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MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

VACCINE VARIATION GUIDELINE

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Table of Contents

ABBREVIATIONS AND ACRONYMS

CTD -	Common Technical Dossier (CTD)
EAC -	East Africa Community
EMA -	European Medicines Agency
EWG -	Experts Working Group
GMP -	Good Manufacturing Practices
HIV -	Human Immunodeficiency Virus
ICH -	International Council on Harmonization of Technical Requirements for Registration of Human Medicinal Products
IFPMA	International Federation of Pharmaceutical Manufacturers Association
MCB -	Master Cell Bank
MMR -	Measles-Mumps-Rubella
MRH -	Medicines Regulation Harmonization
NMRA-	National Medicines Regulatory Authority
NOAD -	New Onset Autoimmune Disease
NOCD -	New Onset Chronic Disease
PIC/S-	Pharmaceutical Inspection Cooperation Scheme
SDRAs	Stringent Drug Regulatory Authorities
SOP -	Standard Operating Procedure
TSE -	Transmissible spongiform encephalopathies
VVM	Vaccine Vial Monitor
WHO -	World Health Organization

GLOSSARY

The definitions provided below apply to the terms used in this guidance.

Adjuvant

A substance or combination of substances used in conjunction with a vaccine antigen to enhance (for example, increase, accelerate, prolong and/or possibly target) or modulate a specific immune response to the vaccine antigen in order to enhance the clinical effectiveness of the vaccine.

Antigen

The following definitions apply in this document:

a. The active ingredient in a vaccine against which the immune response is induced. Antigens may be: (a) live attenuated or inactivated preparations of bacteria, viruses, or parasites; (b) crude cellular fractions or purified antigens, including recombinant proteins (that is, those derived from recombinant DNA expressed in a host cell); (c) polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids; (d) synthetic antigens; (e) polynucleotides (such as plasmid DNA vaccines); or (f) living vectored cells expressing specific heterologous antigens. Also referred to as “immunogen” in other documents.
b. Also used to describe (a) a component that may undergo chemical change or processing before it becomes the antigen or active ingredient used to formulate the final product (also referred to as an “intermediate” in other documents), or (b) an active ingredient present in an unmodified form in the final product (also referred to as “drug substance” or “active substance” in other documents). For example, in this document, the term “antigen” applies, in the case of a polysaccharide conjugated vaccine, to the polysaccharide intermediate as well as to the conjugated polysaccharide that will not undergo further modification prior to formulation.

Applicant

For the purpose of this document, the term applicant refers to any person or entity who has participated in the procedure for registration of vaccines by submission of the required documentation on a product that has been listed after evaluation as registered.

Authority

Pharmacy and poisons board (PPB)

Cell bank

A collection of vials of cells of uniform composition (though not necessarily clonal) derived from a single tissue or cell and used for the production of a vaccine directly or via a cell bank system. The following terms are used in these Guidelines – master cell bank (MCB): a bank of a cell-substrate from which all subsequent cell banks used for vaccine production will be derived. The MCB represents a well-characterized collection of cells derived from a single tissue or cell; and working cell bank (WCB): a cell bank derived by the propagation of cells from an MCB under defined conditions and used to initiate the production of cell cultures on a lot-by-lot basis. Also referred to as "manufacturer's working cell bank" in other documents.

Change

Refers to a change that includes, but is not limited to, the product composition, manufacturing process, quality controls, equipment, facilities, or product labeling information made to an approved MA or license by the MA holder. Also referred to as "variation" in other documents.

Comparability study

The activities, including study design, conducting of studies, and data evaluation are designed to investigate whether the pre- and post-change products are comparable. In addition to routine analysis performed during production and control of the antigen or final product, these evaluations typically include a comparison of manufacturing process steps and

parameters impacted by the change, characterization studies, and an evaluation of product stability following the change. In some cases, nonclinical or clinical data might contribute to the conclusion reached.

Comparability protocol

Establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of a negative effect of specific manufacturing changes on the safety or effectiveness of the product. A comparability protocol is a highly specific, well-defined plan for the future implementation of quality (that is, manufacturing) change. Also referred to as "post-approval change management protocol" in other documents.

Container closure system

Refers to the following components: (a) a primary container closure system is a packaging component (for example, a vial or pre-filled syringe) that is in, or may come into, direct contact with the final product dosage form, or components that contribute to the container/closure integrity of the primary packaging material for a sterile product; and (b) a secondary container closure system is a packaging component (for example, a carton or tray) that is not, and will not be, in direct contact with the dosage form.

Dosage form

In this document "dosage form" refers to the physical form in which a pharmaceutical product is presented by the manufacturer (a form of presentation) and the form in which it is administered (a form of administration). Also referred to as "pharmaceutical form" in other documents.

Drug product: See immunogenic product

Drug substance: See immunogenic substances

EAC

East African Community

Excipient

Any component of the final product other than the active component/antigen and the packaging material. Also referred to as “inactive ingredient” in other documents. In the context of this document, adjuvants are not considered to be excipients.

Final lot

A collection of sealed final containers that are homogeneous with respect to the composition of the product and the risk of contamination during filling. A final lot must therefore have been filled from a formulated bulk in one continuous working session.

Final product

A finished dosage form (for example, suspension or lyophilized cake) that contains an active ingredient, generally but not necessarily in association with inactive ingredients (excipients) or adjuvants. Also referred to as “finished product” or “drug product” in other documents.

Formulated bulk

An intermediate in the drug product manufacturing process, consisting of the final formulation of antigens, adjuvants, and excipients at the concentration to be filled into primary containers.

Immunogenic Substance

An immunogenic substance is an unformulated active substance that may be subsequently formulated with excipients to produce the medicinal product. The immunogenic substance may be whole bacterial cells, viruses, or parasites (live or

A medicinal product is the finished dosage form of the immunogenic substance. The medicinal product contains the immunogenic substance(s) formulated with other ingredients in the finished dosage form ready for

marketing. Other ingredients, active or inactive, may include adjuvants, preservatives, stabilizers, and/or excipients.

Intermediate

A material produced during steps in the manufacture of a vaccine undergoes further processing before it becomes the final product. See the definition for Antigen above

Manufacturer

Any person or legal entity engaged in the manufacture of a product subject to MA or licensure. In other documents, "manufacturer" may also refer to any person or legal entity that is an applicant or a holder of a MA or product license where the applicant assumes responsibility for compliance with the applicable product and establishment standards. See the definition for Marketing authorization holder below.

Marketing authorization (MA)

A formal authorization for a medicine to be marketed. Once an NMRA approves an MA application for a new medicine, the medicine may be marketed and may be available for physicians to prescribe. Also referred to as "product license" or "license" in this and other documents.

Marketing authorization application (MA application)

A formal application to the NMRA for approval to market a new medicine. The purpose of the MA application is to determine whether the medicine meets the statutory standards for safety, effectiveness, product labelling information, and manufacturing. Also referred to as "license application" in other documents.

Marketing authorization holder (MA holder)

Any person or legal entity that has received MA or licensure to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the MA or license. Also referred to as the "manufacturer" or "applicant" in this and other documents.

NMRA

National Medicines Regulatory Agency

Officially recognized pharmacopeia (or compendium)

Those pharmacopeia's recognized by EAC Partner State's NMRAs (i.e., The International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopeia (USP)).

