National Agency for Food & Drug Administration & Control (NAFDAC)

Drug Registration & Regulatory Affairs (DR&R) Directorate

GUIDELINES ON VARIATIONS TO A REGISTERED VACCINE FOR HUMANS

1. Introduction

This guidance document is technically and structurally inspired by the World Health Organisation's Variation Guideline (TRS 993 Annex 4) on the details of the various categories of variations to the terms of marketing authorizations for prophylactic vaccines for humans. It is intended to provide supportive information on how to present an application to implement a change to an existing registered vaccine product in Nigeria.

An applicant is responsible for the safety, efficacy and quality of a product throughout its life-cycle. Therefore, the applicant is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the registered product.
Such changes, whether administrative or substantive, are referred to as variations and may be subject to approval by NAFDAC prior to implementation.
Technical requirements for the different types of variations are set out in these guidelines in order to facilitate the submission of appropriate documentation by applicants and their assessment by NAFDAC and to ensure that variations to prophylactic human vaccines do not result in health concerns.

1.1 Objectives

These guidelines are intended to:

- Assist applicants with the classification of changes made to the quality part of a registered prophylactic vaccine for humans;
- Provide guidance on the technical and other general data requirements to support changes to the quality attributes of the antigen, intermediate or finished product.

1.2 Scope and application

These guidelines apply to Marketing Authorization (MA) Holders intending to make changes to the quality section of the dossier as well as to the safety, efficacy and product labelling information for an antigen, intermediate or a finished vaccine product. This guidance should be read in conjunction with the NAFDAC Guidelines on Variations to a Registered Pharmaceutical Product.

This guidance document is applicable only to the manufacture and use of approved prophylactic vaccines for humans. However, the general principles set out in this document may also apply to other biological products. The applicant is requested to contact NAFDAC regarding planned variations to such products.

This document provides guidance for MA holders on the regulation of changes to the original MA dossier or product licence for an approved vaccine in terms of: (a) procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable NAFDAC to evaluate the impact of the change on the quality, safety and efficacy of the vaccine.

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 contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

2. General considerations

For each change to the original MA dossier or product licence the MA holder should decide if the information in the original MA or product licence needs to be supplemented (that is, requires the official submission of a supplement or a change application dossier to the NAFDAC) based on the guidance provided in this document. Prior to implementing the change, the MA holder should assess the effects of the change and demonstrate through appropriate studies (analytical testing, functional assays, and/or clinical or nonclinical studies) the absence of any negative effect of the change on the quality, safety and efficacy of the vaccine. A supplement requiring approval prior to implementation of a change is referred to as a prior approval supplement (PAS). In general, no change should be implemented without the approval of the NAFDAC unless otherwise indicated in this document (for example, minor quality changes).

Changes to approved vaccines are categorized on the basis of a risk analysis. When a change affects the manufacturing process, this assessment should include evaluation of the effect of the change on the quality (that is, identity, strength, purity and potency) of the final product as it may relate to the safety and/or efficacy of the vaccine. When a change affects the clinical use or product labelling information, this assessment should include evaluation of the effect of the change on the safety and efficacy of the vaccine. Changes that may potentially have a major or moderate impact require submission of a PAS to the NAFDAC. For each change, the supplement should contain information develop by the MA holder to allow the NAFDAC to assess the effects of the change.

Assessment of the extent to which the quality change (also referred to as manufacturing change) affects the quality attributes (that is identity, strength, purity and potency) of the vaccine is generally accomplished by comparing manufacturing steps and test results from in-process and release testing of pre-change and post-change processes, and determining if the test results are comparable (that is, the antigen, intermediate or final product made after the change should be shown to be comparable to and/or to meet the acceptance criteria of the final product made before the change). However, additional supporting data may be required, as noted in Appendices 1–3 below.

An MA holder making a change to an approved vaccine should also conform to other applicable laws and regulations, including good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP). MA holders should comply with relevant GMP validation and record-keeping requirements and should ensure that relevant records are readily available for examination by authorized NAFDAC personnel during inspections. For example, changes of equipment used in the manufacturing process generally require installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). This information does not need to be included in a PAS for equipment changes but is part of GMP requirements and should be available during inspections. Inspections may occur routinely, may be required before submission of a supplement for a major manufacturing change such as a move to a new facility, or may be triggered by a major manufacturing change such as a change in production capacity or filtration or purification systems.

Certain major changes, such as changes in the vaccine antigen composition (for example, addition of virus or bacterial types), use of new cell substrates (for example, use of cells unrelated to the established master cell bank (MCB) or pre-MCB material) or changes in the composition of vaccine adjuvants are generally considered to be a new product and as such require the submission of a product licence application for a new MA.

Administrative changes related to acquisitions and mergers, company names or contact information should be submitted directly to NAFDAC, when these changes affect the product labelling information, the revised labelling items should be submitted to the NAFDAC (Please see NAFDAC Guidelines on Variations to Registered Pharmaceutical Product) for guidance

If a change has been approved by another competent NRA, the approval documentation may accompany the required information to support the change, as outlined in this document.

3. Glossary

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

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:

- 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.
- 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 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.

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 propagation of cells from an MCB under defined conditions and used to initiate 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 labelling information made to an approved MA or licence by the MA holder. Also referred to as "variation" in this and other documents.

Comparability study

The activities, including study design, conducting of studies and data evaluation that 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 a 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 (form of presentation) and the form in which it is administered (form of administration). Also referred to as "pharmaceutical form" in other documents.

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 is 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.

Intermediate
A material produced during steps in the manufacture of a vaccine that 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 licence 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 NAFDAC 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 licence" or "licence" in this and other documents.

Marketing authorization application (MA application)
A formal application to the NAFDAC 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 "licence 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 licence. Also referred to as the "manufacturer" or "applicant" in this and other documents.

Product labelling information
printed materials that accompany a prescription medicine and all labelling items, namely: (a) Summary of product characteristics or package insert (an instruction circular that provides product information on indication, dosage and administration, safety and efficacy, contra-indications and warnings, along with a description of the product for health care providers).

(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
A 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 the purpose of 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 licence. 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.

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 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.

