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	FORM Title: Guidance for Checklist and Assessment of Post Marketing Authorization of Variation for Vaccines.					
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General Information

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
1. Changes in the name of the antigen				
a)	Changes in the name of the antigen Note: This change generally applies only to influenza vaccines (see section 5.10.2)	None	1, 2	Moderate

Supporting data

1. Revised product labelling information (all labelling items).
2. Information on the proposed nomenclature of the antigen and evidence that the proposed name for the antigen is recognized (for example, proof of acceptance by WHO).

Manufacture

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
2. Changes to an antigen manufacturing facility				
a)	Replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen	None	1 – 4, 6 – 8	Major
		1 – 4	2, 4-8	Moderate
b)	Deletion of a manufacturing facility or manufacturer of an antigen intermediate, or antigen bulk	5, 6	None	Minor

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 either moderate or 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).

Supporting Data:

1. Evidence that the facility is GMP compliant.
2. Name, address and responsibility of the proposed facility.
3. Process validation study reports. Table continued Annex 4 211 Table continued Supporting data.
4. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
5. Justification for the classification of any manufacturing process and/or control changes as moderate or minor.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
7. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability program 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

8. Updated post-approval stability protocol.

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
3. Change to the antigen fermentation, viral propagation or cellular propagation process:				
a)	A critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, incorporation of disposable bioreactor technology)	None	1 – 7, 9, 11	Major
b)	a change with moderate potential to have an impact on the quality of the antigen or final product (for example, extension of the in vitro cell age beyond validated parameters)	2, 4	1 – 6, 8, 10	Moderate
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 or production scale; or duplication of a fermentation train)	1 – 6, 9 -11	1 – 4	Minor
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)	None	1, 2, 5–7, 9, 11, 12	Major

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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	1, 2, 5–7, 10, 11	Moderate
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	1, 2	Minor
5. Change in scale of the manufacturing process				
a)	at the fermentation, viral propagation or cellular propagation stage	3 – 6, 11 – 13	2, 3, 5–7, 9, 11	Moderate
b)	at the purification stage	1, 3, 5, 7	2, 5–7, 9, 11	Moderate
6.	**Change in supplier of raw materials of biological origin (for example, fetal calf serum, human serum albumin, trypsin)**	None	4, 8, 12, 13	Moderate
		8	4-7	Minor
7.	Change in source of raw materials of biological origin	None	4, 7, 12, 13	Moderate
		8	4-7	Minor
8.	**Introduction of reprocessing steps**	14	8, 10, 11, 14	Moderate

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.
4. No change in the impurity profile of the antigen outside the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.

7. The change in scale is linear with respect to the proportionality of production parameters and materials.
8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).
9. The new fermentation train is identical to the approved fermentation train(s).
10. No change in the approved in vitro cell age.
11. The change is not expected to have an impact on the quality, safety or efficacy of the final product.
12. No change in the proportionality of the raw materials (that is, the change in scale is linear).
13. The change in scale involves the use of the same bioreactor (that is, it does not involve the use of a larger bioreactor).
14. The need for reprocessing is not due to recurrent deviations from the validated process and the root cause triggering reprocessing is identified.

Supporting data:

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 sub-cultivations, information on the characterization and testing of the post-production cell bank for recombinant product, or of the antigen for nonrecombinant 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).
5. Process validation study reports.
6. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration

the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.

7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and should be reported by the MA holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale antigen batches produced with the proposed changes under real-time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability program 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least one (1) commercial-scale antigen batch produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability program 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the final product manufactured using the post change antigen into the stability program.
12. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) (5).
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.

Sl. No.	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	Moderate
b)	generation of a new working cell bank (WCB)	2 – 4	1, 2	Moderate
		None		Minor
c)	change in cell bank storage site	7	10	Minor
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	Major
b)	generation of a new working seed lot (WSL)	2, 3	5 – 9, 11	Moderate
		2-4	5-6	Minor
c)	generation of a new WSL by extending the passage level of an existing WSL beyond an approved level	None	5 – 7, 11	Moderate
d)	change in seed lot storage site	7	10	Minor
11.	**Change in cell bank/seed lot testing/storage site**	5, 7	10	Minor

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12.	Change in cell bank/seed lot qualification protocol	None	3, 4	Moderate
		6	4	Minor

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 by the NRA.
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 agreed by the NRA.
8. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
9. Updated post-approval stability protocol.
10. Evidence that the new company/facility is GMP compliant.
11. Revised information on the quality and controls of critical starting materials (for example, specific pathogen-free eggs and chickens) used in the generation of the new WSL, where applicable.

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
13. Change in equipment used in the antigen manufacturing process, such as:				
a)	introduction of new equipment with different operating principles and different product contact material	None	1 – 6	Moderate
b)	introduction of new equipment with the same operating principles but different product contact material	None	1, 3 – 6	Moderate

c)	introduction of new equipment with different operating principles but the same product contact material	None	1 – 3, 5, 6	Moderate
d)	replacement of equipment with equivalent equipment (including filter)	None	1, 5 – 7	Minor

Conditions:

None

Supporting data

1. Information on the in-process control testing.
2. Process validation study reports.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the antigen produced with the approved and proposed product contact equipment/ material. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action).
4. Information on leachable 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.

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
14. Change in specifications for the materials, involving:				
a)	raw materials/intermediates: widening of the approved specification limits for starting materials/intermediates, which may have a	None	1,3 – 6, 8, 11	Moderate

	significant effect on the overall quality of the antigen and/or final product and are not changes to the cell banks or seed lots			
b)	raw materials/intermediates: narrowing of the approved specification limits for starting materials/intermediates	1 – 4	1, 3 – 7	Minor
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	2, 6	Minor
b)	addition of new in-process test and limits	4, 5, 10, 11	2 – 6, 8, 10	Minor
c)	deletion of a non-significant in-process test	4 – 6	2, 6, 9	Minor
d)	widening of the approved in-process limits	None	2 – 6, 8, 10, 11	Moderate
		3 – 5	2 – 6, 8, 10, 11	Minor
e)	deletion of an in-process test which may have a significant effect on the overall quality of the antigen	None	2, 6, 8, 10	Moderate
f)	addition or replacement of an in-process test as a result of a safety or quality issue	None	2 – 6, 8, 10	Moderate
16.	**Change in in-process controls testing site**	3 – 5, 7, 8	12	Minor

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.
4. No change in the impurity profile of the antigen outside the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The test does not concern a critical attribute (for example, content, impurity, any critical physical characteristics or microbial purity).
7. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
8. No change in the in-process controls outside the approved limits.