Product labelling information

Printed materials that accompany a prescription medicine and all labelling items, namely: (a) prescribing information (an instruction circular that provides product information on the indication, dosage, and administration, safety and efficacy, contraindications, and warnings, along with a description of the product for health care providers (also referred to as "summary of product characteristics" or "package insert" in various countries); (b) patient labelling or consumer information; (c) inner label or container label; and (d) outer label or carton.

Quality attribute

A physical, chemical, biological or microbiological property or characteristic. A critical quality attribute refers to a characteristic or property that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Quality change

In the context of this document, quality change refers to a change in the manufacturing process, product composition, quality control testing, equipment, or facility. Also referred to as "chemistry manufacturing and control (CMC) change" in other documents.

Raw materials

A general term used to denote reagents or solvents intended for use in the production of starting materials, intermediates, or final products.

Seed lot

Preparation of live cells (prokaryotic or eukaryotic) or viruses constituting the starting material for the vaccine antigen. A seed lot is of uniform composition (although not necessarily clonal), is derived from a single culture process, and is aliquoted into appropriate storage containers, from which all future vaccine production will be derived either directly or via a seed lot system.

The following derived terms are used in these Guidelines – master seed lot (MSL): a lot or bank of cells or viruses from which all future vaccine production will be derived. The MSL represents a well-characterized collection of cells or viruses of uniform composition. Also referred to as "master virus seed" for virus seeds, "master seed bank" or "master seed antigen" in other documents; and working seed lot (WSL): a cell or viral seed lot derived by propagation from the MSL under defined conditions and used to initiate production of vaccines on a lot-by-lot basis. Also referred to as "working virus seed" for virus seeds, "working seed bank" or "working seed antigen" in other documents.

Specification

The quality standard (that is, tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of antigens (drug substances), final products (drug products), intermediates, raw materials, reagents, components, in-process materials, container closure systems and other materials used in the production of the antigen (drug substance) or final product (drug product). For this definition, acceptance criteria mean numerical limits, ranges, or qualitative criteria for the applied tests.

Starting material

Any material used at the beginning of the manufacturing process, as described in an MA or product license. Generally, the term refers to a substance of defined chemical properties and structure that contributes an important and/or significant structural element (or elements) to the active substance (for example in the case of vaccines, synthetic peptides, synthetic

glycans, and starting materials for adjuvants). The starting material for an antigen (drug substance) obtained from a biological source is considered to consist of: (a) cells; (b) microorganisms; (c) plants, plant parts, macroscopic fungi or algae; or (d) animal tissues, organs or body fluid from which the antigen (drug substance) is derived.

Stringent regulatory authority (SRA)

A National Medicines Regulatory Authority which is strict, precise, and exact with effective and well-functioning systems. Among others, it includes regulatory authorities which are: -

1. Members or observers or associates (before 2015) of the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
2. European Union member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, The Netherlands, and United Kingdom
3. Japan
4. United States
5. Observers: For ICH European Free Trade Association (EFTA) represented by Swiss Medic of Switzerland, and Health Canada (as may be updated from time to time).
6. Associates: through mutual recognition agreements: Australia, Norway, Iceland, and Liechtenstein (as may be updated from time to time).
7. For medicines used exclusively outside the ICH region, positive opinions or tentative approval under any of the following three special regulatory schemes are recognized as stringent approval: -
8. Article 58 of European Union Regulation (EC) No. 726/2004
9. Canada S.C. 2004, c. 23 (Bill C-9) procedure
10. United States FDA tentative approval (for antiretroviral under the PEPFAR program)

11. A regulatory Authority that has been WHO listed to have effective and well-functioning medicines regulation systems.

Supplement:

Written request submitted to the NMRA to approve a change in the original application for MA (or product license) or any other notification to add to (that is, supplement) the information in the original MA or product license file. A prior approval supplement (PAS) is a supplement requiring approval from the NMRA before implementation of the change. Also referred to as "change application dossier" in other documents.

Vaccine

A preparation containing antigens capable of inducing an active immune response for the prevention, amelioration, or treatment of infectious diseases.

Vaccine efficacy

The relative reduction in disease incidence or severity in vaccinated individuals compared to unvaccinated individuals was measured in a randomized, placebo-controlled clinical trial. In the context of these Guidelines, vaccine efficacy has a broad meaning and relates to all clinical data obtained to ensure vaccine efficacy, immunogenicity, or field effectiveness.

WHO

The World Health Organization

LEGAL FRAMEWORK

The Pharmacy and Poisons Board will ensure that the vaccine variation applications submitted for market authorization are complying with requirements as stipulated in the technical guidelines and by the relevant policies, laws, legal frameworks, guidelines, manuals, and procedures existing in Kenya.

SCOPE

This guideline applies to applicants intending to make changes in the production, quality control, indications, or other to a registered vaccine. This includes the antigenic substance responsible for eliciting an immune response in the human body. This guideline should be read in conjunction with other applicable guidelines including the PPB Guidelines for Registration of Human Vaccines

INTRODUCTION

A Marketing Authorization Holder (MAH) of a registered vaccine is responsible for the quality, safety, and efficacy of a registered vaccine, and in this regard administrative, technical, and scientific progress arising during the lifecycle of the vaccine should be taken into consideration by the MAH

Therefore, changes to a registered vaccine may be inevitable during its lifecycle and such changes may span from administrative to other substantial changes that enable a registered vaccine to be manufactured and controlled by methods that are scientifically relevant throughout its lifecycle.

The variation guideline is, therefore, intended to guide applicants on the conditions to fulfil and the type of documentation to provide before a proposed change can be approved. Three categories of changes that require an application for variation are described in the guidelines. The changes are Notification (N), Minor changes (Vmin), and Major changes (Vmaj).

A change is classified as major only in those instances where the level of risk is considered to be high, and it is deemed necessary to provide PPB with adequate time for an assessment of the supporting documentation. PPB shall make decisions on such changes. Where the proposed change has low risk and lower reporting requirements, it is classified as a notification or minor change.

Also, the guidelines assist in understanding the possible consequences of the listed changes and are useful as a risk management tool to promote best practices. The guidelines also enhance flexibility in approaches and therefore, alternate approaches to the principles and justified. Alternate approaches should be discussed in advance with PPB before implementation.

As a corollary to the above, it is equally important to note that PPB reserves the right to request information or material, or define conditions not explicitly described in this guideline, to allow for adequate assessment of proposed change in relation to the quality, safety, and efficacy of a registered vaccine.

Applicants are urged to read and follow these guidelines fully so that applications for variations to registered vaccines meet submission requirements as outlined in these guidelines. Besides, comments are welcome for continuous improvement of these guidelines.

1.0 BACKGROUND

The requirements specified in the Guidelines have been adapted from the current WHO Guidelines on procedures and data requirements for changes to approved vaccines. It is intended to provide supportive information on how to present an application to implement a change to a vaccine.

An applicant is responsible for the safety, efficacy, and quality of a vaccine throughout its life cycle. Necessarily, therefore, the applicant is required to make changes to the details of the vaccine to accommodate technical and scientific progress or to improve or introduce additional safeguards for the registered vaccine. Such changes, whether administrative or substantive, are referred to as variations and may be subject to acceptance by EAC Partner State's NMRAs before implementation.