4. Reporting categories for quality changes
Based on the potential effect of the quality change (for example, manufacturing change) on the quality attributes (that is, identity, strength, purity and potency) of the vaccine, and the potential impact of this on the safety or efficacy of the vaccine, a change should be categorized and identified as:

- A major quality change
- A moderate quality change, or
- A minor quality change.

4.1 Major quality changes
Major quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have significant potential to have an impact on the quality, safety or efficacy of the vaccine. The MA holder should submit an application and receive a

notification of approval from the NAFDAC before implementing the change. For a change in this category, the application should specify the products concerned and should include a detailed description of the proposed change. Additional supporting information is needed, as noted in Appendix 2 for the antigen and in Appendix 3 for the final product, and should include information on: (a) the methods used and studies performed to evaluate the effect of the change on the product's quality attributes; (b) the data derived from those studies; (c) relevant validation protocols and results; updated product labelling information; and (e) summaries of relevant standard operating procedures (SOPs) or a list referencing previously approved relevant SOPs. In some cases, major quality changes may also require nonclinical and/ or clinical data.

4.2 Moderate quality changes

Moderate quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a moderate potential to have an impact on the quality, safety or efficacy of the vaccine. The MA holder should submit a variation application and receive a notification of approval from the NAFDAC before implementing the change. The requirements for the supplement content of the moderate quality changes are the same as for the major quality changes (see section 5.1 above). However, the amount of supporting data required will generally be less than for major changes and the review time will be shorter.

4.3 Minor quality changes

Minor quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a minimal potential to have an impact on the quality, safety or efficacy of the vaccine. The changes included in this category may be implemented by the MA holder without prior review by the NAFDAC (that is, such changes do not need to be reported to and approved by the NAFDAC). However, these changes must be retained as part of the product's record by the manufacturer or MA holder, must comply with GMP requirements and must be available for review during GMP inspections.

When a minor quality change affects the lot release specifications (for example, narrowing of a specification, or compliance with pharmacopoeia changes) and affects the quality control testing as summarized in the vaccine lot release protocol, the MA holder should inform the institution responsible for reviewing the release of vaccine lots

For each approved product, the MA holder or manufacturer should maintain a comprehensive chronological list of all quality changes, including minor quality changes that occur in all production areas. Additionally, this list should include a description of the manufacturing and quality control changes, including the manufacturing site(s) or area(s) involved, the date each change was made, and the references of relevant validations and SOPs. The data to support minor quality changes, as listed in Appendices 1 and 2, should be available to the NRA upon request or during inspections.

When minor quality changes are related to a major or moderate change, they should be described in the supplement for the major or moderate quality change.

Appendices 1 and 2 provide a comprehensive list of major, moderate and minor quality changes, and the information required to support each change. Appendix 2 includes changes to the antigen or intermediates and Appendix 3 includes changes to the final product. The quality changes listed in Appendices 1 and 2 should be reported or recorded in the appropriate categories, as recommended in this section and in the appendices. If a quality change may potentially have an

impact on the quality, safety or efficacy of the vaccine, but is not included in Appendix 1 or 2, NAFDAC may be consulted for the correct classification.

5. Reporting categories for safety, efficacy and/ or product labelling information changes

After assessing the effect of a change related to clinical use or to 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;
- An urgent product labelling information change; or
- An administrative product labelling information change (in cases where prior approval before implementation is needed).

The product labelling information includes prescribing information (or package insert) for health care providers or patients, outer label (carton), and inner label (container label). After approval, the MA holder should promptly revise all promotional and advertising items relating to the vaccine to make them consistent with implementation of the product labelling information change.

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 4.

5.1 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 submission of Variation application and approval prior to implementation.

These changes may relate to the clinical use of the vaccine, for example:

- Addition or expansion of a safety claim or efficacy claim, including expansion of the population that is exposed;
- Change in the strength or route of administration
- Change in the recommended dose and/or dosing schedule, including the addition of a booster dose;
- Co-administration with other vaccines or medicines;

- Deletion or reduction of existing risk-management measures (such as contraindications, adverse events, warnings or cautionary text/ statements in the product labelling information).

The type and scope of the required supporting nonclinical and/or clinical safety and efficacy data are determined case by case on the basis of 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 level 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 NAFDAC on the adequacy of the clinical data needed to support a safety and efficacy change if deemed necessary. Additionally, some changes such as dosage form, content of excipients or residual components, or delivery device may require clinical data as well as revision of the product labelling information. NAFDAC may also be consulted on the data required to support such changes.

For a change under this category, the MA holder should submit a supplement to the NAFDAC 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 plan.

5.2 Product labelling 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 favorable;
- Addition or strengthening of risk-management measures, including instructions on dosing or any other conditions of use.

Product labelling information changes require an application and approval prior to distribution of the product. 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 a change under this category, the MA holder should submit a variation application to the NAFDAC that may include the following:

- Detailed description and rationale of the proposed change
- Pharmacovigilance reports and statistical analysis of results
- Amended product labelling information.

5.3 Urgent product labelling information changes

Urgent product labelling information changes are changes to the labelling items that need to be implemented in an expedited manner in order to mitigate a potential risk to the population currently approved for use of the vaccine. MA holders should consult with the NAFDAC and agree on the supporting documentation required prior to this category of variation application.

5.4 Administrative product labelling information changes

Administrative product labelling information changes are changes that are not expected to affect the safe and efficacious use of the vaccine. In some cases, these changes may require reporting to the NAFDAC and receipt of approval prior to implementation (Please refer to NAFDAC Guidelines on Variations to a registered Pharmaceutical Product for guidance) in this regard.

6 Guidance for Submission of Variation Applications

Variation applications can be submitted for Minor or Major Variations.

The following steps should be followed for filling and submission of all Minor & Major Variations:

1. Applicants should download the application form: Variation Application form: 'Vaccine Variation-Application-Form_Major_Moderate.docx'
2. All relevant fields should be properly filled out with information pertaining to the product of concern. Please note that a separate application should be made for each Vaccine product.

