
	1, 2	1–3	BMiV-PA156
b. Addition of a cautionary statement	None	1, 3, 4	BMaV-105
	1	1, 3, 4	BMiV-PA157
c. Deletion of a cautionary statement	None	1, 3, 5	BMiV-PA158
Conditions 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.			
Supporting data 1. Proposed storage conditions and shelf-life. 2. Updated post-approval stability protocol and stability commitment. 3. Justification of the change in the storage conditions/cautionary statement. 4. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on one commercial-scale batch). 5. Results of stability testing (that is, full real time/real temperature stability data covering the proposed shelf-life generated on at least three commercial-scale batches).			

IV. CHANGES TO THE FINAL PRODUCT

T. Description and Composition of the Drug Product

Description of change	Conditions to be fulfilled	Supporting data	Reporting Category
94. Change in the description or composition of the drug product, involving the following:			
a. Addition of a dosage form (for example, lyophilised powder to liquid)	New registration application		
b. Change in the formulation (for example, addition or removal of an excipient) change in the formulation (for example, addition or removal of an excipient)	New registration application		
c. Change in the formulation (for example, qualitative or quantitative change of excipient, or new diluents for lyophilized product)	1	1–10	BMaV-106
d. Change in fill volume (same concentration, different volume)	1, 2	1, 5, 7, 9, 10	BMaV-107
e. Change in the concentration of the active ingredient (for example, 20 units/ml versus 10 units/ml)	New registration application		

f. Change of presentation (for example, from pre-filled syringe to vial) change of presentation (for example, from prefilled syringe to vial)	1	1, 5, 7–10	BMaV-108
g. Addition of a new presentation (for example, addition of a new pre-filled syringe where the approved presentation is a vial for a biotherapeutic in a liquid dosage form)	1	1, 5, 7–11	BMaV-109

Conditions

1. Change will need to comply with the finished product specifications, for example release and shelf-life specifications of the drug product remain unchanged, except for the update of product description with respect to presentation/appearance/fill volume as a consequence of the change (where applicable). If there are other changes to the specification of drug product, the applicant shall file for the applicable change/s. *See **changes 111, 112, 114** and **127**.*
2. The packaging material remains unchanged.

Supporting data

1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).
2. Characterization data demonstrating comparability of the new formulation.
3. Comparative tabulated format of the currently approved and proposed packaging presentations/primary packaging materials/diluents or product formulations with calculated changes highlighted (state changes in the percentage of the proposed excipient out of the total target dosage form weight, where applicable).
4. Discussion of the components of the drug product, as appropriate (for example, choice of excipients, compatibility of drug substance and excipients, leachates, compatibility with new container closure system).
5. Information on the batch formula, manufacturing process and process controls, controls of critical steps and intermediates, process validation results.
6. Control of excipients if new excipients are proposed (for example, specification).
7. 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 consecutive commercial-scale batches should be provided). Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
8. Information on the container closure system and leachables and extractables, if any of the components have changed (for example, description, materials of construction and summary of specification).
9. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/ hold-time of the drug product under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified.
10. Supporting clinical data or a justification for why such studies are not needed.
11. Amended relevant ACTD/ICH CTD section/s.

U. Description and Composition of the Drug Product: Change to a Diluent

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
95. Change to the diluent, involving the following: *Note: Inclusion or replacement of the diluent for the drug product, see **BMaV-106**.*			
a. Change in manufacturing process	None	1–4, 10	BMiV-PA159
b. Replacement of the source of a diluent	None	1–6, 9	BMiV-PA160
c. Addition to the source of a diluent	None	1–7, 9	BMiV-PA161
d. Change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5, 9	BMiV-PA162
e. Addition of a diluent filling line	1, 2, 4	1, 3, 5, 10	BMiV-PA163
f. Deletion of a diluent	None	8	BMiV-N29
Conditions 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 a preservative, and there is no change to its composition. 2. After reconstitution, there is no change in the drug product specification outside the approved limits. 3. The addition of the diluent filling line is in an approved filling facility.			
Supporting data 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 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 diluent. 5. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned. 6. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable). 7. Amended relevant ACTD/ICH CTD section/s. 8. Reason for withdrawal/deletion. 9. Comparative tabulated format of information on the currently registered and proposed production facilities (such as name, address and responsibilities). 10. Comparative tabulated format of the description of the current and proposed manufacturing processes or lines, including in-process controls, with changes highlighted.			

V. Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
96. Change in the approved design space, involving the following:			

a. Establishment of a new design space	None	1	BMaV-110
b. Expansion of the approved design space	None	1	BMaV-111
c. Reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space)	1	1	BMiV-PA164
Conditions 1. The reduction in design space is not necessitated by recurring problems that have arisen during manufacture.			
Supporting data 1. Pharmaceutical development data to support the establishment or changes to the design space.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
97. Change involving a drug product manufacturer/manufacturing facility, involving the following:			
a. Replacement of a manufacturing facility for the drug product (including formulation/filling and primary packaging)	None	1–7	BMaV-112
	1–5	1–3, 5–8	BMaV-113
b. Addition of a manufacturing facility for the drug product (including formulation/filling and primary packaging)	None	1–7, 11	BMaV-114
	1–5	1–3, 5–8, 11	BMaV-115
c. Conversion of a drug product manufacturing facility from single-product to multiproduct facility	None	9, 10	BMaV-116
d. Replacement of a secondary packaging facility, including secondary functional packaging (that is, assembly) facility	2, 3	1–3	BMiV-PA165
e. Addition of a secondary packaging facility, including secondary functional packaging (that is, assembly) facility	2, 3	1–3, 11	BMiV-PA166
f. Replacement of the company or party responsible for batch release	10	1, 2, 13, 14	BMiV-PA167
g. Addition of the company or party responsible for batch release	10	1, 2, 11, 13, 14	BMiV-PA168
h. Deletion of a drug product manufacturing facility/packaging site/batch releaser	6, 7	12, 13	BMiV-N30
i. Change of the name or address (for example: postal code, street name) of the manufacturer/packager of drug product or company responsible for batch release	8, 9	2, 13, 15	BMiV-N31
j. Change of product owner	8, 11	13, 16–18	BMiV-N32
Conditions 1. The proposed facility is an approved formulation/filling facility (for the same company/marketing authorization holder). 2. If there is/are changes in the composition, manufacturing process, and/or final product specification, the applicant shall file for the applicable change/s. *See* ***changes 94, 95, 98, 111, 112, 114, and 127***. 3. If there is/are changes in the container/closure system and storage conditions. the applicant shall file for the applicable change/s. *See* ***changes 121, 122, and 128***.			