Technical requirements for the different types of variations are set out in this guideline to facilitate the submission of appropriate documentation by applicants and their assessment by EAC Partner State's NMRAs and to ensure that variations to the vaccine do not give rise to public health concerns.

1.1 OBJECTIVES

This guideline is intended to:

(a) assist applicants with the classification of changes made to a registered vaccine;

(b) guide the technical and other general data requirements to support changes that may potentially impact the quality, safety, and efficacy attributes of a registered vaccine.

2.O APPLICATION FOR VARIATION OF A REGISTERED MEDICINAL PRODUCT

All applications for variation to a registered vaccine shall be made according to requirements stipulated in this Guideline and clearly outlined in the Variation application form (refer to the variation application form for Registered products)

2.1 PAYMENT OF FEES

Every application shall be accompanied by requisite fees at the time of application. Any application that will not be accompanied by requisite fees will not be accepted (PSURs are exempted).
Mode of Payment: Payments by crossed or bankers' cheque shall be made payable to PHARMACY AND POISONS BOARD.

3.0 GENERAL GUIDANCE

Whenever vaccines have been registered based on approval by a stringent regulatory authority (SRA) (innovator products or generic products) or WHO prequalification, subsequent applications for variations should also be approved by the same SRA and WHO PQP, and EAC procedure, PPB shall be notified of the approval of the changes and the applicant shall submit proof of acceptance of such changes from the respective agency, if applicable.

When a variation leads to a revision of the summary of product characteristics (SmPC), patient information leaflet (PIL), labelling and packaging leaflet, updated product information has to be submitted as part of the application.

For variations that require the generation of stability data on the drug substance or drug product, the stability studies required, including commitment batches should always be continued to cover the currently accepted shelf-life period. PPB should be informed immediately if any problems with the stability appear during storage, e.g. if the outside specification or potentially outside specification data are observed.

Applicants should be aware that some variations may require the submission of additional consequential variations. Therefore, for any given change the applicant should consider if one or more variations may be required to be submitted.

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the substance of the variation submitted.

For this document 'test procedure' has the same meaning as 'analytical procedure' and 'limits' have the same meaning as 'acceptance criteria. 'Specification parameter' means the quality attribute for which a test procedure and limits are set, e.g. assay, identity, and water content. The addition or deletion of a specification parameter, therefore, includes its corresponding test method and limits.

4.0 Guidance for implementation

4.1 Reporting types for quality changes

The definitions outlined in the following reporting types are intended to guide the classification of administrative, quality, safety, and efficacy-related changes. Specific change examples are provided in this guideline. However, it is to be noted that a change not cited in this guideline, should be decided on a case-by-case basis. Whenever the applicant is unclear about the classification of a particular change, EAC Partner State's NMRAs should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety, and efficacy of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure.

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

Applicants are also advised to exercise caution whenever several changes to the same finished product are envisaged. Although individual changes may be classified as a particular reporting type, classification at a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact EAC Partner State's NMRAs before submission of the variation application to obtain guidance in classifying such changes.

4.1.1. Notifications (N)

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy, and quality of the vaccine. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by EAC Partner State's NMRAs within two (2) months of the date of acknowledgment of receipt of the application.

It should be highlighted that a notification may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

4.1.2. Minor variation (Vmin)

Minor variations are changes that may have minor effects on the overall safety, efficacy, and quality of the vaccine. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

Such variations can be implemented if no objection letter has been issued within four (4) months. Should questions arise during the specified period; the change can only be implemented on receipt of a letter of acceptance from EAC Partner State's NMRAs.

4.1.3. Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy, and quality of the vaccine. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by EAC Partner State's NMRAs is required before the changes can be implemented. A letter of acceptance will be issued for all major variations when the variation is considered acceptable. These variations will be handled within a period of six (6) months.

If the EAC Partner State's NMRAs consider that a change(s) has been inappropriately classified, the manufacturer shall be notified accordingly.

4.1.4. New applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. For these cases, a new dossier must be submitted. Examples of such changes are listed in Appendix 2.

4.1.5. Labelling information

For any change to labelling information (SmPC, PIL, labels) not covered by the categories described in this document, under section 4.4.2 below, EAC Partner State's NMRAs must be notified and submission of the revised labelling information is expected as per the EAC Guidelines on Submission for Documentation of Marketing Authorization of Human Vaccines.

Changes in primary and secondary pack label design, and/or package insert design shall be applied as notifications. The applicant shall be expected to submit revised pack label artwork and two (2) commercial samples of the product.

4.2 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (N, or Vmin) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a major variation.

In some circumstances, Vmaj categories have been specifically stated for a given variation. This has been done to indicate to applicants what documents should be considered to be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes, it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy, or quality of the vaccine.

4.3 Documentation required

For each variation, certain documents have been identified as supporting data. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation.

a) a variation application form (a template can be downloaded from the website). All sections of this form shall be completed and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF file, shall be provided;

b) replacement of the relevant sections of the dossier;

c) copies of SmPC, PIL, and labels, if relevant.

4.4 Reporting types for safety, efficacy, and/or product labelling information changes

After assessing the effect of a change related to clinical use or product labelling information on the safe and effective use of a vaccine, MA holders should classify this change as belonging to one of the following categories:

- a safety and efficacy change;

- a product labelling information change.

The product labelling information includes prescribing information (or package insert) for health care providers or patients, outer label (carton), and inner label (container label). Further information on each category is provided in the following sections, with examples of efficacy, safety, and product labelling information changes considered to be appropriate for each category provided in Appendix 1.

4.4.1 Safety and efficacy changes

Safety and efficacy changes are changes that have an impact on the clinical use of the vaccine in relation to safety, efficacy, dosage, and administration, and that require data from clinical studies to support the change. Safety and efficacy changes require approval before implementation.

Generally, safety and efficacy changes affect the product labelling information and have the potential to increase or decrease the exposure levels of the vaccine, either by expanding the population that is exposed or by changing dosage or dosing. These changes may relate to the clinical use of the vaccine. Therefore, all safety and efficacy changes are classified as Major variations (Vmaj). Examples of these changes are provided in Appendix 1.

The type and scope of the required supporting nonclinical and/or clinical safety and efficacy data are determined case by case based on risk-benefit considerations related to the impact of the changes, the vaccine attributes and the disease that the vaccine is designed to prevent. Other considerations include:

- robustness of the immune response elicited by the vaccine and availability of a correlate of protection (that is, data establishing a threshold of antibody needed to protect against the development of disease following exposure);
- availability of animal models;

- vaccine attributes (for example, live as opposed to inactivated vaccines).

MA holders are encouraged to consult with NMRAs on the adequacy of the clinical data needed to support a safety and efficacy change if deemed necessary.

For a change under this category, the MA holder should submit an application to the NMRA that may include the following:

- detailed description and rationale of the proposed change;
- summary of the methods used and studies performed to evaluate the effect of the change on the vaccine's safety or efficacy;
- amended product labelling information;
- clinical studies (protocol, statistical analysis plan, and clinical study report);
- clinical assay methods (including SOPs) and validations;
- the pharmacovigilance plans.