3. The supporting documentation should be searchable pdf and in line with the CTD structure. (e.g. stability data provided in support of shelf-life extension/reduction should follow the format under 3.2.P.8.3 of the CTD).
4. The filled application form should be submitted as hard copy with one electronic copy (in searchable pdf) provided in the accompanying CD containing the supporting documentation.
5. Information on the contact person should be provided. The primary contact person should be the local representative authorized by the Vaccine manufacturer (if different from the manufacturer) for communication for this specific application. Two additional contact persons who will be copied during the course of evaluation can also be included.
6. A summary of the proposed change should be provided under section 2. Please note that for multiple variations (grouped variations), this section should be reproduced and separate summaries for each proposed variation should be provided.
7. The variation title (e.g Moderate Variation #30a – Change involving an approved chemical/synthetic adjuvant — change in supplier of a chemical synthetic adjuvant) should be provided under section 2.1.8) A summary of the status and the proposed change should be provided under section 2.2. Please note that the table provided under this section should be used.
8. Major quality changes that contain quality, safety and efficacy data (from clinical studies) and revised product labelling information, should be labelled "Major quality change and safety and efficacy change" and the results from clinical studies and revised product labelling information item should be included in the submission.
9. The reason for the proposed change should be provided under section 2.3.
10. All supporting documentation attached to the application should be indicated on the checklist provided under section 3.
11. Please note that there is no need to state the name of each document. The check boxes provided should be used.
12. Under section 4 – Declaration, all boxes should be checked and the full name and signature of the responsible officer filing the application should be provided.
13. One (1) hard copy of the application and accompanying CD containing supporting documents should be submitted to Director Registration and Regulatory Affairs Directorate.

6.1 Further Notes:

a) The supporting documents should be provided in line with the CTD structure.

b) Please ensure that a soft copy (in pdf) of the application form is saved in the CD containing supporting documentation.

c) Variation applications should be specific for one Vaccine product (i.e. separate application should be submitted for different products).

d) If a CTD dossier was not submitted during initial registration, additional documents may be required during evaluation of variation applications. This will be handled on a case by case basis.

e) Applications not meeting the submission requirements will not be accepted for processing.

6.2 Multiple changes

Multiple related changes, involving various combinations of individual changes, may be submitted in the same application. For example, a site change may also involve changes to the equipment and manufacturing process, or a vaccine component change may necessitate a change in a specification. For submissions that include multiple changes, the MA holder should clearly specify which data support each change.

Multiple major or moderate quality changes for the same vaccine may be filed in a single submission provided that the changes are related and/ or supported by the same information. Minor quality changes that were implemented previously and that are related to a moderate or major quality change should be included in the supplement for the moderate or major quality change. If the changes are related, the MA holder should indicate the association between the proposed changes. Such changes could affect both the antigen and the final product. If too many changes are filed within the same submission, or if major issues are identified with a change and extensive time would be required to review them, NAFDAC may ask the MA holder to divide the changes into separate submissions and to re-submit the file. If the recommended reporting categories for the individual changes differ, the submission will be in accordance with the most restrictive of the categories recommended for the individual changes. In the case of numerous changes of the same category, the NAFDAC may reclassify the submission to the next higher level on the basis of the potential impact of the totality of the changes on the quality, safety and efficacy of the vaccine

6.3 Production documents

Production documents (that is, executed lot records) are not required to support changes to the MA dossier or product licence. However, such documents may be requested during review and should be available to NAFDAC upon request or during inspections.

7. Special considerations

7.1 Adjuvants

Because adjuvants are components of vaccines, each new adjuvanted vaccine isconsidered 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 on the basis of 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, the clinical indications and the impact of the change.

7.3 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) in accordance with the available evidence for the northern and southern hemispheres (13, 14). WHO and NAFDAC recommend the use of certain vaccine virus strains on the basis of 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 moderate quality changes because of extensive experience with such changes and in order to maximize the flexibility and brevity of the review process. MA holders of approved seasonal vaccines are expected to submit a variation application for a moderate quality change to support annual changes in the influenza strain composition. To allow for the timely distribution of vaccines, NAFDAC will review the variation application as part of a streamlined and prompt process. The supporting quality information should 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 product 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 (13).

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 Appendices 2–4, 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 prior to the start of the influenza season.

7.4 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. 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, amount of ingredients, adjuvants, preservatives or reactogenic residual components from the manufacturing process).

Appendix 1

Changes to the antigen

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information for a vaccine antigen. The information summarized in the antigen table below provides recommendations on:

- The conditions to be fulfilled for a given change to be classified as major, moderate or minor (if any of the conditions outlined for a given change are not fulfilled, the change is automatically considered to be the next higher level of change
  – for example, if any conditions recommended for a moderate quality change are not fulfilled, the change is considered to be a major quality change);
- The supporting data for a given change, either to be submitted to the NAFDAC or maintained by the MA holder (if any of the supporting data outlined for a given change are not provided, are different or are not considered applicable then adequate scientific justification should be provided);
- The reporting category (that is, major, moderate or minor quality change).

It is important to note that the NAFDAC reserves the right to request additional information or material, as deemed appropriate, or to define conditions not specifically described in this document in order to allow for adequate assessment of the quality, safety and efficacy of a vaccine. In addition, MA holders should contact the NAFDAC if a change not included in the antigen table below has the potential to impact upon vaccine quality.

General information

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
1. Change in the name of the antigen *Note: This change generally applies only to influenza vaccines (see section 7.3).*	None	1, 2	Moderate
Conditions None			

Supporting data

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

Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
2. Change to an antigen manufacturing facility:			
a. replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen	None	1–4, 6–8	Major
	1–4	2, 4–8	Moderate
b. deletion of a manufacturing facility or manufacturer of an antigen intermediate, or antigen bulk	5, 6	None	Minor

Conditions

1. The new manufacturing facility/suite is an approved antigen manufacturing site.
2. Any changes to the manufacturing process and/or controls are considered either moderate or minor.
3. The new facility/suite is under the same quality assurance/quality control (QA/QC) oversight.
4. The proposed change does not involve additional containment requirements.
5. There should remain at least one site/manufacturer, as previously authorized, performing the same function as the one(s) to be deleted.
6. The deletion should not be due to critical deficiencies in manufacturing (such as recurrent deviations, recurrent out-of-specification events, environmental monitoring failures and so on).