4. The same validated manufacturing process at critical steps (that is, compounding and filling) is used.
5. The newly introduced product is in the same family of product(s), or in the same therapeutic classification, as the products already approved at the site, and also uses the same filling process/equipment.
6. There should remain at least one site/manufacturer, as previously authorized, performing the same function as the one(s) to be deleted.
7. The deletion should not be due to critical deficiencies in manufacturing (for example, recurrent out-of-specification events, environmental monitoring failures, etc.).
8. The manufacturing/packaging/batch release site remains unchanged.
9. Not applicable in case it involves change in ownership of the manufacturer.
10. Method transfer from the currently approved to the proposed site or test laboratory has been successfully completed.
11. This shall cover imported drug products only. For locally manufactured drug products, see conditions and requirements stipulated in **BMiV-N41**.

Supporting data

1. Comparative tabulated format of information on the currently registered and proposed production facilities (such as name, address and responsibilities) involved in the manufacture of the drug product including bulk, packaging and release.
2. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned. In the case of **BMiV-N31**, a valid FDA-issued GMP Certificate reflecting the proposed name and/or address of the manufacturer.
3. Confirmation that the description of the manufacturing process of the drug product has not changed (other than the change in facility), or submission of supporting data on the revised description of the manufacturing process if the process has changed.
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. Summary of the process validation studies and results.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug 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-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/ hold-time of the drug product under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified.
8. Rationale for considering the proposed formulation/filling facility as equivalent.

9. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If there are no revisions, the manufacturer should state that no changes were made to the change-over procedures.
10. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.
11. Amended relevant ACTD/ICH CTD section/s.
12. Reason for withdrawal/deletion.
13. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).
14. Official letter from product owner authorizing the company/manufacturer to be responsible for batch release (where applicable).
15. Official letter from product owner authorizing the manufacturer with proposed name/address to manufacture/release the drug product.
16. Declaration on the transfer of ownership between the currently approved and the proposed product owner.
17. Official letter from the proposed product owner declaring the change and authorizing the local license holder to be responsible for the product license.
18. If the proposed product owner is not the manufacturer of the drug product, an official letter by the proposed product owner authorizing the manufacturer to manufacture the drug product on its behalf, and letter of acceptance from the manufacturer that it will be held responsible for manufacturing and ensuring the efficacy, quality and safety aspect of the drug product.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
98. Change in the drug product manufacturing process, involving the following:			
a. Scale-up of the manufacturing process at the formulation/filling stage	9, 10	1–6, 10	BMaV-117
b. Addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, lyophilizer)	9, 10	1–7	BMaV-118
	5, 9, 10	2, 7, 8	BMiV-PA169
c. Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	9, 10	1, 3–5, 10	BMaV-119
	1–4, 8, 9	1, 4, 10	BMiV-PA170
d. Addition of a new step (for example, filtration)	3, 9, 10	1–6, 10	BMaV-120
e. Product-contact equipment change from dedicated to shared (for example, formulation tank, filter housing, filling line and head, lyophilizer)	6, 7, 9, 10	2, 9	BMiV-PA171

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 standard operating procedures are utilized). If there are changes to the in-process controls applied during the manufacture of drug product, the applicant shall file for the applicable change/s. *See **change 99.***
3. The change should not be a result of recurring events that have arisen during manufacture or because of stability concerns.

4. There is no change in the principle of the sterilization procedures of the drug 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).
6. The site is approved as a multi-product facility.
7. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.
8. The change does not affect the lyophilization step.
9. If there are changes to the specification of drug product, the applicant shall file for the applicable change/s. *See **changes 111, 112, 114** and **127**.*
10. If there are changes to the in-process controls applied during the manufacture of drug product, the applicant shall file for the applicable change/s. *See **change 99.***

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 drug product.
2. Information on the in-process control testing, as applicable.
3. Process validation results (for example, media fills), as appropriate.
4. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug 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-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/ hold-time of the drug product under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified.
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. The rationale for regarding the equipment as similar/comparable, as applicable.
9. Information describing the change-over procedures for the shared product-contact equipment.
10. Comparative tabulated format of the description of the current and proposed manufacturing processes, including in-process controls, with changes highlighted (where applicable).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
99. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, involving the following:			
a. Narrowing of approved in-process limits	1–3, 7	1, 4, 10	BMiV-PA172
b. Addition of new in-process test and limits	1–3, 6	1–5, 8, 10	BMiV-PA173

c. Deletion of a non-significant in-process test	1–4	1, 4, 7, 10	BMiV-PA174
d. Widening of the approved in-process limits	1	1–4, 6, 8, 10	BMaV-121
	1–3	1, 4, 5, 8, 10	BMiV-PA175
e. Deletion of an in-process test which may have a significant effect on the overall quality of the drug product	1	1, 4, 6, 8, 10	BMaV-122
f. Addition or replacement of an in-process test as a result of a safety or quality issue	1	1–4, 6, 8, 10	BMaV-123
100. Change in in-process controls testing site	1–3, 5, 6	9	BMiV-N33

Conditions

1. Drug product specifications remain unchanged. If there are changes to the specification of the drug product, the applicant shall file for the applicable change/s. *See **changes 111**, **112**, **114** and **127**.*
2. There is no change in the impurity profile of the drug product outside the approved limits.
3. The change is not necessitated by recurring events arising during 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 improves precision, accuracy, specificity and sensitivity, if applicable.
6. There is 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.