4.4.2 Product labeling information changes

Product labelling information changes are changes to the labelling items that have the potential to improve the management of risk to the population currently approved for use of the vaccine through:

- identification or characterization of any adverse event following immunization (AEFI) resulting in the addition or strengthening of risk-management measures for an adverse event identified to be consistent with a causal association to immunization with the vaccine concerned;
- identification of subgroups for which the benefit-to-risk profile of the vaccine has the potential to be less favourable;
- addition or strengthening of risk-management measures, including instructions on dosing or any other conditions of use.

Product labelling information changes require prior approval by the NMRA. Applications for product labelling information changes related to clinical use often require data from pharmacovigilance reports ("periodic safety update reports"). Changes supported by large clinical or nonclinical studies are usually not considered as product labelling information changes but as safety and efficacy changes.

For purposes of this guidance, product labelling information changes are classified as Minor variations (Vmin). Examples of these changes are provided in Appendix 1.

For a change under this category, the MA holder should submit an application to the NMRA that may include the following:

- detailed description and rationale of the proposed change
- pharmacovigilance reports and statistical analysis results
- amended product labelling information.

4.5 Application Process

Applicants are expected to apply for variations using the variation application form (Annex I) together with a cover letter signed and dated by the MAH.

5.0 Special Considerations

5.1 Adjuvants

Because adjuvants are considered to be components of vaccines, each new adjuvanted vaccine is considered to be a new entity that will require appropriate physicochemical characterization and nonclinical and clinical evaluation. It is the specific antigen-adjuvant formulation (as a whole) that is tested in nonclinical and clinical trials and which receives MA or licensure based on demonstration of safety and efficacy.

There is substantial diversity among vaccine adjuvants, antigens, and the diseases they are designed to prevent. Therefore, the supporting information needed for adjuvant-related changes will depend upon product-specific features, clinical indications , and the impact of the change. The

recommendations in WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines should be followed.

5.2 Influenza vaccines

To ensure that influenza vaccines are effective against circulating influenza viruses, WHO reviews global virological and epidemiological data twice a year, and if necessary, recommends new vaccine strain(s) by the available evidence for the northern and southern hemispheres, WHO and NMRAs recommend the use of certain vaccine virus strains based on their antigenic characteristics. Influenza vaccine viruses are usually derived from isolates obtained from laboratories in the WHO Global Influenza Surveillance and Response System.

For seasonal influenza vaccines, annual changes in the vaccine strain composition are considered to be moderate quality changes because of extensive experience with such changes and to maximize the flexibility and brevity of the review process. MA holders of approved seasonal vaccines are expected to submit a supplement for a minor quality change to support annual changes in the influenza strain composition. To allow for the timely distribution of vaccines, NMRAs should review the supplement as part of a streamlined and prompt process. The supporting quality information generally consists of: (a) information on the source of the seed viruses; (b) passage history until establishment of working seeds; (c) results of quality release tests performed on working virus seeds (including identity confirmation); and (d) specific validation data (including inactivation kinetics). Generally, stability data for antigen bulks or final drug products produced in the previous influenza season are expected to be submitted to continuously support the approved shelf-life. In addition, updated product labelling information items (package insert and inner and outer labels with relevant strain composition and formula year) should be provided.

Changes to the manufacturing processes, posology and product labelling information of influenza vaccines that are not related to the annual update should follow the normal categorization process, as described in sections 6.2 and 6.3, and should not be included in the strain change supplements to

avoid delays in the approval process. Due to time constraints related to the seasonality of influenza vaccines, changes that are not related to vaccine strain composition should be timed such that approval will allow for vaccines manufactured with the change to be distributed before the start of the influenza season.

5.3 Bridging studies

Clinical bridging studies are trials in which a parameter of interest (such as manufacturing process, formulation, or dosing schedule) is directly compared with a changed version of that parameter with respect to the effect of the change on the product's clinical performance. The comparison of immune responses and safety outcomes (for example, rates of common and serious AEFIs) is often the primary objective. If the immune response and safety profiles are similar, the safety and efficacy of the vaccine can be inferred.

In some cases, safety and efficacy data comparing the approved vaccine to the vaccine produced with the change may be required by NMRAs. The following are examples of manufacturing changes that may require clinical bridging studies:

- use of a new or re-derived antigen (that is, re-derived virus seed or bacterial cell bank) or host cell line (that is, re-derived MCB);
- new agents used for inactivation or splitting of the antigen;
- a new dosage form;
- a new formulation (for example, the amount of ingredients, adjuvants, preservatives, or reactogenic residual components from the manufacturing process).

6.0 Summary of changes

6.1 Administrative changes

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
1a	Change in the name	1	1	N

	and/or corporate address of the Marketing Authorization Holder (MAH) of the vaccine			
1b	Company sale, purchase, merger	2	1, 2, 3	N
Conditions to be fulfilled				
1) Authorization of change from the previous MAH 2) The marketing authorization holder shall remain the same legal entity				
Documentation required				
1) A formal document from a relevant official body (e.g. the national medicines regulatory authority (NMRA)) in which the new name and/or address is mentioned. 2) Approval for sale/purchase as per statutory requirements 3) Revised labelling				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
2	Change in the name and/or address of a manufacturer of the vaccine	1	1,2	N
Conditions to be fulfilled				
1) No change in the location of the manufacturing site and in the manufacturing operations.				
Documentation required				

1) Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned. 2) Two (2) commercial samples/coloured mock up samples with name and address of the current manufacturing site.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
3	Deletion of a manufacturing site or manufacturer involving:			
	production, packaging or testing of the intermediate or vaccine	1-2	1,2	N
Conditions to be fulfilled				
1) At least one other site continues to perform the same function(s) as the site(s) intended to be deleted. 2) The deletion of site is not a result of critical deficiencies in manufacturing.				
Documentation required				
1) Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application. 2) Two (2) commercial samples/coloured mock up samples of the vaccine required ONLY if deleted manufacturing site appears on registered product label				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
4	Change of Local Technical Representative (LTR)	None	1-3	Vmaj
Documentation required				

1) Letter of appointment from the product Marketing Authorization Holder 2) Letter of acceptance from the proposed LTR and a copy of termination notice of previous LTR. 3) List of affected products, including registration numbers. Affected products should appear on the current Drug Register.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
5	Change of product name (brand name)	None	1,2	Vmin
Conditions to be fulfilled				
1) Refer to EAC Guidelines on Naming of Medicinal Products				
Documentation required				
1) Revised product information 2) Approval from trademark agency within the Partner States 3) Two (2) commercial samples/ coloured mock up samples of the product				

6.2 Changes to the antigen

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
1	Change in the name of the antigen Note: This change generally applies only to influenza vaccines (see section 5.2).	None	1,2	Vmin
Documentation required				
1) Revised product labelling information 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).				

6.3 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
2	Change to an antigen manufacturing facility:			
2a	Replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen	None	1-4, 6-8	Vmaj
		1-4	2,4-8	Vmin
2b	Deletion of a manufacturing facility or manufacture of an antigen intermediate, or antigen bulk	5-6	None	N

Conditions to be fulfilled

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 minor or Immediate Notification
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).

Documentation required

1) Evidence that the facility is GMP compliant
2) Name, address and responsibility of the proposed facility
3) Process validation study reports

4) Comparability of the pre-and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
5) Justification for the classification of any manufacturing process and/or control changes as minor or Immediate Notification.
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 NMRA.
7) Comparative pre-and post-change test results for the manufacturer's characterized key stability indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life /hold-time of the antigen under its normal storage conditions and to report to the NMRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, and/or 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 NMRA.