9. The test procedure remains the same, or changes in the test procedure are minor.
10. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
11. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).

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 by the MA holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
9. Justification/risk assessment showing that the attribute is non-significant.
10. Justification for the new in-process test and limits.

11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale final product batches produced with the proposed changes under real time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/ or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
12. Evidence that the new company/facility is GMP compliant

Control of Antigen

Sl. No.	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 license	1 – 3	1, 2	Minor
b)	transfer of the QC testing activities for a pharmacopoeial assay to a new company not approved in the current MA or license	1	1, 2	Minor

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

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Supporting data

1. Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant

Sl. No.	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	Moderate
b)	addition of a test	1 – 3	1 – 3, 5	Minor
c)	replacement of an analytical procedure	None	1 – 5	Moderate
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	Moderate
e)	minor changes to an approved analytical procedure	4 – 7	1, 4, 5	Minor
f)	change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure	4, 7	1 – 3	Minor
g)	widening of an acceptance criterion	None	1, 5, 8	Moderate
h)	narrowing of an acceptance criterion	1, 8, 9	1	Minor

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.

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.

Reference Standards or Materials

Sl. No.	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	Moderate

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20.	Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	Moderate
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	Minor
22.	Change to reference standard qualification protocol	None	3, 4	Moderate
23.	Extension of reference standard shelf-life	2	5	Minor

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.

Container Closure System

Sl. No.	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	Moderate
		1	1,3,5	Minor

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 shelflife/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated

temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

5. Comparative table of pre- and post-change specifications

Sl. No.	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	Minor
b)	addition of a test	3	1 – 3	Minor
c)	replacement of an analytical procedure	6, 7	1 – 3	Minor
d)	minor changes to an analytical procedure	4 – 7	1 – 3	Minor
e)	widening of an acceptance criterion	None	1, 2	Moderate
f)	narrowing of an acceptance criterion	8	1	Minor

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.

Stability

Sl. No.	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	Moderate
		1 – 5	1,2,5	Minor
b)	reduction	None	1 – 5	Moderate
		6	2-4	Minor

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).

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2. Proposed storage conditions and shelf-life, as appropriate.
3. Updated post-approval stability protocol and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the antigen. Under special circumstances and with prior agreement of the NRA, interim stability testing results and a commitment to notify the NRA of any failures in the ongoing long-term stability studies may be provided.

Sl. No.	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, replacement of an analytical procedure or change in storage temperature	None	1 – 6	Moderate
		1	1,2,4-6	Minor
b)	addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c)	addition of test(s) into the post-approval stability protocol	2	1, 2, 4, 6	Minor
d)	deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e)	deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 6	Minor

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.

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.

Sl. No.	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	Moderate
		1, 2	1-3	Minor

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).

Changes to Final Product

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
29. Change in the description or composition of the final product, involving:				
a)	addition of a dosage form or change in the formulation (for example, lyophilized powder to liquid, change in the amount of excipient or new diluent 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. MA holders are encouraged to contact the NRA for further guidance.	None	1 – 10	Major
b)	change in fill volume (that is, same concentration, different volume)	None	1, 5, 7, 10	Major
		1,2	1,5,7	Moderate
		1-3	5,7	Minor
c)	addition of a new presentation (for example, addition of a new prefilled syringe where the approved presentation is a vial for a vaccine in a liquid dosage form)	None	1, 5, 7 – 10	Major

Conditions

1. No changes classified as major in the manufacturing process to accommodate the new fill volume.
2. No change in the dose recommended.
3. Narrowing of fill volume while maintaining the lower limit of extractable volume

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Supporting data

1. Revised final product labelling information (as applicable).
2. Characterization data demonstrating that the conformation and immunogenicity of the antigen is comparable in the new dosage form and/or formulation.
3. Description and composition of the dosage form if there are changes to the composition or dose.
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 leach ables 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Supporting clinical data or a justification for why such studies are not needed

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Description and composition of the final product change to an adjuvant

Note:

Change in type/structure of a chemical adjuvant, in the type of a biological adjuvant or in a component of a biological adjuvant may necessitate the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.

For additional guidance on the required supporting data for quality changes for chemical and biological adjuvants, see recommendations for other changes to the final product, such as changes to facilities, equipment, manufacturing process, quality control, shelf-life, and so on, as applicable.

Sl. No.	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	Moderate
		1 – 3	5	Minor
b)	change in manufacture of a chemical/synthetic adjuvant	None	3 – 5, 10, 11	Moderate
c)	change in specification of a chemical/synthetic adjuvant (including tests and/or the analytical procedures)	None	7 – 11	Moderate
		1, 3	7-9	Minor
31. Change involving a biological adjuvant				
a)	change in supplier of a biological adjuvant	None	1 – 7, 10 – 13	Major
b)	change in manufacture of a biological adjuvant	None	1 – 7, 10 – 12	Major
		4		Moderate
c)	change in specification of a biological adjuvant (including tests and/or the analytical procedures)	None	6 – 10	Moderate
		1,3	7-8	Minor

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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 aluminum salt.
3. The change in specification consists of the addition of a new test or of a minor change to an analytical procedure.
4. There is no change in the manufacturer and/or supplier of the adjuvant.

Supporting data

1. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, BSE/TSE risk) (5).
2. Information on the quality and controls of the materials (for example, raw materials, starting materials) used in the manufacture of the proposed adjuvant.
3. Flow diagram of the proposed manufacturing process(es), a brief narrative description of the proposed manufacturing process(es), and information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.
4. Process validation study reports (for example, for manufacture of the adjuvant) unless otherwise justified.
5. Description of the general properties, including stability, characteristic features and characterization data of the adjuvant, as appropriate.
6. Comparability of the pre- and post-change adjuvant with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies should be determined on a case-by case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the adjuvant, existing relevant nonclinical and clinical data, and aspects of vaccine use.
7. Updated copy of the proposed specification for the adjuvant (and updated analytical procedures if applicable).
8. Copies or summaries of analytical procedures, if new analytical procedures are used.
9. Validation study reports, if new analytical procedures are used.