Supporting data

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
2. Updated drug product specification if changed.
3. Copies or summaries of analytical procedures if new analytical procedures are used.
4. Comparative table or description, where applicable, of current and proposed in-process tests.
5. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for one commercial scale batch of the pre-change and post-change drug 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. Batch data on the next two full-production batches should be made available on request and reported by the marketing authorization holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug 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.
7. Justification/risk assessment showing that the attribute is non-significant.
8. Justification for the new in-process test and limits.
9. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned.
10. Comparative tabulated format of description of the current and proposed test procedures/in-process controls with changes highlighted.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
101. Change in the specification/analytical procedure used to release the excipient, involving:			

a. Deletion of a test	5, 8	1, 3, 4	BMiV-PA176
b. Addition of a test	4	1–3, 4	BMiV-PA177
c. Replacement of an analytical procedure	1–3	1, 2, 4	BMiV-PA178
d. Minor changes to an approved analytical procedure	None	1, 2, 4	BMiV-PA179
e. Change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1, 2, 4	BMiV-PA180
f. Widening of an approved acceptance criterion	None	1, 3, 4	BMiV-PA181
g. Narrowing of an approved acceptance criterion	3, 4, 6, 7	1, 4	BMiV-PA182

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or improves precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect the new 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 a 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, 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 drug product).
4. Comparative tabulated format of the current and revised specifications and/or test procedures of the excipient with changes highlighted.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
102. Change in the standard/monograph (that is, specifications and/or test procedures) claimed for the excipient	None	1–6	BMiV-N34
	1–5	1–6	BMiV-N35

Conditions

1. The change is from a House standard to a pharmacopoeial standard/monograph.
2. The change is made exclusively to comply with a pharmacopoeial standard/monograph.
3. There is no change to the specifications for the functional properties of the excipient outside the approved ranges, and no change that results in a potential impact on the performance of the drug product.
4. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph.
5. There is no deletion or change to any analytical procedures, except to comply with a pharmacopoeial standard/monograph.

Supporting data

1. Updated excipient specifications.
2. Where a House analytical procedure is used and a pharmacopoeial/compendial standard/monograph is claimed, results of an equivalency study between the House and compendial methods.
3. Justification of the proposed excipient specifications (for example, demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).
4. A declaration that consistency of quality and of the production process of the excipient is maintained.
5. Comparative tabulated format of the current and revised specifications and/or test procedures of the excipient with changes highlighted.
6. Copy of the official monograph containing the proposed specification and/or test procedure.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
103. 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	1	2–7, 11	BMaV-124
104. Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source	1	1, 3, 5, 6, 11	BMiV-PA183
105. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source (for example, different animal source, different country of origin)	1, 5, 6	2–7, 11	BMiV-PA184
106. Change in manufacture of a biological excipient	None	2–7	BMaV-125
	2	2–7	BMiV-PA185
	1, 2	2–7	BMiV-PA186
107. Change in supplier for a plasma-derived excipient (for example, human serum albumin)	None	3–8	BMaV-126
	1, 3, 4	5, 6, 9	BMiV-PA187
108. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient)	1	2, 3, 5–7	BMiV-PA188
	1, 5, 6	3	BMiV-PA189
109. Change in excipient testing site	1	10	BMiV-N36

Conditions

1. There is no change to the specification of the excipient or drug product outside the approved limits. If there are other changes to the specification of the excipient or drug product, the applicant shall file for the applicable change/s. *See* ***changes 101, 102, 111, 112 and 114***.
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.
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 commercial-scale batches of the proposed excipient.
6. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/ hold-time of the drug product under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified
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. A 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.
11. Comparative tabulated format of the information on the current and proposed sources of the excipient (for example, animal species, country of origin).

W. Control of the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
110. Change affecting the QC testing of the drug product (release and stability), involving:			
a. Transfer of the quality control testing activities for a non-pharmacopoeial assay (in-house) to a new company not approved in the current marketing authorization or licence or to a different site within the same company	1	1–3	BMiV-PA190
b. Transfer of the quality control testing activities for a pharmacopoeial assay to a new company not approved in the current marketing authorization or licence	1	1–3	BMiV-PA191
c. Addition or replacement of the company or party responsible for quality control/stability testing (different from the batch release site)	1	1–3	BMiV-PA192