8) Updated post approval stability protocol.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
3	Change to the antigen fermentation, viral propagation or cellular propagation process			
3a	A critical change (a change with high potential to impact the quality of the antigen or final product) (e.g. incorporation of disposable bioreactor technology)	None	1-7, 9, 11	Vmaj
3b	A change with moderate potential to impact quality of the antigen or final product (e.g. extension of the in vitro cell age beyond validated parameters)	2,4	1-6, 8, 10	Vmin
3c	A non-critical change with minimal potential to impact the quality of the antigen or final product (e.g. change in harvesting and/or pooling procedures which <u>does not</u> affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of	1-6, 9-11	1-4	N

	detection of adventitious agents, or production scale; or duplication of a fermentation train)			
4	Change to the antigen purification process involving;			
4a	A critical change (a change with high potential to impact the quality of the antigen or final product) (e.g. change that could potentially impact the viral clearance capacity of the process or the impurity profile of the antigen)	None	1,2,5-7,9,11,12	Vmaj
4b	A change with moderate potential to impact quality of the antigen or final product (e.g. change in the chemical separation method, for example ion-exchange HPLC to reverse phase HPLC)	2,4	1,2,5-7, 10,11	Vmin
4c	A non-critical change with minimal potential to impact the quality of the antigen or final product (e.g. addition of an in-line filtration step equivalent	1-5	1,2	N

	to the approved filtration step)			
5	Change in scale of the manufacturing process:			
5a	At the fermentation, viral propagation or cellular propagation stage	3-6, 11-13	2,3,5-7,9,11	Vmin
5b	At the purification stage	1,3,5,7	2,5-7,9,11	Vmin
6	Change in supplier of raw materials/reagents of biological origin (e.g. fetal calf serum, insulin, human serum albumin)	None	4,8,12,13	Vmin
		8	4,8	N
7	Change in source of raw materials/reagents of biological origin	None	4,7,12,13	Vmin
		8	4,7	N
8	Introduction of reprocessing steps	14	8,10,11,14	Vmin

Conditions to be fulfilled

1) No change in the principles of the sterilization procedures of the antigen
2) The change does not impact the viral clearance data or the chemical nature of an inactivating agent.
3) No change in the antigen specification outside of the approved limits.
4) No change in the impurity profile of the antigen outside of 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 (i.e. the change in scale is linear)
13) The change in scale involves the use of the same bioreactor (i.e. 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.

Documentation required

1) Justification for the classification of the change(s) as major, minor or immediate notification 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 non-recombinant product.
4) For antigens obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative,

country of origin of the source animals, and use and previous acceptance of the material).

5) Process validation study reports
6) Comparability of the pre-and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
7) Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre-and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NMRA.
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 NMRA.
9) Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale antigen batches produced with the proposed changes

under real-time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NMRA 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 NMRA.

10) Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least one (1) commercial-scale antigen batch produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NMRA 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 NMRA.
11) Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the final product manufactured using the post-change antigen into the stability programme.
12) Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk)

13) Information demonstrating comparability of the raw materials/reagents of both sources.

14) Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times and resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the antigen.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
9	Changes to the cell banks: Note: New cell substrates that are unrelated to the MCB or pre-MCB material generally require a new application for marketing authorization			
9a	generation of a new Master Cell Bank	1	1,2,5,7-9	Vmin
9b	generation of a new Working Cell Bank (WCB)	None	1,2	Vmin
		2-4	1,2	N
9c	Change in cell bank storage site	7	10	N
10	Changes to the seed lots: Note: New viral or bacterial seeds that are unrelated to the MSL or pre-MSL material generally require a new application for marketing authorization			
10a	generation of a new Master Seed Lot (MSL)	1	1,5-9, 11	Vmaj
10b	generation of a new Working Seed Lot (WSL)	2,3	5-9, 11	Vmin
		2-4	5-6, 11	N
10c	Generation of a new	None	5-7,11	Vmin

	Working Seed Lot (WSL) by extending the passage level of an existing WSL beyond an approved level			
10d	Change in seed lot storage site	7	10	N
11	Change in cell bank/seed lot testing site	5,7	10	N
12	Change in cell bank/seed lot qualification protocol	None	3,4	Vmin
		7	4	N
Conditions to be fulfilled				
1) The new MCB is generated from 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 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 (i.e. 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 lots have been validated.				
Documentation to be supplied				

1) Qualification of the cell bank or seed lot according to guidelines considered acceptable by the NMRA.
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 the 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 NMRA.

8) Comparative pre and post change test results for the manufacturer's characterized key stability indicating attributes with 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 NMRA 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 NMRA.
9) Update 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.

6.4 Change in equipment used

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
13	Change in equipment used in the antigen manufacturing process, such as;			
13a	Introduction of new equipment with different operating principles and different product contact material	None	1-6	Vmin

13b	Introduction of new equipment with the same operating principles and different product contact material	None	1,3-6	Vmin
13c	Introduction of new equipment with the different operating principles but the same product contact material	None	1-3, 5,6	Vmin
13d	Replacement of equipment with equivalent equipment (including filter)	None	1,5-7	N
Conditions to be fulfilled				
None				
Documentation required				
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 leachables and extractables. 5) Information on the new equipment and comparison of similarities and difference 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.				

6.5 Change in specifications for Materials

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
14	Change in specification for the materials, involving:			
14a	Raw materials/intermediates: widening of the approved specification limits for starting materials/intermediates, which may have a significant effect on the overall quality of the antigen and/or final product and are not changes to the cell banks or seed lots	None	1,3-6, 8,11	Vmin
14b	Raw materials/intermediates: narrowing of the approved specification limits for starting materials/intermediates	1-4	1,3-7	N
15	Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen, involving:			
15a	Narrowing of in-process limits	3,5,8,9	2,6	Vmin

15b	Addition of new in-process test and limits	4,5,10,11	2-6,8,10	Vmin
15c	Deletion of a non-significant in-process test	4-6	2,6,9	Vmin
15d	Widening of the approved in-process limits	None	2-6,8,10,11	Vmin
		3-5	2,6,8,10,11	Vmin
15e	Deletion of an in-process test which may have a significant effect on the overall quality of the antigen	None	2,6,8,10	Vmin
15f	Addition or replacement of an in-process test as a result of a safety or quality issue	None	2-6,8,10	Vmin
16	Change in in-process controls testing site	3-5,7,8	12	N
Conditions to be fulfilled				

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 pharmacopeial microbiological methods).
Documentation to be supplied

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 result 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 NMRA.
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 NMRA.
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 NMRA 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 NMRA.

12) Evidence that the new company/facility is GMP compliant.