10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the final product with the pre-change (approved) and post-change (proposed) adjuvant, as applicable. Comparative test results for the approved adjuvant do not need to be generated concurrently; relevant historical testing results are acceptable.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
12. Supporting nonclinical and clinical data, if applicable.
13. Evidence that the facility is GMP compliant.

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.

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
32. Change to the diluent, involving				
a)	change in manufacturing process	None	1 – 5	Moderate
		1,3	1 – 4	Minor
b)	replacement of or addition to the source of a diluent	None	1 – 5	Moderate
		1 -3	1 -3	Minor

c)	change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5	Minor
d)	addition of a diluent filling line	1, 2, 4	1, 3, 5	Minor
e)	addition of a diluent into an approved filling line	1, 2	1, 3, 5	Minor
f)	deletion of a diluent	None	None	Minor

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 proposed diluent is commercially available in the NRA country/jurisdiction.
4. The addition of the diluent filling line is in an approved filling facility.

Supporting data

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. Evidence that the facility is GMP compliant.

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Manufacture

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
33. Change involving a final product manufacturer/ manufacturing facility, such as				
a)	replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)	None	1 – 7	Major
		1 – 5	1 – 3, 5 – 8	Moderate
b)	replacement or addition of a secondary packaging facility, a labelling/storage facility or a distribution facility	2, 3	1 – 3	Minor
c)	deletion of a final product manufacturing facility	None	None	Minor

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
2. There is no change in the composition, manufacturing process and final product specification.
3. There is no change in the container/closure system and storage conditions.
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.

Supporting data

1. Name, address and responsibility of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP compliant.
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.

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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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
8. Rationale for considering the proposed formulation/filling facility as equivalent.

Sl. No.	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	Moderate
b)	addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, and lyophilizer); see change 13 above	None	1 – 8	Moderate
		5	2, 7– 9	Minor

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c)	addition of a new scale bracketed by the approved scales or scaledown of the manufacturing process	1 – 4	1, 4	Minor
d)	addition of a new step (for example, filtration)	3	1 – 6	Moderate

Conditions

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

Supporting data

1. Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
2. Information on the in-process control testing, as applicable.
3. Process validation study reports (for example, media fills), as appropriate.
4. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
5. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant

historical results for lots on the stability programme are acceptable. The data should cover a minimum of 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

6. Information on leachable 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.
10.

Sl. No.	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	2, 3, 7	1, 5	Minor
b)	addition of new in-process test and limits	2, 3, 8, 9	1 – 6, 8	Minor
c)	deletion of a non-significant in-process test	2 – 4	1, 5, 7	Minor
d)	widening of the approved in-process limits	None	1 – 6, 8, 9	Major
		1 – 3	1,5,6,8,9	Moderate
e)	deletion of an in-process test which may have a significant effect on the overall quality of the final product	None	1, 5, 6, 8	Major
f)	addition or replacement of an in-process test as a result of a safety or quality issue	None	1 – 6, 8	Moderate
36.	**Change in in-process controls testing site**	1 – 3, 5, 6	10	Minor

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Conditions

1. No change in final product specification outside the approved limits.
2. No change in the impurity profile of the final product outside the approved limits.
3. The change is not necessitated by recurring events arising during 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

10. Evidence that the new company/facility is GMP compliant.

Sl. No.	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 above for details (changes 30 and 31)				
a)	deletion of a test	5, 8	1, 3	Minor
b)	addition of a test	4	1 – 3	Minor
c)	replacement of an analytical procedure	1 – 3	1, 2	Minor
d)	minor changes to an approved analytical procedure	None	1, 2	Minor
e)	change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1, 2	Minor
f)	widening of an acceptance criterion	None	1, 3	Moderate
g)	narrowing of an acceptance criterion	3, 4, 6, 7	1	Minor

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.

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).

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
38.	Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk	None	2 – 7	Major
39.	Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source	None	1, 3, 5, 6	Moderate
40.	Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5, 6	2 – 7	Minor

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)	None	2 – 7	Major
		2	2-7	Moderate
		1,2	2-7	Minor
42.	Change in supplier for a plasma derived excipient (for example, human serum albumin)	None	3 – 8	Major
		3,4	5,6,9	Moderate
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)	None	2, 3, 5 – 7	Moderate
		1,5,6	3	Minor
44.	Change in excipient testing site	1	10	Minor

Conditions

1. No change in the specification of the excipient or final product outside the approved limits.
2. The change does not concern a human plasma-derived excipient.
3. The human plasma-derived excipient from the new supplier is an approved medicinal product and no manufacturing changes were made by the supplier of the new excipient since its last approval in the country/jurisdiction of the NRA.
4. The excipient does not influence the structure/conformation of the active ingredient.
5. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material (5).
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 (5).
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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
7. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, or BSE/TSE risk (5)) 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.

Control of the Final Product

Sl. No.	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 Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections.				

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	None	1, 2	Moderate
b)	transfer of the QC testing activities for a pharmacopoeial assay to a new company	1	1, 2	Minor

Conditions

1. The transferred QC test is not a potency assay or a bioassay.

Supporting data

1. Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant

Sl. No.	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	Major
b)	. deletion of a test	None	2, 9, 10	Moderate
c)	addition of a test	1, 2, 9	2 – 4, 8	Minor
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	Moderate
e)	replacement of an analytical procedure	None	2 – 4, 7, 8	Moderate
f)	minor changes to an approved analytical procedure	3 – 6	3, 8	Minor
g)	change from an in-house analytical procedure to a recognized compendial analytical procedure	3, 6	2 – 4	Minor

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h)	widening of an acceptance criterion	None	2, 8, 10	Moderate
i)	narrowing of an acceptance criterion	7 – 10	2	Minor

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.

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).

Reference Standards or Materials

Sl. No.	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	Moderate
48.	Change of the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	Moderate
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	Minor
50.	Change to the reference standard qualification protocol	None	3, 4	Moderate
51.	Extension of the shelf-life of the reference standard	2	5	Minor

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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.

Container Closure System

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
52.	Modification of a primary container closure system (for example, new coating, adhesive, stopper or type of glass) 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 change 29.c above	None	1 – 7	Moderate
		1-3	3	Minor
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	Moderate
54.	Deletion of a container closure system Note: The NRA should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate.	None	1	Minor

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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).