Conditions 1. The manufacturer of the drug product remains unchanged. If there are changes to the manufacturer of the drug product, the applicant shall file for the applicable change/s. *See **change 97**.*
Supporting data 1. Information demonstrating technology transfer qualification for the non-pharmacopoeial assays or verification for the pharmacopoeial assays. 2. A valid FDA-issued Good Manufacturing Practice (GMP) Certificate substantiating that the proposed site is appropriately authorized for the product and/or activity concerned.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
111. Change in the standard/monograph (that is, specifications and/or test procedures) claimed for the drug product, involving the following:			
a. A change from a pharmacopoeial standard/ monograph to an in-house standard	None	1–6	BMaV-127
b. A change from an in-house standard to a pharmacopoeial standard/monograph or from one pharmacopoeial standard/ monograph to a different pharmacopoeial standard/monograph	1–4	1–3, 6, 7	BMiV-PA193
112. Change in the specifications and/or test procedures for the drug product to comply with an updated pharmacopoeial standard/monograph	1, 2	1–3, 6, 7	BMiV-N37
Conditions 1. The change is made exclusively to comply with a pharmacopoeial monograph. 2. There is no change in drug product specifications outside the approved ranges. If there are other changes to the specification of drug product, the applicant shall file for the applicable change/s. *See **changes 111**, **112**, **114** and **127**.* 3. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph. 4. There is no deletion or change to any analytical procedures, except to comply with a pharmacopoeial standard/monograph. If there are changes to the specification of drug substance, the applicant shall apply for the applicable change/s. *See **changes 78, 79, 81** and **92**.*			
Supporting data 1. Revised drug product labelling information, as applicable. 2. An updated copy of the proposed drug product specifications. 3. Where an in-house analytical procedure is used and a pharmacopoeial standard/ monograph is claimed, results of an equivalency study between the in-house and pharmacopoeial methods. 4. Copies or summaries of validation reports if new analytical procedures are used. 5. Justification of specifications with data. 6. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the drug product with changes highlighted. 7. Copy of the official monograph containing the proposed specification and/or test procedure.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
113. Changes in the control strategy of the drug product, involving the following:			

a. Change from end-product testing to upstream controls for some test(s) (for example, real-time release testing, process analytical technology)	None	1–3, 5	BMaV-128
b. Addition of a new critical quality attribute to the control strategy	None	1–5	BMaV-129
c. Deletion of a critical quality attribute from the control strategy	None	1, 5	BMaV-130
Conditions None			
Supporting data 1. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed product. 2. An updated copy of the proposed drug product specifications. 3. Copies or summaries of analytical procedures if new analytical procedures are used. 4. Copies or summaries of validation reports if new analytical procedures are used to monitor the new critical quality attribute at release. 5. Justification and supporting data for each proposed change to the control strategy.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
114. Change in the specification/analytical procedure used to release the drug product, involving the following:			
a. Deletion of a test analytical procedure and/or an acceptance criterion	8	1, 6–8	BMaV-131
b. Addition of a test	1, 2, 7, 8	1–3, 5, 8	BMiV-PA194
c. Replacement of an analytical procedure	8	1–5, 8	BMaV-132
	4, 5, 8	1, 4, 5, 8	BMiV-PA195
d. Changes to an approved analytical procedure	8	1–5, 8	BMaV-133
	1, 3–5, 8	2, 4, 5, 8	BMiV-PA196
e. Change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1–5, 8	BMiV-PA197
	1, 5	1–3, 8	BMiV-PA198
f. Widening of an approved acceptance criterion	8	1, 5, 7, 8	BMaV-134
g. Narrowing of an approved acceptance criterion	1, 3, 6, 7, 8	1, 8	BMiV-PA199
Conditions 1. There is no change to the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability. 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. 4. The modified analytical procedure maintains or improves the performance parameters of the method. 5. The change does not concern potency-testing. 6. 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). 7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, or impurity content outside the approved limits). 8. Applicable to non-compendial specifications and/or test procedures. For changes in the standard/monograph (specifications and/or test procedures) claimed for the drug product, or change of specifications of the drug product following the updates in the compendium, see ***changes 111***, and ***112*** respectively.			
Supporting data			

1. An updated copy of the proposed drug product specification.
2. Copies or summaries of analytical procedures if new analytical procedures are used.
3. Validation/qualification results if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification for the change to the analytical procedure (for example, demonstration of the suitability of the analytical procedure in monitoring the drug product, including the degradation products) or for the change to the specification (for example, demonstration of the suitability of the revised acceptance criterion to control the drug product).
6. Justification for the deletion of the test (for example, demonstration of the suitability of the revised specification in controlling the final product).
7. Documented evidence that consistency of quality and of the production process is maintained.
8. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the drug product with changes highlighted.

X. Reference standards

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
115. Replacement of a primary reference standard	None	1, 2	BMaV-135
116. Change of the reference standards from a pharmacopoeial or international standard to in-house (no relationship with international standard)	None	1, 2	BMaV-136
117. Change of the reference standard from in-house (no relationship with international standard) to a pharmacopoeial or international standard	3	1, 2	BMiV-PA200
118. Qualification of a new batch of reference standard against the approved reference standard (including qualification of a new batch of a secondary reference standard against the approved primary standard)	1	2	BMiV-PA201
119. Change to the reference standard qualification protocol	None	3, 4	BMiV-PA202
120. Extension of the reference standard shelf-life or re-test period	2	5	BMiV-PA203

Conditions

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.
3. The reference standard is used for a physicochemical test.

Supporting data

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, 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.

Y. Drug product container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
121. Modification of a container closure system *Note:* ▪ *The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation (see **BMaV-109**).*			
a. Change in primary container closure system (for example, new coating, adhesive, stopper or type of glass)	None	1–8	BMaV-137
	4	1, 3, 7, 8	BMiV-PA204
	1–3	1, 3, 8	BMiV-PA205
b. Change in any part of the packaging material not directly in contact with the finished product formulation such as change in the bossing (from direct printing to use of sticker) on the labeling materials, inclusion/deletion of an aluminum pouch, and inclusion/deletion of blister pack enclosing the primary packaging of a drug product	5	1, 3, 6, 8	BMiV-PA206
122. 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, 8	BMaV-138
123. Deletion of a container closure system	None	1	BMiV-N38

Conditions

1. There is no change in the type of container closure or materials of construction.
2. There is 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).
4. The modified part is not in contact with the drug product.
5. For the change in the bossing on the labeling materials, the layout and information on the labels remain unchanged. If there are changes to labeling material, the applicant shall file for the applicable change/s. *See **change 137.***

Supporting data

1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).
2. For sterilized products, process validation results, unless otherwise justified.
3. Update dossier containing information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary packaging components).
4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and biological reactivity tests.
5. Summary of release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug 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-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced

(unless otherwise justified) with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug product under its normal storage conditions and to report any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified.