Supporting data

1. Evidence that the facility is GMP compliant.
2. Name, address and responsibility of the proposed facility.
3. Process validation study reports.
4. Comparability of the pre- and post-change antigen with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
5. Justification for the classification of any manufacturing process and/or control changes as moderate or minor.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-

change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches,

and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.

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

	Description of change	Conditions to be fulfilled	Supporting data	Reporting category
3.	**Change to the antigen fermentation, viral propagation or cellular propagation process:**			
a.	a.critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, incorporation of disposable bioreactor technology	None	1–7, 9, 11	Major
	b. a change with moderate potential quality of antigen or final product (for example, extension of the invitro cell age beyond validated parameters	2, 4	1–6, 8, 10	Moderate
	c. a noncritical change with minimal potential to have an impact on the quality of the antigen or final product (for example, a change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of detection of adventitious agents or production scale; or duplication of a fermentation train)	1–6, 9–11	1–4	Minor

Table continued

Description of change	Conditions to befulfilled	Supporting data	Reporting category
4. Change to the antigen Purification involving:			
a. a critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, a change that could potentially have an impact on the viral clearance capacity of the process or the impurity profile of the antigen)	None	1, 2, 5–7, 9, 11, 12	Major
b. a change with moderate potential to have an impact on the quality of the antigen or final product (for example, a change in the chemical separation method, such as from ion-exchange HPLC to reverse-phase HPLC)	2, 4	1, 2, 5–7, 10, 11	Moderate
c. a noncritical change with minimal potential to have animpact on the quality of the antigen or final product (for example, addition of an in-line filtration step equivalent to the approved filtration step)	1–5	1, 2	Minor
5. Change in scale of the manufacturing process:			
a. at the fermentation, viral propagation or cellular propagation stage	3–6, 11–13	2, 3, 5–7, 9, 11	Moderate
b. at the purification stage	1, 3, 5, 7	2, 5–7, 9, 11	Moderate
6. Change in supplier of raw materials of biological origin (for example fetal calf serum, example, fetal calf serum, human serum albumin trypsin)	None 8	4, 8, 12, 13 4, 8	Moderate Minor

7. Change in source of raw materials of biologic origin	None	4, 7, 12, 13	Moderate
	8	4, 7	Minor
8. Introduction of reprocessing steps	14	8, 10, 11, 14	Moderate

Conditions

1. No change in the principle of the sterilization procedures of the antigen.
2. The change does not have an impact on the viral clearance data or the chemical nature of an inactivating agent.
3. No change in the antigen specification outside the approved limits.
4. No change in the impurity profile of the antigen outside the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The change in scale is linear with respect to the proportionality of production parameters and materials.
8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).
9. The new fermentation train is identical to the approved fermentation train(s).
10. No change in the approved in vitro cell age.
11. The change is not expected to have an impact on the quality, safety or efficacy of thefinal product.
12. No change in the proportionality of the raw materials (that is, the change in scale is linear).
13. The change in scale involves the use of the same bioreactor (that is, it does not involve the use of a larger bioreactor).
14. The need for reprocessing is not due to recurrent deviations from the validated processand the root cause triggering reprocessing is identified.

Supporting data

1. Justification for the classification of the change(s) as critical, moderate or noncritical as this relates to the impact on the quality of the antigen.

2. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).

3. If the change results in an increase in the number of population doublings or sub cultivations, information on the characterization and testing of the post-productioncell 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).

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 agreedby the NRA.

8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and should be reported by the MA holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.

9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability 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 NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

10. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least one (1) commercial-scale antigen batch produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated

concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the final product manufactured using the post-change antigen into the stability 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) (5).

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

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
9. Change to the cell banks:	2, 4	1, 2, 5–7,	Moderate
Note: New cell substrates that are unrelated to the licensed master cell bank (MCB) or pre-MCB material generally require a new application for MA or licence application.			
a. generation of a new MCB	1	1, 2, 5, 7–9	Moderate
b. generation of a new working cell bank (WCB)	None	1, 2	Moderate
	2–4	1, 2	Minor
c. change in cell bank storage site	7	10	Minor
10. Change to the seed lots:			
Note: New viral or bacterial seeds that are unrelated to the master seed lot (MSL) or pre-MSL material generally require a new application for MA or licence application.			
a. generation of a new MSL	1	1, 5–9, 11	Major
b. generation of a new working seed lot (WSL)	2,3	5–9,11	Moderate
	2–4	5–6	Minor

c. generation of a new WSL by extending the passage level of an existing WSL beyond an approved level	None	5–7, 11	Moderate
d. change in seed lot storage site	7	10	Minor
11. Change in cell bank/seed lot testing/storage site	5, 7	10	Minor
12. Change in cell bank/seed lot qualification protocol	None	3, 4	Moderate
	6	4	Minor

Conditions

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

Supporting data

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

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

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
13. Change in equipment used in the antigen manufacturing process, such as:			
a. introduction of new equipment with different operating principles and different product contact material	None	1–6	Moderate
b. introduction of new equipment with the same operating principles but different product contact material	None	1, 3–6	Moderate

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

Conditions

None

Supporting data

1. Information on the in-process control testing.
2. Process validation study reports.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the antigen produced with the approved and proposed product contact equipment/ material. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action).
4. Information on leachables and extractables.
5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
6. Information demonstrating requalification of the equipment or requalification of the change.
7. Rationale for regarding the equipment as similar/comparable, as applicable.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
14. Change in specification for the materials, involving:			
a. raw materials/intermediates: widening of the approved specification limits for starting materials/intermediates, which may have a significant effect on the overall quality of the antigen and/or final product and are not changes to the cell banks or seed lots	None	1, 3–6, 8, 11	Moderate
b. raw materials/intermediates: narrowing of the approved specification limits for starting materials/intermediates	1–4	1, 3–7	Minor