6.6 Control of the antigen

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
17	Change affecting the quality control (QC) (release and stability) testing of the antigen, involving:			
17a	transfer of the QC testing activities for a non-pharmacopoeia assay to a new company not approved in	1-3	1,2	N

	the current MA or licence			
17b	transfer of the QC testing activities for a pharmacopoeia assay to a new company not approved in the current MA or licence	1	1,2	N
Conditions to be fulfilled				
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.				
Documentation required				
1) Information demonstrating technology transfer qualification. 2) Evidence that the new company/facility is GMP compliant.				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
18	Change in the specification used to release the antigen, involving:			
18a	deletion of a test	None	1,5,8	Vmin
18b	addition of a test	1-3	1-3, 5	N
18c	replacement of an analytical procedure	None	1-5	Vmin
18d	change in animal species/strains for a test (for example, new	None	6,7	Vmin

	species/strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)			
18e	minor changes to an approved analytical procedure	4-7	1,4,5	N
18f	change from an in-house analytical procedure to a recognized compendial/pharmacopeial analytical procedure	4,7	1-3	N
18g	widening of an acceptance criterion	None	1,5,8	Vmin
18h	narrowing of an acceptance criterion	1,8,9,	1	N
Conditions to be fulfilled				
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 pharmacopeial requirements). 9) The analytical procedure remains the same, or changes to the analytical procedure are minor.
Documentation required
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.

6.7 Reference standards or materials

Description of change	Conditions to	Documentation	Reporting

		be fulfilled	required	type
19	Qualification of a new reference standard against a new primary international standard	None	1,2	Vmin
20	Change in the reference standard from in-house (no relationship with international standard) to pharmacopeial or international standard	None	1,2	Vmin
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	Vmin
22	Change to reference standard qualification protocol	None	3,4	Vmin

23	Extension of reference standard shelf-life	2	5	N
Conditions to be fulfilled				
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.				
Documentation required				
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.				

6.8 Container closure system

Description of change		Conditions to be fulfilled	Documentation to be supplied	Reporting type
24	Change in the primary container closure system(s) for the storage and shipment of the antigen	None	1,2,4,5	Vmin
		1	1,3,5	N
Conditions to be fulfilled				
1) The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.				
Documentation required				

1) Information on the proposed container closure system (for example, description, composition, materials of construction of primary packaging components and specification).
2) Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3) Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (for example, results of transportation or interaction studies, and extractable/leachable studies).
4) Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf life/ hold-time of the antigen under its normal storage conditions and to report to the NMRA 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 NMRA.
5) Comparative table of pre- and post-change specifications.

Description of change		Conditions to be fulfilled	Documentation to be supplied	Reporting type
25	Change in the specification of the primary container closure system for the antigen, involving:			
25a	deletion of a test	1,2	1,2	N
25b	addition of a test	3	1-3	N

25c	replacement of an analytical procedure	6,7	1-3	N
25d	minor changes to an analytical procedure	4-7	1-3	N
25e	widening of an acceptance criterion	None	1,2	Vmin
25f	Narrowing of an acceptance criterion	8	1	N

Conditions to be fulfilled

1) The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopeial 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 pharmacopeial monograph specification for the container closure component.

Documentation to be supplied

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.

6.9 Stability of the drug substance or intermediate

Description of change		Conditions to be fulfilled	Documentation required	Report-ing type
26	Change in the shelf-life/hold-time for the antigen or for a stored intermediate of the antigen, involving:			
26a	Extension	None	1-5	Vmin
		1-5	1,2,5	N
26b	reduction	None	1-5	Vmin
		6	2-4	N
Conditions to be fulfilled				
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.				
Documentation required				

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

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
27	Change in the post-approval stability protocol of the antigen, involving:			
27a	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	Vmin
		1	1,2,4-6	N
27b	addition of time point(s) into the post-approval stability protocol	None	4,6	N

27c	addition of test(s) into the post approval stability protocol	2	1,2,4,6	N
27d	deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4,6	N
27e	deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4,6	N

Conditions to be fulfilled

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.

Documentation to be supplied

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.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
28	Change in the storage conditions for the antigen, involving:			
28a	addition or change of storage condition for the antigen (for example, widening or narrowing of a temperature criterion)	None	1-4	Vmin
		1,2	1-3	N
Conditions to be fulfilled				
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.				
Documentation to be supplied				
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).				

6.10 Changes to the final product

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
29	Change in the description or composition of the final product, involving:			
29a	addition of a dosage form or	None	1-10	Vmaj

	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 NMRA for further guidance.			
29b	change in fill volume (that is, same concentration, different volume)	None	1,5,7,10	Vmaj
		1,2	1,5,7	Vmin
		1-3	5,7	N
29c	addition of a new presentation (for example, addition of a new prefilled	None	1,5,7-10	Vmaj

	syringe where the approved presentation is a vial for a vaccine in a liquid dosage form)			

Conditions to be fulfilled

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.

Documentation required

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 leachable 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 NMRA 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 NMRA.
10) Supporting clinical data or a justification for why such studies are not needed.

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

Note:

a. Change in the type/structure of a chemical adjuvant, in the type of a biological adjuvant, or 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 NMRA for further guidance.
b. For additional guidance on the required supporting data for quality changes for chemical and biological adjuvants, see recommendations for other changes to the final product, such as changes to facilities,

equipment, manufacturing process, quality control, shelf-life, and so on, as applicable

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
30	Change involving an approved chemical/synthetic adjuvant:			
30a	change in supplier of a chemical/ synthetic adjuvant	None	4,5,10,11	Vmin
		1-3	5	N
30b	change in manufacture of a chemical/synthetic adjuvant	None	3-5, 10,11	Vmin
30c	change in specification of a chemical/synthetic adjuvant (including tests and/or the analytical procedures)	None	7-11	Vmin
		1,3	7-9	Vmin
31	Change involving a biological adjuvant:			
31a	change in supplier of a biological adjuvant	None	1-7, 10-13	Vmaj
31b	change in manufacture of a biological adjuvant	None	1-7, 10-12	Vmaj
		4	1-7, 10-12	Vmin
31c	change in specification of a biological adjuvant (including tests and/or the analytical procedures)	None	6-10	Vmin
		1,3	7- 8	Vmin
Conditions to be fulfilled				

1. The specification of the adjuvant is equal to or narrower than the approved limits (that is, narrowing of acceptance criterion). 2. The adjuvant is an aluminium salt. 3. The change in specification consists of the addition of a new test or of a minor change to an analytical procedure 4. There is no change in the manufacturer and/or supplier of the adjuvant.
Documentation required
1. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, BSE/TSE risk). 2. Information on the quality and controls of the materials (for example, raw materials, starting materials) used in the manufacture of the proposed adjuvant. 3. Flow diagram of the proposed manufacturing process(es), a brief narrative description of the proposed manufacturing process(es), and information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant. 4. Process validation study reports (for example, for manufacture of the adjuvant) unless otherwise justified. 5. Description of the general properties, including stability, characteristic features and characterization data of the adjuvant, as appropriate. 6. Comparability of the pre- and post-change adjuvant with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies should be determined on a case-by case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the adjuvant, existing relevant nonclinical and clinical data, and aspects of vaccine use

7. Updated copy of the proposed specification for the adjuvant (and updated analytical procedures if applicable).
8. Copies or summaries of analytical procedures, if new analytical procedures are used.
9. Validation study reports, if new analytical procedures are used.
10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the final product with the pre-change (approved) and post-change (proposed) adjuvant, as applicable. Comparative test results for the approved adjuvant do not need to be generated concurrently; relevant historical testing results are acceptable.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NMRA 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 NMRA.
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 the final product (not diluent) should be applied.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
32	Change to the diluent, involving:			
32a	change in manufacturing process	None	1-5	Vmin
		1,3	1-4	N
32b	replacement of or addition to the source of a diluent	None	1-5	Vmin
		1-3	1-3	N
32c	change in facility used to manufacture a diluent (same company)	1,2	1,3,5	N
32d	addition of a diluent filling line	1,2,4	1,3,5	N
32e	addition of a diluent into an approved filling line	1,2	1,3,5	N
32f	deletion of a diluent	None	None	N

Conditions to be fulfilled

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 NMRA country/jurisdiction.
4. The addition of the diluent filling line is in an approved filling facility.