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 interaction studies demonstrating preservation of protein integrity and maintenance of sterility for sterile products; maintenance of sterility in multidose containers; user testing).
8. Comparative tabulated format of descriptions and specifications of the current and proposed packaging materials, including illustrations.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
124. Change in the supplier for a primary container closure component, involving:			
a. Replacement or addition of a supplier	1, 2	1, 2	BMiV-PA207
b. Deletion of a supplier	None	3	BMiV-N39

Conditions

1. There is 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.
2. There is no change in the specification of the container closure component outside the approved acceptance criteria. If there are changes to the specification of the container closure, the applicant shall file for the applicable change/s. *See **change 125***.

Supporting data

1. Letter from the marketing authorization holder certifying that there are no changes to the container closure system.
2. Certificate of analysis, or equivalent, for the container provided by the new supplier and comparison with the certificate of analysis, or equivalent, for the approved container.
3. Reason for withdrawal/deletion.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
125. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving the following:			
a. Deletion of a test	1, 2	1, 2, 4	BMiV-PA208
b. Addition of a test	3	1, 2, 4	BMiV-PA209
c. Replacement of an analytical procedure	6, 7	1–4	BMiV-PA210
d. Minor changes to an analytical procedure	4–7	1–4	BMiV-PA211
e. Widening of an acceptance criterion	None	1, 2, 4	BMiV-PA212
f. Narrowing of an acceptance criterion	8	1, 4	BMiV-PA213

Conditions

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 and does not have a potential impact on the performance of the drug product. 3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. 4. There is no change to 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 improves precision, accuracy, specificity and sensitivity. 8. The change is within the range of approved acceptance criteria.
Supporting data 1. An 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. 4. Comparative tabulated format of the currently approved and proposed specifications and/or test procedures of the container closure with changes highlighted.

Z. Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
126. Change in the shelf-life of the drug product, involving the following:			
a. Extension (includes extension of shelf-life of the drug product as packaged for sale, and hold-time after opening and after dilution or reconstitution)	None	1–5	BMaV-139
b. Reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1–5	BMiV-PA214
Conditions None			
Supporting data 1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable). 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 commercial-scale batches unless otherwise justified.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
127. Change in the post-approval stability protocol of the drug product, involving:			
a. Substantial change to the post-approval stability protocol or stability commitment, such as deletion of a test parameter or limit,	None	1–6	BMaV-140

replacement/deletion of an analytical procedure, or change in storage temperature			
b. Addition of test(s) into the post-approval stability protocol or tightening of specification limits	1	1, 2, 4–6	BMiV-PA215
c. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 6	BMiV-PA216
d. Replacement of sterility testing by the container/closure system integrity testing	None	1, 2, 4–6	BMaV-141
	3	4–6	BMiV-PA217
e. Change to the post-approval stability protocol, such as change in specifications and/or test procedures following the updates in the compendium	4	4, 6−8	BMiV-N40
Conditions 1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities. 2. Deletion of time point(s) is done according to relevant guidelines. 3. The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application related to the drug product. 4. Applicable to compendial specifications and/or test procedures only. Change is made exclusively to comply with an update of the relevant monograph of the same compendium.			
Supporting data 1. Copies or summaries of analytical procedures if new analytical procedures are used. 2. Validation results if new analytical procedures are used. 3. Proposed storage conditions and or shelf-life, as appropriate. 4. Updated post-approval stability protocol, including justification for the change, and stability commitment. 5. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent if new analytical procedures are used. 6. Comparative tabulated format of the currently approved and proposed stability protocols or stability commitments with changes highlighted. 7. For change in test procedure, appropriate verification data of the proposed test procedure. 8. Copy of the official monograph of the updated compendium.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
128. Change in the labelled storage conditions for the drug product or the diluted or reconstituted biotherapeutic products, involving the following:			
a. Addition or change of storage condition(s) for the drug product, diluted or reconstituted drug product (for example, widening or narrowing of a temperature criterion, addition of or change to controlled temperature chain conditions)	None	1–4, 6	BMiV-PA218
b. Addition of a cautionary statement (for example, “Do not freeze”)	None	1, 2, 4, 5	BMiV-PA219
c. Deletion of a cautionary statement (for example, “Do not freeze”)	None	1, 2, 4, 6	BMiV-PA220
Conditions None			
Supporting data			

1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where 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 commercial-scale batch unless otherwise justified.
6. Results of stability testing under appropriate conditions covering the proposed shelf-life, generated on at least three commercial-scale batches unless otherwise justified.