Supporting data

1. Revised product labelling information, as appropriate.
2. For sterile products, process validation study reports, or providing equivalency rationale. For a secondary functional container closure system, validation testing report.
3. Information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary/secondary packaging components, performance specification).
4. Results demonstrating protection against leakage, no leaching of undesirable substance and compatibility with the product, and results from the toxicity and biological reactivity tests.
5. Summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
6. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

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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).

Sl. No.	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 Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data such as is shown for change 52 above.	1, 2	4, 5	Minor
b)	deletion of a supplier	None	None	Minor

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.

Supporting data

1. Information on the supplier and make of the proposed container closure system (for example, certificate of analysis, description, materials of construction of primary packaging components, specification).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3. 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 to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

4. Letter from the MA holder certifying that there are no changes to the container closure system.
5. Certificate of analysis for the container provided by the new supplier and comparison with the certificate of analysis for the approved container.

Sl. No.	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	Minor
b)	addition of a test	3	1, 2	Minor
c)	replacement of an analytical procedure	6, 7	1 – 3	Minor
d)	minor changes to an analytical procedure	4 – 7	1 – 3	Minor
e)	widening of an acceptance criterion	None	1, 2	Moderate
f)	narrowing of an acceptance criterion	8	1	Minor

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.

Stability

Sl. No.	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	Moderate
b)	reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1 – 5	Moderate

Conditions

None

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Supporting data

1. Updated product labelling information, as appropriate.
2. Proposed storage conditions and shelf-life, as appropriate.
3. Updated post-approval stability protocol.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing under real-time/real-temperature conditions covering the proposed shelf-life generated on at least three (3) commercial-scale batches.

Sl. No.	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, replacement of an analytical procedure or change in storage temperature	None	1 – 6	Moderate
b)	addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c)	addition of test(s) into the post-approval stability protocol	1	4, 6	Minor
d)	deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e)	deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 6	Minor
f)	replacement of the sterility testing by the container/closure system integrity testing	None	1, 2, 4, 6	Moderate
		3	4,6	Minor

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.

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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.

Sl. No.	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	Moderate
b)	addition of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 5	Moderate

Conditions

None

Supporting data

1. Revised product labelling information, as applicable.
2. Proposed storage conditions and shelf-life.
3. Updated post-approval stability protocol and stability commitment.
4. Justification of the change in the labelled storage conditions/cautionary statement.
5. Results of stability testing under appropriate stability conditions covering the proposed shelf-life, generated on one (1) commercial-scale batch unless otherwise justified.

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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.

Product Labelling Information Changes

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
60. Change in the product labelling information, involving				
a)	Addition of an adverse event identified as consistent with a causal association with immunization with the vaccine concerned	None	1	Moderate
b)	Change in the frequency of occurrence of a given adverse reaction	None	1	Moderate
c)	Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example, required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks)	None	1	Moderate
d)	Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions	None	1	Moderate
e)	Revisions to the instructions for use, including dosage, administration and preparation for administration to optimize the safe use of the vaccine	None	1	Moderate

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Conditions

None

Supporting data

1. Revised product labelling information, as applicable.

Urgent Product Labelling Information Changes

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
61. Change in the product labelling information, involving				
a)	Addition of an adverse event identified as consistent with a causal association with immunization with the vaccine concerned	None	1	Moderate
b)	Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example, required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks)	None	1	Moderate
c)	Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions	None	1	Moderate

Conditions

None

Supporting data

1. Revised product labelling information, as applicable.

Administrative Product Labelling Information Changes

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
62. Change in the product labelling information, involving				
a)	Change in the name of the MA holder and/or manufacturer (such as change of name due to a merger)	None	1	Moderate
b)	Change in the trade name of the vaccine	None	1	Moderate

Conditions

None

Supporting data

1. Revised product labelling information, as applicable.

Changes of Strains of Influenza Vaccine

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
63. Change in Strains of Influenza Vaccine				
a)	Annual changes in the vaccine strain composition	None	1-6	Moderate

Conditions

None

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Supporting data

1. Information on the source of the seed viruses.
2. Passage history until establishment of working seeds.
3. Results of quality release tests performed on working virus seeds (including identity confirmation).
4. Specific validation data (including inactivation kinetics).
5. Generally, stability data for antigen bulks or final drug product produced in the previous influenza season are expected to be submitted to continuously support the approved shelf-life.
6. Updated product labelling information items (package insert and inner and outer labels with relevant strain composition and formula year) should be provided.

Safety and Efficacy Changes

Sl. No.	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
64. Change to the indication, involving				
a)	addition of a new indication (such as prevention of a previously unspecified disease)	None	1-4	Moderate
b)	modification of an approved indication (such as expansion of the age of use or restriction of an indication based on clinical studies demonstrating lack of efficacy)	None	1-4	Moderate
65. Change in the recommended dose and/or dosing schedule, involving				
a)	addition of a new vaccination regimen (such as addition of accelerated vaccination regimens),	None	1-4	Moderate
b)	addition or modification of the existing vaccination regimen (such as addition of a booster dose or modification of the recommended time interval for booster vaccinations)	None	1-4	Moderate

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66.	Change to add information on shedding and transmission	None	1-4	Moderate
67.	Change to the use in specific at-risk groups (such as addition of information on use in pregnant women or immunocompromised patients)	None	1-4	Moderate
68.	Change to add information on co-administration with other vaccines or medicines	None	1-4	Moderate
69.	Change to add a new route of administration	None	1-4	Moderate
70.	Change to add a new dosage form1 (such as replacement of a suspension for injection with a lyophilized cake)	None	1-4	Moderate
71.	Change to add a new strength	None	1-4	Moderate
72.	Change to add a new delivery device.1 (such as adding a needle-free jet injector)	None	1-4	Moderate
73. Change in existing risk-management measures, involving				
a)	deletion of an existing route of administration, dosage form and/or strength due to safety reasons	None	1-4	Moderate
b)	deletion of a contraindication (such as use in pregnant women).	None	1-4	Moderate

Conditions

None

Supporting data

1. Clinical Studies Data where applicable.
2. Post-marketing observational studies report if applicable.
3. Extensive post-marketing safety data if applicable.
4. Bridging clinical studies data if applicable.