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
15. Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen, involving:			
a. narrowing of in-process limits	3, 5, 8, 9	2, 6	Minor
b. addition of new in-process test and limits	4, 5, 10, 11	2–6, 8, 10	Minor
c. deletion of a non-significant in-process test	4–6	2, 6, 9	Minor
d. widening of the approved in-process limits	None	2–6, 8, 10, 11	Moderate
	3–5	2, 6, 8, 10, 11	Minor
e. deletion of an in-process test which may have a significant effect on the overall quality of the antigen	None	2, 6, 8, 10	Moderate
f. addition or replacement of an in-process test because of a safety or quality issue	None	2–6, 8, 10	Moderate
16. Change in in-process controls testing site	3–5, 7, 8	12	Minor

Conditions

1. The change in specification for the materials is within the approved limits.
2. The grade of the materials is the same or is of higher quality, where appropriate.
3. No change in the antigen specification outside the approved limits.
4. No change in the impurity profile of the antigen outside the approved limits
5. The change is not necessitated by recurring events arising during manufacture or becauseof stability concerns.
6. The test does not concern a critical attribute (for example, content, impurity, any critical physical characteristics or microbial purity).
7. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
8. No change in the in-process controls outside the approved limits.
9. The test procedure remains the same, or changes in the test procedure are minor.
10. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

11. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).

Supporting data

1. Revised information on the quality and controls of the materials (for example, raw materials, starting materials, solvents, reagents and catalysts) used in the manufacture of the post-change antigen.
2. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen.
3. Updated antigen specification, if changed.
4. Copies or summaries of analytical procedures if new analytical procedures are used.
5. Validation study reports if new analytical procedures are used.
6. Comparative table or description, where applicable, of pre- and post-change in-process tests/limits.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
9. Justification/risk assessment showing that the attribute is non-significant.
10. Justification for the new in-process test and limits.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/ hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing,

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

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

Control of antigen

Description of change	Conditions to befulfilled	Supporting data	Reporting category
17. Change affecting the quality control (QC) (release and stability) testing of the antigen, involving:			
a. transfer of the QC testing activities for a non-pharmacopoeia assay to a new company not approved inthe current MA or licence	1–3	1, 2	Minor
b. 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	Minor

Conditions

1. The transferred QC test is not a potency assay (for example, the test may be a bioassay such as an endotoxin assay or sterility assay).
2. No changes to the test method.
3. Transfer within a site approved in the current MA for the performance of other tests.

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
18. Change in the specification used to release the antigen, involving:			
a. deletion of a test	None	1, 5, 8	Moderate
b. addition of a test	1–3	1–3, 5	Minor
c. replacement of an analytical procedure	None	1–5	Moderate
d. change in animal species/strains for a test (for example, new species/strains, animals of different	None	6, 7	Moderate

	age, new supplier where genotype of the animal cannot be confirmed)			
e.	minor changes to an approved analytical procedure	4–7	1, 4, 5	Minor
f.	change from an in-house analytical procedure to a recognized compendial/pharmacopoeia analytical procedure	4, 7	1–3	Minor
g.	widening of an acceptance criterion	None	1, 5, 8	Moderate
h.	narrowing of an acceptance criterion	1, 8, 9	1	Minor

Conditions

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

Supporting data

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

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

Reference standards or materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
19. Qualification of a new reference standard against a new primary international standard	None	1, 2	Moderate
20. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	Moderate
21. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	1, 2	Minor
22. Change to reference standard qualification protocol	None	3, 4	Moderate
23. Extension of reference standard shelf-life	2	5	Minor

Conditions

1. Qualification of the new reference standard is according to an approved protocol.
2. The extension of the shelf-life is according to an approved protocol.

Supporting data

1. Justification for the change in reference standard.

2. Information demonstrating qualification of the proposed reference standards or materials (for example, source, characterization, certificate of analysis and comparability data).
3. Justification of the change to the reference standard qualification protocol.
4. Updated reference standard qualification protocol.
5. Summary of stability testing and results to support the extension of reference standard shelf-life.

Container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
24. Change in the primary container closure system(s) for the storage and shipment of the antigen	None	1, 2, 4, 5	Moderate
	1	1, 3, 5	Minor

Conditions

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.

Supporting data

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

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
25. Change in the specification of the primary container closure system for the antigen, involving:			
a. deletion of a test	1, 2	1, 2	Minor
b. addition of a test	3	1–3	Minor
c. replacement of an analytical procedure	6, 7	1–3	Minor
d. minor changes to an analytical procedure	4–7	1–3	Minor
e. widening of an acceptance criterion	None	1, 2	Moderate
f. narrowing of an acceptance criterion	8	1	Minor

Conditions

1. The deleted test has been demonstrated to be redundant compared tothe remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the antigen.
3. The change is not necessitated by recurring events arising duringmanufacture or because of stability concerns.
4. There is no change in the acceptance criteria outside the approved limits.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect a new pharmacopoeial monograph specification for the container closure component.

Supporting data

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

Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
26. Change in the shelf-life/hold-time for the antigen or for a stored intermediate of , the involving:			
a. extension	None	1–5	Moderate
	1–5	1, 2, 5	Minor
b. reduction	None	1–5	Moderate
	6	2–4	Minor

Conditions

1. No changes to the container closure system in direct contact with the antigen with the potential of impact on the antigen, or to the recommended storage conditions of the antigen.
2. The approved shelf-life is at least 24 months.
3. Full long-term stability data are available covering the proposed shelf-life and are based on stability data generated on at least three (3) commercial-scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes were not observed in the stability data.
6. The reduction in the shelf-life is not necessitated by recurring events arising during manufacture or because of stability concerns. Note: Problems arising during manufacturing or stability concerns should be reported for evaluation.

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
27. Change in the post-approval protocol stability of the antigen, involving			
a. significant change to the post approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature	None	1–6 1, 2, 4–6	Moderate minor
b. addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c. addition of test(s) into the post-approval stability protocol	2	1, 2, 4, 6	Minor
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 6	Minor

Conditions

1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
3. The approved antigen shelf-life is at least 24 months.