SECTION 3: PHILIPPINE-SPECIFIC POST-APPROVAL CHANGES

Administrative Changes

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
129. Change in brand name, involving:			
a. Change or inclusion of drug proprietary product name/product brand name	1–5	1–5	BMiV-PA221
b. Deletion of drug proprietary product name/product brand name	1	2, 3	BMiV-PA222
Conditions 1. There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the product name. Otherwise, the applicant shall apply for the corresponding variation/s together with this variation under a single DTN. 2. No confusion with another drug product either when spoken or written. 3. The proposed name does not (i) suggest greater safety or efficacy than supported by clinical data (ii) imply a therapeutic use (iii) imply superiority over another similar product and (iv) imply the presence of substance(s) not present in the product. 4. Names that are identical to those already registered with the FDA in the same product classification shall not be allowed. 5. Names that are offensive, obscene, scandalous or otherwise contrary to public morals and policy shall not be allowed.			
Supporting data 1. Official letter from product owner or marketing authorization holder authorizing the change of product name and committing to inform users of the relevant changes (where applicable). 2. A declaration from the marketing authorization holder that there is no other changes to the product/label except for the drug product name change. 3. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change. 4. Updated Certificate of Pharmaceutical Product (CPP) (where applicable). 5. Notarized affidavit of undertaking (a) to change the brand name so submitted should the proper authority decides with finality that he/she/it has no right to appropriate and utilize the brand name; and (b) to acknowledge and to agree to indemnify and/or hold FDA free and harmless against any and all third-party claims arising from the acceptance of such brand name of the product for registration with FDA. (As per A.O. No. 2005-0016). Alternatively, trademark certificate issued by Intellectual Property Office of the Philippines (IPOPHL) may also be provided (where applicable).			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
130. Change in Marketing Authorization Holder (MAH):			
a. Change of Marketing Authorization Holder (MAH)	1–3	1–4	BMiV-N41
b. Change in name and/or address (for example: postal code, street name) of the Marketing Authorization Holder (MAH)	1–5	1, 4, 5	BMiV-N42
Conditions 1. The source of the pharmaceutical product (foreign manufacturer/exporter, local manufacturer) remains unchanged. 2. Administrative change referring only to change of local trader/importer/distributor.			

3. The MAH of a certain drug product shall be assigned as follows:
    a. For locally manufactured drug products:
        i. PCPR or Regular CPR – The drug trader is primarily considered as the MAH. If no drug trader, then the drug manufacturer shall be the MAH.
        ii. CLIDP – The corresponding drug distributor shall be considered as the MAH.
    b. For imported drug products:
        i. PCPR or Regular CPR – The drug importer shall be considered as the MAH.
        ii. CLIDP – The corresponding drug distributor shall be considered as the MAH.
4. The name change refers to the renaming of a company or organization.
5. The change does not include transfer of marketing authorization to another company.

Supporting data

1. Copy of valid License to Operate.
2. Termination of Contract/Deed of Assignment.
3. Agreement between the manufacturer and the proposed trader/importer/distributor, or agreement between the trader/exporter/importer and the proposed distributor, whichever is applicable.
4. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change.
5. Letter by the product owner authorizing the proposed name of MAH to hold the product license (where applicable).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
131. Change/inclusion/deletion of drug distributor	1–3	1–4	BMiV-N43

Conditions

1. The MAH remains unchanged. Otherwise, BMiV-N41 shall be applied together with this variation.
2. For the change in the distributor of products with a CLIDP, please refer to BMiV-N41.
3. This change is applicable for products with a valid CPR or those that have been converted to a Principal Certificate of Product Registration (PCPR) following A.O. 2005-0031 and Bureau Circular No. 11 s. 2006.

Supporting data

1. Termination of Contract/Deed of Assignment.
2. Letter of Authorization (LOA) or Agreement between MAH and proposed distributor (where applicable).
3. Valid LTO of proposed distributor.
4. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
132. Administrative changes affecting entities other than the MAH	1, 2	1–5	BMiV-N44

Conditions

1. The manufacturer and the MAH of the drug product remain unchanged.
2. The quality attributes – including but not limited to the formulation, manufacture and specifications/controls – of the drug product, drug substance and/or excipients remain unchanged.

Supporting data

1. Valid LTO reflecting the proposed change/s (where applicable).

2. Manufacturing License or any official document from relevant authority of the proposed companies/establishments. 3. Termination of agreement with the previous supplier (where applicable). 4. Agreement between the MAH/product owner and the proposed establishment. 5. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
133. Subsequent changes to the CLIDP following the approved variation/s of the PCPR	1–3	1–4	BMiV-N45
Conditions 1. Same variation fees as the PCPR shall be applied. 2. The applicant may request for reconstruction of CPR reflecting the changes approved/acknowledged in the PCPR, with a corresponding fee. 3. This change does not include variations equivalent to initial registration as per Section V.C.1.c of FDA Circular No. 2023-_____ unless updated accordingly.			
Supporting data 1. Certificate of approval/acknowledgment of notification of the variation/s applied for the PCPR. 2. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change/s (where applicable).			

Quality Changes

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
134. Change in the European Pharmacopoeial Certificate of Suitability (CEP), involving:			
a. Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance and/or excipient and/or raw material	None	1–6	BMiV-N46
b. Renewal of European Pharmacopoeial Certificate of Suitability (CEP)	1	1	BMiV-N47
Conditions 1. Only applicable if the renewal of CEP does not involve any variation.			
Supporting data 1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance/excipient/raw material, latest version, with all annexes issued by EDQM. 2. Specifications of drug substance/excipient/raw material (where applicable). 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional tests/limits listed on the CEP (where applicable). 4. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) from the raw material/excipient manufacturer demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP (where applicable). 5. Additional data to address any relevant parameter(s) not addressed in the CEP such as stability data (S7), if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc.), if applicable. 6. If this change is due to drug substance specification, a declaration from the applicant that the relevant stability studies of the drug product in accordance with ICH Q5C (Stability Testing of			

Biotechnological/Biological Products) have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).