Documentation required

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.

6.11 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
33	Change involving a final product manufacturer/ manufacturing facility, such as:			
33a	replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)	None	1-7	Vmaj
		1-5	1-3, 5-8	Vmin
33b	replacement or addition of a secondary packaging facility, a labelling/storage facility or a distribution facility	2,3	1-3	N
33c	deletion of a final product manufacturing facility	None	None	N
Conditions to be fulfilled				

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.
Documentation required

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.
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 NMRA 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 NMRA.

8. Rationale for considering the proposed formulation/filling facility as equivalent.

6.12 Change in the final product manufacturing process

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
34	Change in the final product manufacturing process, such as:			
34a	scale-up of the manufacturing process at the formulation/filling stage	1-4	1-6	Vmin
34b	addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, and lyophilized); see change 13 above.	None	1-8	Vmin
		5	2, 7-9	N
34c	addition of a new scale bracketed by the approved scales or scale down of the manufacturing process	1-4	1,4	N
34d	addition of a new step (for example, filtration)	3	1-6	Vmin
Conditions to be fulfilled				

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).

Documentation required

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 NMRA 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 NMRA. 6. Information on leachables and extractables, as applicable. 7. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment. 8. Information demonstrating requalification of the equipment or requalification of the change. 9. Rationale for regarding the equipment as similar/comparable, as applicable.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
35	Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:			
35a	narrowing of in-process limits	2,3,7	1,5	N
35b	addition of new in-process test and limits	2,3,8,9	1-6,8	N
35c	deletion of a non-significant in-process test	2-4	1,5,7	N
35d		None	1-6, 8,9	Vmaj

	widening of the approved in-process limits	1-3	1,5,6,8,9	Vmin
35e	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	Vmaj
35f	addition or replacement of an in-process test as a result of a safety or quality issue	None	1-6,8	Vmin
36	Change in in-process controls testing site	1-3, 5,6	10	N

Conditions to be fulfilled

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 pharmacopeial microbiological methods)

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

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
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).			
37a	deletion of a test	5,8	1,3	N
37b	addition of a test	4	1-3	N
37c	replacement of an analytical procedure	1-3	1,2	N
37d	minor changes to an approved analytical procedure	None	1,2	N
37e	change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1,2	N
37f	widening of an acceptance criterion	None	1,3	Vmin
37g	narrowing of an acceptance criterion	3,4,6,7	1	N
Conditions to be fulfilled				
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 pharmacopeial 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 pharmacopeial requirements). 5. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopeial 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.
Documentation required
1. Updated excipient specification. 2. Where an in-house analytical procedure is used and a recognized compendial standard is claimed, results of an equivalency study between the in-house and compendial methods. 3. Justification of the proposed excipient specification (for example, demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the final product).

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
38	Change in the source of an excipient from a vegetable or synthetic source to a human or	None	2-7	Vmaj

	animal source that may pose a TSE or viral risk			
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	Vmin
40	Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5,6	2-7	N
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	Vmaj
		2	2-7	Vmin
		1,2	2-7	N
42		None	3-8	Vmaj

	Change in supplier for a plasma derived excipient (for example, human serum albumin)	3,4	5,6,9	Vmin
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	Vmin
		1,5,6	3	N
44	Change in excipient testing site	1	10	N
Conditions to be fulfilled				
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 approve 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 NMRA.				

4. The excipient does not influence the structure/conformation of the active ingredient.
5. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material.
6. Any new excipient does not require the assessment of viral safety data.

Documentation required

1. Declaration from the manufacturer of the excipient that the excipient is entirely of vegetable or synthetic origin.
2. Details of the source of the excipient (for example, animal species, country of origin) and the steps undertaken during processing to minimize the risk of TSE exposure
3. Information demonstrating comparability in terms of physicochemical properties, and the impurity profile of the proposed excipient compared to the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed excipient.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial-scale batches of the proposed excipient.
6. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NMRA 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 NMRA.

7. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, or BSE/TSE risk including viral safety documentation where necessary.
8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
9. Letter from the supplier certifying that no changes were made to the plasma-derived excipient compared to the currently approved corresponding medicinal product.
10. Evidence that the new company/facility is GMP compliant.

6.14 Control of the final product

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
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.			
45a	transfer of the QC testing activities for a non-pharmacopeial assay (in-house) to a new company or to a different site within the same company	None	1,2	Vmin

45b	transfer of the QC testing activities for a pharmacopeial assay to a new company	1	1,2	N
Conditions to be fulfilled				
1. The transferred QC test is not a potency assay or a bioassay.				
Documentation required				
1. Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant.				

6.15 Change in the specification used to release the final product

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
46	Change in the specification used to release the final product, involving:			
46a	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	Vmaj
46b	deletion of a test	None	2,9,10	Vmin
46c	addition of a test	1,2,9	2-4,8	N
46d	change in animal species/strains for a test (for example, new species/strains, animals of different ages, and/or new supplier where genotype of	None	5,11	Vmin

	the animal cannot be confirmed)			
46e	replacement of an analytical procedure	None	2-4,7,8	Vmin
46f	minor changes to an approved analytical procedure	3-6	3,8	N
46g	change from an in-house analytical procedure to a recognized compendial analytical procedure	3,6	2-4	N
46h	widening of an acceptance criterion	None	2,8,10	Vmin
46i	narrowing of an acceptance criterion	7-10	2	N
Conditions to be fulfilled				
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 approve acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopeial 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.

Documentation required

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).

6.15 Reference standards or materials

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
47	Qualification of a reference standard against a new primary international standard	None	1,2	Vmin
48	Change of the reference standard from in-house (no relationship with international standard) to pharmacopeial or international standard	None	1,2	Vmin
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	N
50	Change to the reference standard qualification protocol	None	3,4	Vmin
51	Extension of the shelf-life of the reference standard	2	5	N
Conditions to be fulfilled				

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.
Documentation required
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.

6.16 Container closure system

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
52	Modification of a primary container	None	1-7	Vmin

	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.	1-3	3	N
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	Vmin
54	Deletion of a container closure system Note: The NMRA should be notified of the deletion of a container closure system, and product labelling	None	1	N

	information should be updated, as appropriate.			

Conditions to be fulfilled

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).

Documentation required

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 NMRA 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 NMRA.

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

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
55	Change in the supplier for a primary container closure component, involving:			
55a	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	N
55b	deletion of a supplier	None	None	N

Conditions to be fulfilled
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.
Documentation required
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 NMRA 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 NMRA. 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.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
56	Change in the specification used to release a primary container closure component or functional secondary container closure component, involving:			
56a	deletion of a test	1,2	1,2	N
56b	addition of a test	3	1,2	N
56c	replacement of an analytical procedure	6,7	1-3	N
56d	minor changes to an analytical procedure	4-7	1-3	N
56e	widening of an acceptance criterion	None	1,2	Vmin
56f	narrowing of an acceptance criterion	8	1	N

Conditions to be fulfilled

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeia 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 pharmacopoeia monograph specifications for the container closure component.
Documentation required
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.