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
General Information									
1) Changes in the name of the antigen									
a) Changes in the name of the antigen (Note: This change generally applies only to influenza vaccines)									
1.	1 & 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Manufacture									
2. Changes to an antigen manufacturing facility									
a) Replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen									
1.	1, 2, 3, 4, 6, 7 & 8 from Annexure-1	☐	☐	☐	1, 2, 3 & 4 from Annexure-1	☐	☐	☐	
b) Deletion of a manufacturing facility or manufacturer of an antigen intermediate, or antigen bulk									
1.	5 & 6 from Annexure-1	☐	☒	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture									
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)								
1.	1, 2, 3, 4, 6, 7, 9 & 11 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
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)								
1.	1, 2, 3, 4, 5, 6, 8 & 10 from Annexure-1	☐	☐	☐	2 & 4 from Annexure-1	☐	☐	☐	
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 or production scale; or duplication of a fermentation train)								
1.	1, 2, 3 & 4 from Annexure-1	☐	☐	☐	1, 2, 3, 4, 5, 6, 9, 10 & 11 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture									
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)								
1.	1, 2, 5–7, 9, 11, 12 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
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)								
1.	1, 2, 5–7, 10, 11 from Annexure-1	☐	☐	☐	2 & 4 from Annexure-1	☐	☐	☐	
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.	1 & 2 from Annexure-1	☐	☐	☐	1 – 5 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted?			Conditions	Met?			DGDA Screening
		Yes	No	NA		Yes	No	NA	Assessment Outcome
Manufacture									
5. Change in scale of the manufacturing process									
a) at the fermentation, viral propagation or cellular propagation stage									
1.	2, 3, 5–7, 9, 11 from Annexure-1	☐	☐	☐	3 – 6, 11 – 13 from Annexure-1	☐	☐	☐	
b) at the purification stage									
1.	2, 5–7, 9, 11 from Annexure-1	☐	☐	☐	1, 3, 5, 7 from Annexure-1	☐	☐	☐	
6. Change in supplier of raw materials of biological origin (for example, fetal calf serum, human serum albumin, trypsin)									
1.	4, 8, 12, 13 from Annexure-1	☐	☐	☐	8 from Annexure-1	☐	☐	☐	
7. Change in source of raw materials of biological origin									
1.	4, 7, 12, 13 from Annexure-1	☐	☐	☐	8 from Annexure-1	☐	☐	☐	
8. Introduction of reprocessing steps									
1.	8, 10, 11, 14 from Annexure-1	☐	☐	☐	14 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture									
9. Change to the cell banks									
a) generation of a new MCB									
1.	1, 2, 5 7 – 9 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
b) generation of a new working cell bank (WCB)									
1.	1 & 2 from Annexure-1	☐	☐	☐	2 – 4 from Annexure-1	☐	☐	☐	
c) change in cell bank storage site									
1.	10 from Annexure-1	☐	☐	☐	7 from Annexure-1	☐	☐	☐	
10. Change to the seed lots									
a) generation of a new MSL									
1.	1, 5 – 9, 11 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
b) generation of a new working seed lot (WSL)									
1.	5 – 9, 11 from Annexure-1	☐	☐	☐	2 – 4 from Annexure-1	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture									
c) generation of a new WSL by extending the passage level of an existing WSL beyond an approved level									
1.	5 – 7, 11 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
d) change in seed lot storage site									
1.	10 from Annexure-1	☐	☐	☐	7 from Annexure-1	☐	☐	☐	
11. Change in cell bank/seed lot testing/storage site									
1.	10 from Annexure-1	☐	☐	☐	5 & 7 from Annexure-1	☐	☐	☐	
12. Change in cell bank/seed lot qualification protocol									
1.	3 & 4 from Annexure-1	☐	☐	☐	6 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture									
13. Change in equipment used in the antigen manufacturing process									
a) introduction of new equipment with different operating principles and different product contact material									
1.	1 – 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) introduction of new equipment with the same operating principles but different product contact material									
1.	1, 3 – 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) introduction of new equipment with different operating principles but the same product contact material									
1.	1 – 3, 5, 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
d) replacement of equipment with equivalent equipment (including filter)									
1.	1, 5 – 7 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture									
14. Change in specifications for the materials									
a) raw materials/intermediates: widening of the approved specification limits for starting materials/intermediates, which may have a significant effect on the overall quality of the antigen and/or final product and are not changes to the cell banks or seed lots									
1.	1,3 – 6, 8, 11 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) raw materials/intermediates: narrowing of the approved specification limits for starting materials/intermediates									
1.	1, 3 – 7 from Annexure-1	☐	☐	☐	1-4 from Annexure-1	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
15. Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen									
a) narrowing of in-process limits									
1.	2 & 6 from Annexure-1	☐	☐	☐	3, 5, 8, 9 from Annexure-1	☐	☐	☐	
b) addition of new in-process test and limits									
1.	2 – 6, 8, 10 from Annexure-1	☐	☐	☐	4, 5, 10, 11 from Annexure-1	☐	☐	☐	
c) deletion of a non-significant in-process test									
1.	2, 6 & 9 from Annexure-1	☐	☐	☐	4-6 from Annexure-1	☐	☐	☐	
d) widening of the approved in-process limits									
1.	2 – 6, 8, 10, 11 from Annexure-1	☐	☐	☐	3-5 from Annexure-1	☐	☐	☐	
e) deletion of an in-process test which may have a significant effect on the overall quality of the antigen									
1.	2, 6, 8, 10 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
f) addition or replacement of an in-process test as a result of a safety or quality issue									
1.	2 – 6, 8, 10 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
16. Change in in-process controls testing site									
1.	12 from Annexure-1	☐	☐	☐	3 – 5, 7, 8 from Annexure-1	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Control of Antigen									
17. Change affecting the quality control (QC) (release and stability) testing of the antigen									
a) transfer of the QC testing activities for a non-pharmacopoeial assay to a new company not approved in the current MA or license									
1.	1 & 2 from Annexure-1	☐	☐	☐	1 – 3 Annexure-1	☐	☐	☐	
b) transfer of the QC testing activities for a pharmacopoeial assay to a new company not approved in the current MA or license									
1.	1 & 2 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
18. Change in the specification used to release the antigen									
45. deletion of a test									
1.	1, 5, 8 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
46. addition of a test									
1.	1 – 3, 5 from Annexure-1	☐	☐	☐	1 – 3 from Annexure-1	☐	☐	☐	
c) replacement of an analytical procedure									
1.	1 – 5 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
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Control of Antigen									
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)									
1.	6 & 7 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
e) minor changes to an approved analytical procedure									
1.	1, 4, 5 from Annexure-1	☐	☐	☐	4 – 7 from Annexure-1	☐	☐	☐	
f) change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure									
1.	1 – 3 from Annexure-1	☐	☐	☐	4, 7 from Annexure-1	☐	☐	☐	
g) widening of an acceptance criterion									
1.	1, 5, 8 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
h) narrowing of an acceptance criterion									
1.	1 from Annexure-1	☐	☐	☐	1, 8, 9 from Annexure-1	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Reference Standards or Materials									
19. Qualification of a new reference standard against a new primary international standard									
1.	1 & 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
20. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard									
1.	1 & 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
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 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
22. Change to reference standard qualification protocol									
1.	3, 4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
23. Extension of reference standard shelf-life									
1.	5 from Annexure-1	☐	☐	☐	2 from Annexure-1	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Container Closure System									
24. Change in the primary container closure system(s) for the storage and shipment of the antigen									
1.	1 - 5 from Annexure-1	☐	☐	☐	1	☐	☐	☐	
25. Change in the specification of the primary container closure system for the antigen									
a) deletion of a test									
1.	1, 2 from Annexure-1	☐	☐	☐	1, 2 from Annexure-1	☐	☐	☐	
b) addition of a test									
1.	1 – 3 from Annexure-1	☐	☐	☐	3	☐	☐	☐	
c) replacement of an analytical procedure									
1.	1 – 3 from Annexure-1	☐	☐	☐	6, 7 from Annexure-1	☐	☐	☐	
d) minor changes to an analytical procedure									
1.	1, 3 from Annexure-1	☐	☐	☐	4 – 7 from Annexure-1	☐	☐	☐	
e) widening of an acceptance criterion									