*If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house, etc.), data covering S4.1to S4.5 from the drug product manufacturer should be submitted.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
135. Change in the overage that is used for the drug substance, involving:			
a. Introduction or increase in the overage	New registration application		
b. Reduction or removal of overage	1	1–4	BMiV-PA223
Conditions 1. Changes of approved manufacturing overages of drug substance only. 2. Release and shelf-life specifications of drug product remain unchanged. If there are changes in the specification of drug product, the applicant shall apply for ***changes 46, 58, 111, 112, 114, and 127*** (whichever is applicable) together with this variation under a single DTN.			
Supporting data 1. Justification for the change with supporting scientific evidences. 2. Comparative tabulated format of currently approved and proposed batch manufacturing formulae. 3. Certificate of analysis and/or batch analysis data (in a comparative tabulated format) for three batches of the finished product. 4. Stability data as per ICH Q5C (Stability Testing of Biotechnological/Biological Products), and report if any results fall outside shelf-life specifications (with proposed action).			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
136. Change of pack size for a drug product:			
a. Change or addition of outer carton pack sizes for a drug product	1–3	1–3	BMiV-N48
b. Deletion of pack size for a product	3	1, 2	BMiV-N49
Conditions 1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a drug product. For the change of the pack size and content in the primary packaging of a drug product, refer to ***changes 29***, ***52***, ***94***, and ***121***. 3. The remaining pack sizes are adequate to accommodate the dosing regimen as per the approved product labeling.			
Supporting data 1. Currently approved and revised drafts (clean and annotated version) of the package insert and labeling incorporating the proposed change (where applicable). 2. Reason for the change/addition/deletion of pack size. 3. Notice of Award, or any equivalent document issued by the Department of Health, Local Government Unit or any related government agency (where applicable).			

Safety and Efficacy Changes

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
137. Change in the labelling of the drug product, involving the following:			
a. Change and/or addition of indication/dosing regimen/patient population and/or inclusion of clinical information extending the usage of the product	1	1–9	BMaV-142
b. Change of content of product labeling	1–2	1–5	BMaV-143
c. Change of product labeling (in accordance with country specific labeling requirements), including: i. Addition/strengthening of warnings, precautions, contraindications and/or adverse events/effects to the approved product labeling. ii. Tightening of product's target population. iii. Deletion of indication.	3	1–3, 5	BMiV-PA224
d. Change of product labelling, including: i. Change/s in labeling design. ii. Change/s in layout (positioning of graphic designs). iii. Printing of product information inside the carton without change in text. iv. Addition or replacement of Global Product Identification Number (GPIN). i. Change in dimension of box, sticker label and/or package insert without change in pack size. ii. Change of text limited to administrative information without altering the content and meaning of the labeling, i.e. unapproved indication, warnings, precautions, contraindications, and/or adverse events/effects.	3–4	1–3	BMiV-N50
Conditions 1. As a subsequent change due to revision of Summary of Product Characteristics (SmPC) or equivalent document (USPI). 2. The change is not a minor variation and not within the scope of **BMaV-142**. 3. The change is not considered major and does not contain promotional information. 4. The change does not alter the content and meaning on the product information.			
Supporting data 1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Summary of changes (in a comparative tabulated format) of the current and proposed product information. 4. Approved PI/SmPC/PIL from an approved reference regulatory agency or the country of origin containing the proposed changes. 5. Technical justification for the proposed change with supporting scientific evidences (where applicable). 6. Clinical documents as per ACTD Part IV/ICH CTD Module 5 (where applicable).			

7. For registered Similar Biotherapeutic Products, documents to support the extrapolation of clinical data for the additional indications relative to the Reference Biotherapeutic Product (where applicable). 8. Risk Management Plan relative to the proposed change. 9. Periodic Safety Update Report (PSUR) or Periodic Benefit Risk Evaluation Report (PBRER) relative to the proposed change.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
138. Change in the route of administration, involving the following:			
a. Addition of a new route of administration	1–3	1–6	BMaV-144
	None	New registration application	
b. Deletion of a route of administration	4	1, 2, 7	BMiV-PA225
Conditions 1. A newly proposed route of administration in addition to the existing approved route. 2. Product formulation remains unchanged as compared to the currently approved formulation. 3. Drug product is administered via parenteral administration. 4. An alternative route is registered.			
Supporting data 1. Currently approved product labeling. 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Justification for the proposed change with supporting scientific evidences. 4. Approved PI/SmPC/PIL from a reference regulatory agency or the country of origin containing the proposed changes (where applicable). 5. Clinical documents as per ACTD Part IV or ICH CTD Module 5. 6. Reason for deletion.			

Other Changes

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
139. Other changes not covered by the country-specific regulations	1–2	1–3	B-OTH
Conditions 1. This only covers variations not specified in the Philippine Variation Guidelines for Biological Products. 2. Proposed variation/s should affect the drug substance, excipients, raw materials and/or drug product, with respect to its quality (e.g. formulation, manufacture, specifications and container closure), safety and efficacy (e.g. product information).			
Supporting data 1. Reference variation classification/code with justification on why the change is considered to be unclassified in the variation guidelines. 2. Summary of changes (in a comparative tabulated format). 3. Supporting documents for the change, including amendment of the relevant sections of the dossier following the requirements for registration based on ACTD/ICH CTD.			

7 FEES FOR POST-APPROVAL CHANGE APPLICATION

Variation	Fee (Php) (excluding LRF[1])
Major Variation	
BMaV-1	500
BMaV-2	500
BMaV-3	500
BMaV-4	500
BMaV-5	500
BMaV-6	500
BMaV-7	500
BMaV-8	500
BMaV-9	500
BMaV-10	500
BMaV-11	500
BMaV-12	500
BMaV-13	500
BMaV-14	500
BMaV-15	500
BMaV-16	500
BMaV-17	500
BMaV-18	500
BMaV-19	500
BMaV-20	500
BMaV-21	500
BMaV-22	500
BMaV-23	500
BMaV-24	500
BMaV-25	500
BMaV-26	500
BMaV-27	500
BMaV-28	500
BMaV-29	500
BMaV-30	500
BMaV-31	500
BMaV-32	500
BMaV-33	500
BMaV-34	Initial fee[2]
BMaV-35	Initial fee[2]
BMaV-36	Initial fee[2]
BMaV-37	Initial fee[2]
BMaV-38	500
BMaV-39	500
BMaV-40	Initial fee[2]
BMaV-41	Initial fee[2]
BMaV-42	Initial fee[2]
BMaV-43	Initial fee[2]
BMaV-44	500
BMaV-45	500
BMaV-46	500
BMaV-47	500
BMaV-48	500
BMaV-49	500
BMaV-50	500
BMaV-51	500
BMaV-52	500
BMaV-53	500
BMaV-54	500
BMaV-55	500
BMaV-56	500
BMaV-57	500
BMaV-58	Initial fee[2]
BMaV-59	Initial fee[2]
BMaV-60	1,000
BMaV-61	500
BMaV-62	500
BMaV-63	500
BMaV-64	500
BMaV-65	500
BMaV-66	500
BMaV-67	500
BMaV-68	500
BMaV-69	500
BMaV-70	500
BMaV-71	500
BMaV-72	500
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BMaV-82	500
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BMaV-87	500
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BMaV-102	500
BMaV-103	500
BMaV-104	500
BMaV-105	500
BMaV-106	500
BMaV-107	500
BMaV-108	500
BMaV-109	500