6.17 Stability of the Final product

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
57	Change in the shelf-life of the final product, involving:			
57a	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	Vmin
57b	reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1-5	Vmin
Conditions to be fulfilled				
None				
Documentation required				
1. Updated product labelling information, as appropriate. 2. Proposed storage conditions and shelf-life, as appropriate. 3. Updated post-approval stability protocol.				

4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing under real-time/real-temperature conditions covering the proposed shelf-life generated on at least three (3) commercial-scale batches.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
58	Change in the post-approval stability protocol of the final product, involving:			
58a	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	Vmaj
58b	addition of time point(s) into the post-approval stability protocol	None	4,6	N
58c	addition of test(s) into the post approval stability protocol	1	4,6	N
58d	deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4,6	N
58e	deletion of time point(s) from the post-approval	2	4,6	N

	stability protocol within the approved shelf-life			
58f	replacement of the sterility testing by the container/closure system integrity testing	None	1,2,4,6	Vmin
		3	4,6	N
Conditions to be fulfilled				
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.				
Documentation required				
1. Copies or summaries of analytical procedures, if new analytical procedures are used. 2. Validation study reports, if new analytical procedures are used. 3. Proposed storage conditions and or shelf-life, as appropriate. 4. Updated post-approval stability protocol and stability commitment. 5. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (for example, data showing greater reliability of the alternative test). 6. Justification of the change to the post-approval stability protocol or stability commitment.				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
59	Change in the labelled storage conditions for the final product or the diluted or reconstituted vaccine, involving:			
59a	addition or change of storage condition(s) for	None	1-4,6	Vmin

	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)			
59b	addition of a cautionary statement (for example, “Do not freeze	None	1,2,4,5	Vmin
59c	deletion of a cautionary statement (for example, “Do not freeze”)	None	1,2,4,6	Vmin
Conditions to be fulfilled				
None				
Documentation required				
1. Revised product labelling information, as applicable. 2. Proposed storage conditions and shelf-life. 3. Updated post-approval stability protocol and stability commitment. 4. Justification of the change in the labelled storage conditions/cautionary statement. 5. Results of stability testing under appropriate stability conditions covering the proposed shelf-life, generated on one (1) commercial-scale batch unless otherwise justified. 6. Results of stability testing under appropriate conditions covering the proposed shelf-life, generated on at least three (3) commercial-scale batches unless otherwise justified.				

9. Literature References

Guidelines on procedures and data requirements for changes to approved vaccines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report. Geneva, World Health Organization, 2015, Annex 4 (WHO Technical Report Series, No. 993).

EAC Guidelines for Variation of Registered medicinal products

10. REVISION HISTORY

Revision No:	Date	Author/Reviewer	Section(s) revised	Description of change
Rev.0.	19/07/2022	QAO, DPER	Second Page	Added section on Recommended citations. Included the PPB Website
				Removed section on "No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form, or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, without the prior permission in writing from the pharmacy and Poisons Board"
			Appendix 1	Addition of an introduction to the section i.e. The examples of safety and efficacy changes, and product labelling information changes given in this appendix are provided for clarification. However, such changes are not limited to those included in this appendix. They may also result in changes to the product labelling information for health care providers and patients, and inner and outer vaccine labels.
				Addition of number vii, Viii and ix) of Appendix 1(safety and Efficacy) . Addition of the note i.e. The amount of safety and efficacy data needed to support a change may vary according to the impact of the change, risk–benefit considerations and product-specific characteristics (that is, there is no "one size fits all" approach). " Addition of a note i.e. In some cases, the safety-related changes listed in the labelling section may be urgent and may require rapid implementation (for example, the addition of a contraindication or warning). To allow for the rapid processing of such requests, the supplements for these changes should be

				labelled as “Urgent product labelling information changes” and should be submitted after prior agreement between the NRA and the MA holder
			Appendix 2	Addition of number v and vi

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12.O. APPENDICES

Appendix 1

Safety, efficacy and product labelling information changes

The examples of safety and efficacy changes, and product labelling information changes given in this appendix are provided for clarification. However, such changes are not limited to those included in this appendix. They may also result in changes to the product labelling information for health care providers and patients, and inner and outer vaccine labels.

Safety and efficacy changes

For safety and efficacy change,the supplements require approval prior to implementation of the change and are generally submitted for changes related to clinical practice, safety and indication claims.

Examples of safety and efficacy changes that require data from clinical studies, post-marketing observational studies, or extensive post-marketing safety data include:

i. Change to the indication:
    a) addition of a new indication (such as prevention of a previously unspecified disease);
    b) modification of an approved indication (such as the expansion of the age of use or restriction of an indication based on clinical studies demonstrating a lack of efficacy).

ii. Change in the recommended dose and/or dosing schedule:
    a) addition of a new vaccination regimen (such as the addition of accelerated vaccination regiments);
    b) addition or modification of the existing vaccination regimen (such as the addition of a booster dose or modification of the recommended time interval for booster vaccinations).

iii. Change to add information on shedding and transmission

iv. Change to the use in specific at-risk groups (such as the addition of information on use in pregnant women or immunocompromised patients).

v. Change to add information on co-administration with other vaccines or medicines.
vi. Change in existing risk-management measures:
   a) deletion of an existing route of administration, dosage form, and/or strength due to safety reasons
   b) deletion of a contraindication (such as use in pregnant women).
vii. Any other addition or expansion of a safety claim, indication, or efficacy claim, whether explicit or implicit
viii. Identification or characterization of any adverse events
ix. The identification of subgroups, or conditions of use, for which the benefit to the risk profile of the vaccine has the potential to be favourable.

NB:The amount of safety and efficacy data needed to support a change may vary according to the impact of the change, risk–benefit considerations and product-specific characteristics (that is, there is no "one size fits all" approach).

Product labelling information changes

Examples of product labelling information changes associated with changes that have an **impact on clinical** use include:

i. The addition of an adverse event was identified as consistent with a causal association with immunization with the vaccine concerned.
ii. A change in the frequency of occurrence of a gives an adverse reaction.
iii. 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 before vaccination, specific monitoring following vaccination, and ensuring patient awareness of certain risks).
iv. Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions, and adverse reactions.

v. Revisions to the instructions for use, including dosage, administration, and preparation for administration to optimize the safe use of the vaccine.

NB: In some cases, the safety-related changes listed above may be urgent and may require rapid implementation (for example, the addition of a contraindication or warning). To allow for the rapid processing of such requests, the supplements for these changes should be labelled as "Urgent product labelling information changes" and should be submitted after prior agreement between the NRA and the MA holder

Appendix 2
Changes that make a new application necessary

These include the following:

i. Change to add new route of administration
ii. Change to add a new dosage form (such as replacement of a suspension for injection with a lyophilized cake
iii. Change to add a new strength
iv. Change to add a new delivery device (such as adding a needle-free jet injector)
v. New cell substrates that are unrelated to the MCB or pre-MCB material
vi. Change in the type/structure of a chemical adjuvant, in the type of a biological adjuvant, or a component of a biological adjuvant

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