Supporting data

1. Copies or summaries of analytical procedures, if new analytical procedures are used.
2. Validation study reports, if new analytical procedures are used.
3. Proposed storage conditions and/or shelf-life, as appropriate.
4. Updated post-approval stability protocol and stability commitment.
5. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (for example, data showing greater reliability of the alternative test).
6. Justification for the change to the post-approval stability protocol.

Description of change	Conditions to befulfilled	Supporting data	Reporting category
28. Change in the storage conditions for the antigen, involving:			
a. addition or change of storage	None	1–4	Moderate
condition for the antigen (for example, widening or narrowing of a temperature criterion)	1, 2	1–3	Minor

Conditions

1. The change is not necessitated by recurring events arising during manufacture or becauseof stability concerns.
2. The change consists in the narrowing of a temperature criterion within the approved ranges.

Supporting data

1. Proposed storage conditions and shelf-life.
2. Updated post-approval stability protocol and stability commitment.
3. Justification of the change in the labelled storage conditions/cautionary statement.
4. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches)

Appendix 2

Changes to the final product

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information of the final product.

Description and composition of the final product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
29. Change in the description or composition of the final product, involving:			
a. addition of a dosage form or change in the formulation (for example, lyophilized powder to liquid, change in the amount of excipient or new diluent for lyophilized product)	None	1	New application /extension application
b. change in fill volume (that is, same concentration, different volume)	None	1	New application/ extension application
	1–3	3, 4	Minor
	1,2	2-4	Moderate
c. addition of a new presentation (for example, addition of a new pre-filled syringe where the approved presentation is a vial for a vaccine in a liquid dosage form)	None	1	New application/ extension application

Conditions

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

Supporting data

1. Documents in fulfilment of the requirements outlined in the NAFDAC Guidelines for the Registration of Pharmaceutical Products for Human Use.
2. Revised final product labelling information (as applicable).
3. Information on the batch formula, manufacturing process and process controls, control of critical steps and intermediates, and process validation study reports.
4. 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.
5. Information on the batch formula, manufacturing process and process controls, control of critical steps and intermediates, and process validation study reports.
6. Control of excipients, if new excipients are proposed (for example, specification).
7. Information on specification, analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three (3) consecutive commercial-scale batches should be provided). Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
8. Information on the container closure system and leachables and extractables, if any of the components have changed (for example, description, materials of construction and summary of specification).
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Supporting clinical data or a justification for why such studies are not needed

Description and composition of the final product:

change to an adjuvant

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
30. Change involving an approved chemical/synthetic adjuvant:			
a. change in supplier of a chemical/ synthetic adjuvant	None	4, 5, 10, 11	Moderate
	1–3	5	Minor
b. change in manufacture of a chemical/synthetic adjuvant	None	3–5, 10, 11	Moderate
c. change in specification of a chemical/synthetic adjuvant (including tests and/or the analytical procedures)	None	7–11	Moderate
	1, 3	7–9	Minor
31. Change involving a biological adjuvant:			
a. change in supplier of a biological adjuvant	None	1–7, 10–13	Major
b. change in manufacture of a biological adjuvant	None	1–7, 10–12	Major
	4	1–7, 10–12	Moderate
c. change in specification of a biological adjuvant (including tests and/or the analytical procedures)	None	6–10	Moderate
	1, 3	7–8	Minor

Conditions

1. The specification of the adjuvant is equal to or narrower than the approved limits (that is, narrowing of acceptance criterion).
2. The adjuvant is an aluminium salt.
3. The change in specification consists of the addition of a new test or of a minor change to an analytical procedure.
4. There is no change in the manufacturer and/or supplier of the adjuvant.

Supporting data

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

Description and composition of the final product: change to a diluent

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
32. Change to the diluent, involving:			
a. change in manufacturing process	None	1–5	Moderate
	1, 3	1–4	Minor
b. replacement of or addition to the source of a diluent	None	1–5	Moderate
	1–3	1–3	Minor
c. change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5	Minor
d. addition of a diluent filling line	1, 2, 4	1, 3, 5	Minor
e. addition of a diluent into an approved filling line	1, 2	1, 3, 5	Minor
f. deletion of a diluent	None	None	Minor

Conditions

1. The diluent is water for injection or a salt solution (including buffered salt solutions) that is, it does not include an ingredient with a functional activity (such as a preservative) and there is no change to its composition.
2. After reconstitution, there is no change in the final product specification outside the approved limits.
3. The proposed diluent is commercially available in the NRA country/jurisdiction.
4. The addition of the diluent filling line is in an approved filling facility.

Supporting data

1. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
2. Updated copy of the proposed specification for the diluent.
3. Description of the batches and summary of results as quantitative data, in acomparative 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.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
33. Change involving a final product manufacturer/manufacturing facility, such as:			
a. replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)	None 1–5	1–7 1–3, 5–8	Major Moderate
b. replacement or addition of a secondary packaging facility, a labelling/storage facility or a distribution facility	2, 3	1–3	Minor
c. deletion of a final product manufacturing facility	None	None	Minor

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
2. There is no change in the composition, manufacturing process and final product specification.
3. There is no change in the container/closure system and storage conditions.
4. The same validated manufacturing process is used.
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the products already approved at the site, and also uses the same filling process/equipment.

Supporting data

1. Name, address and responsibility of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP compliant.
3. Confirmation that the manufacturing process description of the final product has not changed as a result of the submission (other than the change in facility), or revised description of the manufacturing process.
4. Comparative description of the manufacturing process if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
5. Process validation study reports. The data should include transport between sites, if relevant.
6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable.

Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified

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

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

Conditions

1. The proposed scale uses similar/comparable equipment to the approved equipment. Note: Change in equipment size is not considered as using similar/ comparable equipment.
2. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch size (for example, the

same formulation, controls and SOPs are utilized).

3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the final product.
5. Replacement of equipment with equivalent equipment; the change is considered "like for like" (that is, in terms of product contact material, equipment size and operating principles).