BMaV-110	500
BMaV-111	500
BMaV-112	Initial fee[2]
BMaV-113	Initial fee[2]
BMaV-114	Initial fee[2]
BMaV-115	Initial fee[2]
BMaV-116	500
BMaV-117	500
BMaV-118	Initial fee[2]
BMaV-119	500
BMaV-120	500
BMaV-121	500
BMaV-122	500
BMaV-123	500
BMaV-124	500
BMaV-125	500
BMaV-126	500
BMaV-127	500
BMaV-128	500
BMaV-129	500
BMaV-130	500
BMaV-131	500
BMaV-132	500
BMaV-133	500
BMaV-134	500
BMaV-135	500
BMaV-136	500
BMaV-137	Initial fee[2]
BMaV-138	Initial fee[2]
BMaV-139	500
BMaV-140	500
BMaV-141	500
BMaV-142	Initial fee[23]
BMaV-143	500
BMaV-144	Initial fee[23]
Minor Variation – Prior Approval	
BMiV-PA1	500
BMiV-PA2	500
BMiV-PA3	500
BMiV-PA4	500
BMiV-PA5	500
BMiV-PA6	500
BMiV-PA7	500
BMiV-PA8	500
BMiV-PA9	500
BMiV-PA10	500
BMiV-PA11	500
BMiV-PA12	500
BMiV-PA13	500
BMiV-PA14	500
BMiV-PA15	Initial fee[2]
BMiV-PA16	Initial fee[2]
BMiV-PA17	Initial fee[2]
BMiV-PA18	500
BMiV-PA19	500
BMiV-PA20	500
BMiV-PA21	500
BMiV-PA22	500
BMiV-PA23	500
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BMiV-PA26	500
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BMiV-PA51	500
BMiV-PA52	500
BMiV-PA53	500
BMiV-PA54	500
BMiV-PA55	500
BMiV-PA56	Initial fee[2]
BMiV-PA57	500
BMiV-PA58	Initial fee[2]
BMiV-PA59	500
BMiV-PA60	500
BMiV-PA61	500
BMiV-PA62	500
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BMiV-PA86	500

BMiV-PA87	500
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BMiV-PA91	500
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BMiV-PA147	500

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BMiV-PA160	500
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BMiV-PA162	500
BMiV-PA163	500
BMiV-PA164	500
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BMiV-PA166	Initial fee[2]
BMiV-PA167	500
BMiV-PA168	Initial fee[2]
BMiV-PA169	500
BMiV-PA170	500
BMiV-PA171	500
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BMiV-PA203	500
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BMiV-PA205	500
BMiV-PA206	500
BMiV-PA207	500
BMiV-PA208	500

BMiV-PA209	500
BMiV-PA210	500
BMiV-PA211	500
BMiV-PA212	500
BMiV-PA213	500
BMiV-PA214	1,000
BMiV-PA215	500
BMiV-PA216	500
BMiV-PA217	500
BMiV-PA218	500
BMiV-PA219	500
BMiV-PA220	500
BMiV-PA221	2,500 + 500 (for each brand name)
BMiV-PA222	500
BMiV-PA223	500
BMiV-PA224	500
BMiV-PA225	500
Minor Variation – Notification	
BMiV-N1	500
BMiV-N2	500
BMiV-N3	500
BMiV-N4	500
BMiV-N5	500
BMiV-N6	500
BMiV-N7	500
BMiV-N8	500
BMiV-N9	500
BMiV-N10	500
BMiV-N11	500
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BMiV-N16	500
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BMiV-N20	500
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BMiV-N26	500
BMiV-N27	500
BMiV-N28	500
BMiV-N29	500
BMiV-N30	500
BMiV-N31	500
BMiV-N32	500
BMiV-N33	500
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BMiV-N35	500
BMiV-N36	500
BMiV-N37	500
BMiV-N38	500
BMiV-N39	500
BMiV-N40	500
BMiV-N41	500
BMiV-N42	500
BMiV-N43	500
BMiV-N44	500
BMiV-N45	PCPR variation fee[4]
BMiV-N46	500
BMiV-N47	500
BMiV-N48	500
BMiV-N49	500
BMiV-N50	500
Others	
B-OTH	500[5]

[1]Legal Research Fee (LRF) shall be added to the fees for each proposed variation based on FDA Circular Nos. 2011-003 and 2011-003-A
[2]Amount is according to the **previous initial registration fee:**
- Branded Drug Product: Php 15,000.00
- Unbranded Drug Product: Php 10,000.00
- Drug Product under Monitored Release (MR): Php 20,000.00 or Php 33,333.00

[3]For the inclusion or change in the indication (e.g. MaV-1), additional payment shall be made if review by Clinical Research Section (CRS) is necessary.
[4]Amount paid for the variation of PCPR + Php500.00 for reconstruction (upon request).
[5] This shall be on a per change basis.