1.	1 – 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
f) narrowing of an acceptance criterion									
1.	1 from Annexure-1	☐	☐	☐	8 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Stability									
26. Change in the shelf-life/hold-time for the antigen or for a stored intermediate of the antigen									
a) Extension									
1.	1 – 5 from Annexure-1	☐	☐	☐	1 – 5 from Annexure-1	☐	☐	☐	
b) reduction									
1.	1 – 5 from Annexure-1	☐	☐	☐	6 from Annexure-1	☐	☐	☐	
27. Change in the post-approval stability protocol of the antigen									
a) significant change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature									
1.	1 – 6 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
b) addition of time point(s) into the post-approval stability protocol									
1.	4, 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) addition of test(s) into the post-approval stability protocol									
1.	1, 2, 4, 6 from Annexure-1	☐	☐	☐	2 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Stability									
d) deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life									
1.	4, 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
e) deletion of time point(s) from the post-approval stability protocol within the approved shelf-life									
1.	4, 6 from Annexure-1	☐	☐	☐	3 from Annexure-1	☐	☐	☐	
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)									
1.	1 – 4 from Annexure-1	☐	☐	☐	1, 2 from Annexure-1	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Changes to Final Product									
29. Change in the description or composition of the final product									
a) addition of a dosage form or change in the formulation (for example, lyophilized powder to liquid, change in the amount of excipient or new diluent 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. MA holders are encouraged to contact the NRA for further guidance.									
1.	1 – 10 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) change in fill volume (that is, same concentration, different volume)									
1.	1, 5, 7, 10 from Annexure-1	☐	☐	☐	1 – 3 from Annexure-1	☐	☐	☐	
c) addition of a new presentation (for example, addition of a new prefilled syringe where the approved presentation is a vial for a vaccine in a liquid dosage form)									
1.	1, 5, 7 – 10 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Description and composition of the final product change to an adjuvant									
30. Change involving an approved chemical/synthetic adjuvant									
a) change in supplier of a chemical/ synthetic adjuvant									
1.	4, 5, 10, 11 from Annexure-1	☐	☐	☐	1-3 from Annexure-1	☐	☐	☐	
b) change in manufacture of a chemical/synthetic adjuvant									
1.	3 – 5, 10, 11 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) change in specification of a chemical/synthetic adjuvant (including tests and/or the analytical procedures)									
1.	7 – 11 from Annexure-1	☐	☐	☐	1 & 3 from Annexure-1	☐	☐	☐	
31. Change involving a biological adjuvant									
a) change in supplier of a biological adjuvant									
1.	1 – 7, 10 – 13 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) change in manufacture of a biological adjuvant									
1.	1 – 7, 10 – 12 from Annexure-1	☐	☐	☐	4 from Annexure-1	☐	☐	☐	
c) change in specification of a biological adjuvant (including tests and/or the analytical procedures)									
1.	6 – 10 from Annexure-1	☐	☐	☐	1 & 3 from Annexure-1	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	Submitted? No	Submitted? NA	Conditions	Met? Yes	Met? No	Met? NA	DGDA Screening – Assessment Outcome
Description and composition of the final product: change to a diluent									
32. Change to the diluent									
a) change in manufacturing process									
1.	1 – 5 from Annexure-1	☐	☐	☐	1 & 3 from Annexure-1	☐	☐	☐	
b) replacement of or addition to the source of a diluent									
1.	1 – 5 from Annexure-1	☐	☐	☐	1 & 3 from Annexure-1	☐	☐	☐	
c) change in facility used to manufacture a diluent (same company)									
1.	1, 3, 5 from Annexure-1	☐	☐	☐	1 & 2 from Annexure-1	☐	☐	☐	
d) addition of a diluent filling line									
1.	1, 3, 5 from Annexure-1	☐	☐	☐	1, 2, 4 from Annexure-1	☐	☐	☐	
e) addition of a diluent into an approved filling line									
1.	1, 3, 5 from Annexure-1	☐	☐	☐	1, 2 from Annexure-1	☐	☐	☐	
f) deletion of a diluent									
1.	None	☐	☐	☐	None	☐	☐	☐	
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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture (Final Product)									
33. Change involving a final product manufacturer/ manufacturing facility									
a) replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)									
1.	1 – 8 from Annexure-1	☐	☐	☐	1-5 from Annexure-1	☐	☐	☐	
b) replacement or addition of a secondary packaging facility, a labelling/storage facility or a distribution facility									
1.	1– 3 from Annexure-1	☐	☐	☐	2, 3 from Annexure-1	☐	☐	☐	
c) deletion of a final product manufacturing facility									
1.	None	☐	☐	☐	None	☐	☐	☐	
34. Change in the final product manufacturing process									
a) scale-up of the manufacturing process at the formulation/filling stage									
1.	1 – 6 from Annexure-1	☐	☐	☐	1 – 4 from Annexure-1	☐	☐	☐	
b) addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, and lyophilizer); see change 13 above									
1.	1 – 9 from Annexure-1	☐	☐	☐	5 from Annexure-1	☐	☐	☐	
c) addition of a new scale bracketed by the approved scales or scale down of the manufacturing process									
1.	1 & 4 from Annexure-1	☐	☐	☐	1 – 4 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture (Final Product)									
d) addition of a new step (for example, filtration)									
1.	1 – 6 from Annexure-1	☐	☐	☐	3 from Annexure-1	☐	☐	☐	
35. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates									
a) narrowing of in-process limits									
1.	1, 5 from Annexure-1	☐	☐	☐	2, 3, 7 from Annexure-1	☐	☐	☐	
b) addition of new in-process test and limits									
1.	1 – 6, 8 from Annexure-1	☐	☐	☐	2, 3, 8, 9 from Annexure-1	☐	☐	☐	
c) deletion of a non-significant in-process test									
1.	1, 5, 7 from Annexure-1	☐	☐	☐	2 – 4 from Annexure-1	☐	☐	☐	
d) widening of the approved in-process limits									
1.	1 – 6, 8, 9 from Annexure-1	☐	☐	☐	1 – 3 from Annexure-1	☐	☐	☐	
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 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture (Final Product)									
f) addition or replacement of an in-process test as a result of a safety or quality issue									
1.	1 – 6, 8 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
g) addition or replacement of an in-process test as a result of a safety or quality issue									
1.	1 – 6, 8 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
36. Change in in-process controls testing site									
1.	10 from Annexure-1	☐	☐	☐	**1 – 3, 5, 6** from Annexure-1	☐	☐	☐	
37. Change in the specification used to release the excipient									
a) deletion of a test									
1.	1, 3 from Annexure-1	☐	☐	☐	5,8 from Annexure-1	☐	☐	☐	
b) addition of a test									
1.	1 – 3 from Annexure-1	☐	☐	☐	4 from Annexure-1	☐	☐	☐	
c) replacement of an analytical procedure									
1.	1, 2 from Annexure-1	☐	☐	☐	1 – 3 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening: Assessment Outcome
d) minor changes to an approved analytical procedure									
1.	1, 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
e) change from an in-house analytical procedure to a recognized compendial analytical procedure									
1.	1, 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
f) widening of an acceptance criterion									
1.	1, 3 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
g) narrowing of an acceptance criterion									
1.	1 from Annexure-1	☐	☐	☐	3, 4, 6, 7 from Annexure-1	☐	☐	☐	
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									
1.	2 – 7 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
39. 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 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source									
1.	2 – 7 from Annexure-1	☐	☐	☐	5, 6 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Manufacture (Final Product)									
41. Change in manufacture of a biological excipient									
1.	2 – 7 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
42. Change in supplier for a plasma derived excipient (for example, human serum albumin									
1.	1 from Annexure-1	☐	☐	☐	3, 4, 6, 7 from Annexure-1	☐	☐	☐	
43. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient)									
1.	2, 3, 5 – 7 from Annexure-1	☐	☐	☐	1, 5, 6 from Annexure-1	☐	☐	☐	
44. Change in excipient testing site									
1.	10 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Control of Final Product									
45. Change affecting the QC testing of the final product (release and stability)									
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									
1.	1, 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) transfer of the QC testing activities for a pharmacopoeial assay to a new company									
1.	1, 2 from Annexure-1	☐	☐	☐	1 Annexure-1	☐	☐	☐	
46. Change in the specification used to release the final product									
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									
1.	1, 2, 6, 8, 10 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) deletion of a test									
1.	2, 9, 10 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) addition of a test									
1.	2 – 4, 8 from Annexure-1	☐	☐	☐	1, 2, 9 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Control of Final Product									