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
35. Change in the controls (in-process tests and/or acceptance criteria) applied during the, manufacturing process or on intermediate, such as:			
a. narrowing of in-process limits	2, 3, 7	1, 5	Minor

Table continued

b. addition of new in-process test and limits	2, 3, 8, 9	1–6, 8	Minor
c. deletion of a non-significant in-process test	2–4	1, 5, 7	Minor
d. widening of the approved in-process limits	None	1–6, 8, 9	Major
	1–3	1, 5, 6, 8, 9	Moderate
e. deletion of an in-process test which may have a significant effect on the overall quality of the final Product	None	1, 5, 6, 8	Major
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	1–6, 8	Moderate
36. Change in in-process controls testing site	1–3, 5, 6	10	Minor

Conditions

1. No change in final product specification outside the approved limits.
2. No change in the impurity profile of the final product outside the approved limits.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. The test does not concern a critical attribute (for example, content, impurities, any critical physical characteristics or microbialpurity).
5. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
6. No change in the in-process control limits outside the approved limits.
7. The test procedure remains the same, or changes in the test procedure are minor.
8. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
9. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)

Supporting data

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen.
2. Updated final product specification if changed.
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Validation study reports, if new analytical procedures are used.

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

Description of change	Conditions to befulfilled	Supporting data	Reporting category
37. Change in the specification used to release the excipient, involving: Note: This change excludes adjuvants. See adjuvant-specific changes above for details (changes 30 and 31).			
a. deletion of a test	5, 8	1, 3	Minor
b. addition of a test	4	1–3	Minor
c. replacement of an analytical Procedure	1–3	1, 2	Minor
d. minor changes to an approved analytical procedure	None	1, 2	Minor
e. change from an in-house analytical procedure to a recognized compendial analytical Procedure	None	1, 2	Minor

Table continued

f.	widening of an acceptance Criterion	None	1, 3	Moderate
g.	narrowing of an acceptance Criterion	3, 4, 6, 7	1	Minor

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient.
4. Acceptance criteria for residual solvents are within recognized or approvedacceptance limits (for example, within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements).
5. The deleted test has been demonstrated to be redundant compared tothe remaining tests or is no longer a pharmacopoeial requirement.
6. The analytical procedure remains the same, or changes in the test procedure are minor.
7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity or change in total impurity limits).
8. An alternative test analytical procedure is already authorized for the specification attribute/test and this procedure has not been added through a minor change submission.

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
38. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk	None	2–7	Major
39. Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source	None	1, 3, 5, 6	Moderate
40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5, 6	2–7	Minor
41. Change in manufacture of a biological excipient	None	2–7	Major
Note: This change excludes. Biological adjuvants; see adjuvant-specific changes above for details (changes 30 and 31)	2	2–7	Moderate
	1, 2	2–7	Minor
42. Change in supplier for a plasma-derived excipient (for example, human serum albumin)	None	3–8	Major
	3, 4	5, 6, 9	Moderate
43. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient) Note: This change excludes adjuvants; see adjuvant-specific changesabove for details (changes 30 and 31).	None	2, 3, 5–7	Moderate
	1, 5, 6	3	Minor

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
44. Change in excipient testing site	1	10	Minor

Conditions

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

Supporting data

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

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

Control of the final product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
45. Change affecting the QC testing of the final product (release and stability), involving:			
Note: Transfer of testing to a different facility within a GMP-approved Note: Transfer of testing to a different facility within a GMP-approved changes above for details (changes 30 and 31).			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company or to a different site within the same Company	None	1, 2	Moderate
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company	1	1, 2	Minor

Conditions

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

Supporting data

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

Description of change	Conditions to befulfilled	Supporting data	Reporting category
46. Change in the specification used to release final product, involving:			
a. for products or components subject to terminal sterilization by heat (for example, diluent for reconstitution of lyophilized vaccines), replacing the sterility test with process parametric Release	None	1, 2, 6, 8, 10	Major

Table continued

b. deletion of a test	None	2, 9, 10	Moderate
c. addition of a test	1, 2, 9	2–4, 8	Minor
d. change in animal species/strains for a test (for example, new species/strains, animals of different ages, and/or new supplier where genotype of the animal cannot be confirmed)	None	5, 11	Moderate
e. replacement of an analytical Procedure	None	2–4, 7, 8	Moderate
f. minor changes to an approved analytical procedure	3–6	3, 8	Minor
g. change from an in-house analytical procedure to a recognized compendial analytical Procedure	3, 6	2–4	Minor
h. widening of an acceptance Criterion	None	2, 8, 10	Moderate
i. narrowing of an acceptance Criterion	7–10	2	Minor

Conditions

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

Supporting data

1. Process validation study reports on the proposed final product.
2. Updated copy of the proposed final product specification.
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Validation study reports, if new analytical procedures are used.
5. Data demonstrating that the change in animals gives results comparable to those obtained using the approved animals.
6. Description of the batches and summary of results as quantitative data for a sufficient number of batches to support the process parametric release.
7. 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. 8. Justification for the change to the analytical procedure (for example, demonstration of the suitability of the analytical procedure in monitoring the final product, including the degradation products) or for the change to the specification (for example, demonstration of the suitability of the revised acceptance criterion in controlling the final product).
9. Justification for the deletion of the test (for example, demonstration of the suitability of the revised specification in controlling the final product).
10. Declaration/evidence that consistency of quality and of the production process is maintained. 11. Copies of relevant certificates of fitness for use (for example, veterinary certificate)

Reference standards or materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
47. Qualification of a reference standard against a new primary international standard	None	1, 2	Moderate
48. Change of the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international Standard	None	1, 2	Moderate
49. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	2	Minor

50. Change to the reference standard qualification protocol	None	3, 4	Moderate
51. Extension of the shelf-life of the reference standard	2	5	Minor

Conditions

1. The qualification of a new standard is carried out in accordance with an approved protocol.
2. The extension of the shelf-life of the reference standard is carried out in accordance with an approved protocol.

Supporting data

1. Revised product labelling to reflect the change in reference standard (as applicable).
2. Qualification data of the proposed reference standards or materials (for example, source, characterization and certificate of analysis).
3. Justification of the change to the reference standard qualification protocol.
4. Updated reference standard qualification protocol.
5. Summary of stability testing and results or retest data to support the extension of the reference standard shelf-life.

Container closure system

Description of change	Conditions to befulfilled	Supporting data	Reporting category
52. Modification of a primary container closure system (for example, new coating, adhesive stopper or type of glass) Note: The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is onlya vial) is considered a change in presentation; see change 29.c above.	None 1–3	1–7 3	Moderate Minor
53. Change from a reusable container to a disposable container with no changes in product contact material (for example, change from reusable pen to disposable pen)	None	1, 3, 6	Moderate
54. Deletion of a container closure System Note: NAFDAC should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate	None	1	Minor

Conditions

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.
3. The change is made only to improve the quality of the container and does not modify the product contact material (for example, increased thickness of the glass vial without changing interior dimensions).

Supporting data

1. Revised product labelling information, as appropriate.
2. For sterile products, process validation study reports, or providing equivalency rationale. For a secondary functional container closure system, validation testing report.
3. Information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary/secondary packaging components, performance specification).
4. Results demonstrating protection against leakage, no leaching of undesirable substance and compatibility with the product, and results from the toxicity and biological reactivity tests.

5. Summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.

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

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
55. Change in the supplier for a primary container closure component, involving:			
a. replacement or addition of a Supplier Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data such as is shown for change 52 above.	1, 2	4, 5	Minor
b. deletion of a supplier	None	None	Minor

Conditions

1. No change in the type of container closure, materials of construction, shape and dimensions, or in the sterilization process for a sterile container closure component.

2. No change in the specification of the container closure component outside the approved limits.

Supporting data

1. Information on the supplier and make of the proposed container closure system (for example, certificate of analysis, description, materials of construction of primary packaging components, specification).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
5. Letter from the MA holder certifying that there are no changes to the container closure system.
6. Certificate of analysis for the container provided by the new supplier and comparison with the certificate of analysis for the approved container.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
56. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving			
a. deletion of a test	1, 2	1, 2	Minor
b. addition of a test	3	1, 2	Minor
c. replacement of an analytical Procedure	6, 7	1–3	Minor
d. minor changes to an analytical Procedure	4–7	1–3	Minor
e. widening of an acceptance criterion	None	1, 2	Moderate

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f. narrowing of an acceptance Criterion	8	1	Minor

Conditions

1. The deleted test has been demonstrated to be redundant compared tothe remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the final product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. There is no change in the acceptance criteria outside the approved limits.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the container closure component.

Supporting data

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

Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
57. Change in the shelf-life of the final final product involving:			
a. extension (includes extension of shelf-life of the final product as packaged for sale, and hold-time after opening and after dilution or reconstitution)	None	1–5	Moderate
b. reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1–5	Moderate

Conditions

None

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
58. Change in the post-approval stability protocol of the final product, involving:			
a. major change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage Temperature	None	1–6	Moderate
b. addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c. addition of test(s) into the post-approval stability protocol	1	4, 6	Minor
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 6	Minor
f. replacement of the sterility testing by the container/closure system integrity testing	None 3	1, 2, 4, 6 4, 6	Moderate Minor

Conditions

1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities.
2. The approved shelf-life of the final product is at least 24 months.
3. The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application.

Supporting data

1. Copies or summaries of analytical procedures, if new analytical procedures are used.
2. Validation study reports, if new analytical procedures are used.
3. Proposed storage conditions and or shelf-life, as appropriate.
4. Updated post-approval stability protocol and stability commitment.
5. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (for example, data showing greater reliability of the alternative test).
6. Justification of the change to the post-approval stability protocol or stability commitment.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
59. Change in the labelled storage conditions for the final Product or the diluted or reconstituted vaccine, involving:			
a. addition or change of storage condition(s) for the final product, or for diluted or reconstituted vaccine (for example, widening or narrowing of a temperature criterion, or addition of or change to controlled temperature chain conditions)	None	1–4, 6	Moderate
b. addition of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 5	Moderate
c. deletion of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 6	Moderate

Conditions

None

Supporting data

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

Appendix 3

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.

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). This appendix therefore provides a list of examples of changes in the various categories rather than a detailed table linking each change with the data required to support that change (as provided in Appendices 1 and 2 for quality changes). MA holders or applicants are encouraged to contact the NAFDAC for guidance on the data needed to support major changes if deemed necessary.

Safety and efficacy changes

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

In some cases, safety and efficacy data comparing the approved clinical use (for example, indications or dosing regimens) of a vaccine with a new one may be required. Such studies, often referred to as clinical bridging studies, are trials in which a parameter of interest (such as formulation, dosing schedule or population group) is directly compared with a changed version of that parameter to assess the effect of the change on the product's clinical performance. Comparisons of immune responses and safety outcomes (for example, rates of common and serious AEFIs) are often the primary objectives. If the immune response and safety profiles are non-inferior, then the efficacy and safety of the vaccine can be inferred.

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

- 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 expansion of the age of use or restriction of an indication based on clinical studies demonstrating lack of efficacy).
- Change in the recommended dose and/or dosing schedule:
  - (a) addition of a new vaccination regimen (such as addition of accelerated vaccination regimens);

(b) Addition or modification of the existing vaccination regimen (such as addition of a booster dose or modification of the recommended time interval for booster vaccinations).

- Change to add information on shedding and transmission.
- Change to the use in specific at-risk groups (such as addition of information on use in pregnant women or immunocompromised patients).
- Change to add information on co-administration with other vaccines or medicines.
- Change to add a new route of administration.1
- Change to add a new dosage form1 (such as replacement of a suspension for injection with a lyophilized cake).
- Change to add a new strength.1
- Change to add a new delivery device.1 (such as adding a needle-free jet injector).
- 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).

Product labelling information changes

Supplements on product labelling information change should be submitted for changes which do not require clinical efficacy data, safety data or extensive pharmacovigilance (safety surveillance) data. Product labelling information changes require approval prior to implementation of the change.

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

- Addition of an adverse event identified as consistent with a causal association with immunization with the vaccine concerned.

- Change in the frequency of occurrence of a given adverse reaction.
- Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example,

required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks).

- Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions.
- Revisions to the instructions for use, including dosage, administration and preparation for administration to optimize the safe use of the vaccine.

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 NAFDAC and the MA holder (see section 7.3 and Appendix 1).