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)									
1.	5, 11 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
e) replacement of an analytical procedure									
1.	2 – 4, 7, 8 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
f) minor changes to an approved analytical procedure									
1.	3, 8 from Annexure-1	☐	☐	☐	3 – 6 from Annexure-1	☐	☐	☐	
g) change from an in-house analytical procedure to a recognized compendial analytical procedure									
1.	2 – 4, from Annexure-1	☐	☐	☐	3, 6 from Annexure-1	☐	☐	☐	
h) widening of an acceptance criterion									
1.	2, 8, 10 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
i) narrowing of an acceptance criterion									
1.	2 from Annexure-1	☐	☐	☐	7 – 10 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Reference Standards or Materials									
47. Qualification of a reference standard against a new primary international standard									
1.	1, 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
48. Change of the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard									
1.	1, 2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
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 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
50. Change to the reference standard qualification protocol									
1.	3, 4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
51. Extension of the shelf-life of the reference standard									
1.	5 from Annexure-1	☐	☐	☐	2 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Container Closure System									
52. Modification of a primary container closure system (for example, new coating, adhesive, stopper or type of glass)									
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									
1.	1-7 from Annexure-1	☐	☐	☐	1-3 from Annexure-1	☐	☐	☐	
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)									
1.	1, 3, 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
54. Deletion of a container closure system									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
55. Change in the supplier for a primary container closure component									
a) replacement or addition of a supplier									
1.	4, 5 from Annexure-1	☐	☐	☐	1, 2 from Annexure-1	☐	☐	☐	
b) deletion of a supplier									
1.	None	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Container Closure System									
56. Change in the specification used to release a primary container closure component or functional secondary container closure component									
a) deletion of a test									
1.	1, 2 from Annexure-1	☐	☐	☐	1, 2 from Annexure-1	☐	☐	☐	
b) addition of a test									
1.	1, 2 from Annexure-1	☐	☐	☐	3 from Annexure-1	☐	☐	☐	
c) replacement of an analytical procedure									
1.	1-3 from Annexure-1	☐	☐	☐	6,7 from Annexure-1	☐	☐	☐	
d) minor changes to an analytical procedure									
1.	1-3 from Annexure-1	☐	☐	☐	4-7 from Annexure-1	☐	☐	☐	
e) widening of an acceptance criterion									
1.	1-2 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
f) narrowing of an acceptance criterion									
1.	1 from Annexure-1	☐	☐	☐	8 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Stability									
57. Change in the shelf-life of the final product									
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)									
1.	1 – 5 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)									
1.	1 – 5 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
58. Change in the post-approval stability protocol of the final product									
a) major change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature									
1.	1 – 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) addition of time point(s) into the post-approval stability protocol									
1.	4, 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) addition of test(s) into the post-approval stability protocol									
1.	4, 6 from Annexure-1	☐	☐	☐	1 from Annexure-1	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Stability									
d) deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life									
1.	4, 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
e) deletion of time point(s) from the post-approval stability protocol within the approved shelf-life									
1.	4, 6 from Annexure-1	☐	☐	☐	2 from Annexure-1	☐	☐	☐	
f) replacement of the sterility testing by the container/closure system integrity testing									
1.	1, 2, 4, 6 from Annexure-1	☐	☐	☐	3 from Annexure-1	☐	☐	☐	
59. Change in the labelled storage conditions for the final product or the diluted or reconstituted vaccine									
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)									
1.	1 – 4, 6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) addition of a cautionary statement (for example, "Do not freeze")									
1.	1, 2, 4, 5 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted?			Conditions	Met?			DGDA Screening
		Yes	No	NA		Yes	No	NA	Assessment Outcome
Product Labelling Information Changes									
a) Addition of an adverse event identified as consistent with a causal association with immunization with the vaccine concerned									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) Change in the frequency of occurrence of a given adverse reaction									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example, required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks)									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
d) Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
e) Revisions to the instructions for use, including dosage, administration and preparation for administration to optimize the safe use of the vaccine									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Urgent Product Labelling Information Changes									
a) Addition of an adverse event identified as consistent with a causal association with immunization with the vaccine concerned									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) Change in the frequency of occurrence of a given adverse reaction									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example, required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks)									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
d) Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted?			Conditions	Met?			DGDA Screening
		Yes	No	NA		Yes	No	NA	Assessment Outcome
Administrative Product Labelling Information Changes									
a) Change in the name of the MA holder and/or manufacturer (such as change of name due to a merger)									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) Change in the trade name of the vaccine									
1.	1 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted?			Conditions	Met?			DGDA Screening
		Yes	No	NA		Yes	No	NA	Assessment Outcome
Changes of Strains of Influenza Vaccine									
a) Annual changes in the vaccine strain composition									
1.	1-6 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted?			Conditions	Met?			DGDA Screening
		Yes	No	NA		Yes	No	NA	Assessment Outcome
Safety and Efficacy Changes									
a) addition of a new indication (such as prevention of a previously unspecified disease)									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
b) modification of an approved indication (such as expansion of the age of use or restriction of an indication based on clinical studies demonstrating lack of efficacy)									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
c) addition of a new vaccination regimen (such as addition of accelerated vaccination regimens),									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
d) addition or modification of the existing vaccination regimen (such as addition of a booster dose or modification of the recommended time interval for booster vaccinations)									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
e) Change to add information on shedding and transmission									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted?			Conditions	Met?			DGDA Screening
		Yes	No	NA		Yes	No	NA	Assessment Outcome
Safety and Efficacy Changes									
f) Change to the use in specific at-risk groups (such as addition of information on use in pregnant women or immunocompromised patients)									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
g) Change to add information on co-administration with other vaccines or medicines									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
h) Change to add a new route of administration									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
i) Change to add a new dosage form1 (such as replacement of a suspension for injection with a lyophilized cake)									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
j) Change to add a new strength									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Section	Supporting Documents	Submitted? Yes	No	NA	Conditions	Met? Yes	No	NA	DGDA Screening Assessment Outcome
Safety and Efficacy Changes									
k) Change to add a new delivery device (such as adding a needle-free jet injector)									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
l) deletion of an existing route of administration, dosage form and/or strength due to safety reasons									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
m) deletion of a contraindication (such as use in pregnant women).									
1.	1-4 from Annexure-1	☐	☐	☐	None	☐	☐	☐	
Submitted By (Sign & Seal)									

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Assessment Started on		**Assessment Completed on**		Total Duration	
Assessment Summary			**Assessment Done By/Date**		
Recommendation of Head of Vaccine and Biologics			**Head of Vaccine & Biologics Sign/Date**		

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Annexure-3

	FORM Title: Format for the Application form of Variation MA					
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Date

Dairy No

To
Director General
Directorate General of Drug Administration
Aushad Bhavan, Mohakhali, Dhaka-1212, Bangladesh.

Subject: Submission of Application for variation of Marketing Authorization of Product Name(s)

Dear Sir,

We are pleased to submit the application for variation of Marketing Authorization of following product(s)

Proprietary name (trade name) .....

Approved generic name(s) .....

Strength(s) per dosage unit .....

Dosage form.....

Name of License holder.....

Marketing authorization number .....

Date of Marketing Authorization .....

Expiry date of this marketing authorization .....

Nature of variation (s) applied for

1.

2.

3.

Yours sincerely,

<Signature>
<Name>
<Title>
<Phone number>
<Email address>

DIRECTORATE GENERAL OF DRUG ADMINISTRATION

MINISTRY OF HEALTH AND FAMILY WELFARE, BANGLADESH

Authorized Personnel Only

Annexure – 5

	FORM Title: Reporting Categories and Review Timelines for Variations of Vaccines					
Form No.	Version No.	Effective Date	Review Date	Authorized by	Date	Page No.
NRA-MA-003/F05-00	00	JUN' 22	JUN' 27		29.05.22	1 of 1

The review time would start when the supplement has been accepted for review and found to be complete and would end at the time when the initial assessment is shared with the MA holder, either by the issuance of an approval notification or a noncompliance notification with a list of comments and deficiencies. In the case of the latter, the MA holder may seek approval for the change by submitting an amendment to the supplement with responses to all the comments in the notification of noncompliance.

Table: **Review timelines for a prior approval supplement (PAS)**

Category	Supplement	Maximum review period
Quality Changes		
Major quality changes	PAS	6 months
Moderate quality changes	PAS	3 months
Minor quality changes	Do not require notification to DGDA	N/A
Safety, efficacy and product labelling information changes		
Safety and efficacy changes	PAS	10 months
Product labelling information changes	PAS	5 months
Urgent product labelling information changes	PAS for urgent safety restrictions	Immediate implementation on receipt of supplement by DGDA
Administrative product labelling information changes	PAS	30 days
	Do not require approval prior to implementation	N/A
Strain of Influenza Vaccine changes	PAS	30 days