



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

**Vaccines, Biologics & Medical Devices Registration & Regulatory
Affairs (VBM-R&RA) Directorate**

**GUIDELINES ON VARIATIONS TO A REGISTERED
BIOTHERAPEUTIC PRODUCT FOR HUMANS**

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1. Introduction

This guidance document is technically and structurally inspired by the World Health Organization's Guidelines on procedures and data requirements for changes to approved biotherapeutic products (TRS 1011 Annex 3) on the details of the various categories of variations to the terms of marketing authorizations for Biotherapeutics for humans. It is intended to provide supportive information on how to present an application to implement a change to an existing registered Biotherapeutic 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 Biotherapeutics for human 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 Biotherapeutics for humans;
- Provide guidance on the technical and other general data requirements to support changes to the quality attributes of the drug substance, 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 a drug substance, intermediate or a finished biotherapeutic product.

This guidance should be read in conjunction with the NAFDAC Guidelines on Variations to a Registered Vaccine for Humans. This guidance document is applicable only to the

manufacture and use of approved biotherapeutics 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 license for an approved biotherapeutics 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 biologic.

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

Changes to approved biotherapeutic products or SBPs are categorized on the basis of a risk analysis which takes into consideration the complexity of the production process and product, the patient population, and the proposed changes. When a change affects the manufacturing or the control strategy, the assessment should include evaluation of the impact of the change on quality (that is, identity, strength, purity and potency) as it may relate to the safety and/or efficacy of the product. When a change affects the clinical use of a product or of product labelling information, this assessment should include evaluation of the effect of the change on the safety and efficacy of the product. Prior to implementing a change with a potential impact on quality, the marketing authorization holder should demonstrate through appropriate studies (analytical testing, functional assays and, if needed, clinical and/or nonclinical studies) that the pre-change and post-change products are comparable in terms of quality, safety and efficacy.

Certain major changes, such as changes to the molecule (for example, changing amino acid sequence or conjugating to PEG moieties) will lead to a new molecular entity and are not considered post-approval changes. For these changes, submission of a product license application for a new marketing authorization may be required.

A change in the quantity of drug substance per dose of biotherapeutic product also requires a product license application for a new marketing authorization.

A MA holder making a change to an approved biotherapeutic 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 biologic drug substance 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 preMCB material) or changes in the composition of biologic adjuvants are generally considered to be a new product and as such require the submission of a product license 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 NAFDAC for guidance

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

3. Terminology

The definitions given below apply to the terms used in these NAFDAC Guidelines. They may have different meanings in other contexts.

Acceptance criteria: criteria, expressed by numerical limits, ranges or other suitable measures, which should be met to release the drug substance or drug product or materials at different stages of their manufacture.

Biotherapeutic product: a biological medicinal product with the indication of treating human disease. For the purpose of these this Guidelines, biotherapeutic products include all biologically active protein products (including plasma-fractionated products) which are used in the treatment of human diseases, and those intentionally modified by, for example, fusion proteins, PEGylation, conjugation with a cytotoxic drug or modification of rDNA sequences. They also include protein products used for in vivo diagnosis (for example, monoclonal antibody products used for imaging).

Change: refers to a change that includes, but is not limited to, product composition, manufacturing process, quality controls, analytical methods, equipment, facilities or product labelling information made to an approved marketing authorization or license by the marketing authorization holder. Also referred to as “variations” or “post-notice of compliance changes” in other documents.

Comparability exercise: the activities – including study design, conducting of studies and evaluation of data – that are designed to investigate whether a pre-change product and a post-change product are highly similar.

Comparability protocol: a well-defined plan for future implementation of quality change(s) (for example, manufacturing-related changes, change of analytical method or site transfer). Also referred to as “post-approval change management protocol” in other documents. A comparability protocol establishes the tests to be performed, and acceptable limits to be achieved to demonstrate the comparability of pre-change and post-change products following specific quality change(s).

Container closure system refers to the following components:

- A primary container closure system is a packaging component that is in, or may come into, direct contact with the drug product dosage form (for example, vial or pre-filled syringe) or components that contribute to the container/closure integrity of the primary packaging material for a sterile product.
- A secondary container closure system is a packaging component that is not, and will not be, in direct contact with the dosage form (for example, carton or tray).
- A functional secondary container closure system is a packaging material that is not in direct contact with the product, and that provides additional protection or serves to deliver the product.

Control strategy: a planned set of controls derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (16).

Critical quality attribute: a physical, chemical, biological or microbiological property or characteristic that is selected for its ability to indicate the consistent quality of the product within an appropriate limit, range or distribution to ensure the desired product quality (1)

Design space: the multidimensional combination and interaction of input variables (for example, material attributes) and process parameters that have been demonstrated to provide assurance of quality (16).

Dosage form: 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.

Drug product: a pharmaceutical product type in a defined container closure system that contains a drug substance, generally in association with excipients.

Drug substance: the active pharmaceutical ingredient and associated molecules that may be subsequently formulated to produce the drug product.

Excipient: any component of the drug product, other than the active component/drug substance and the packaging material, generally added during formulation. Also referred to as “inactive ingredient” in other documents.

Final batch: a collection of sealed final containers that is homogeneous with respect to the composition of the product. A final batch must have been filled in one continuous working session.

Formulated bulk: an intermediate in the drug product manufacturing process, consisting of the final formulation of drug substance and excipients at the concentration to be filled into primary containers.

In-process control: checks performed during manufacture to monitor or to adjust the process in order to ensure that the intermediate or final product conforms to its specifications. The control of the production environment or equipment may also be regarded as part of in-process control.

Intermediate: a material produced during steps in the manufacture of a biotherapeutic product that undergoes further processing before it becomes the drug product. See also the definition for Drug substance.

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

Marketing authorization: a formal authorization for a medicine to be marketed. Once NAFDAC approves a marketing authorization application for a new medicine, the medicine may be marketed and may be available to be prescribed by physicians. Also referred to as “product license” or “license” in this and other documents.

Marketing authorization application: a formal application to NAFDAC for approval to market a new medicine. The purpose of the market authorization application is to determine whether the medicine meets the statutory standards for safety, efficacy, product labelling information and manufacturing. Also referred to as “product license application” or “license application” in this and other documents.

Marketing authorization holder: any person or legal entity that has received a marketing authorization or license to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or license.

Master cell bank (MCB): an aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions.

Primary packaging site: site involved in the activity of putting a drug in its primary container which is, or may be, in direct contact with the dosage form. **Process validation:** documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

Product labelling information: refers to printed materials that accompany a prescription medicine and all labelling items, namely:

- prescribing information (an instruction circular that provides product information on indication, dosage and administration, safety and efficacy, contraindications, warnings and a description of the product for health-care providers (also referred to as “summary of product characteristics” or “package insert” in various countries);
- patient labelling or consumer information.
- inner label or container label.
- outer label or carton.

Quality attribute: a physical, chemical, biological or microbiological property or characteristic.

Quality change: 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 the culture media components, reagents or solvents intended for use in the production of starting material, drug substance, intermediates or drug products.

Real-time release testing: testing that provides the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls

Reference standards/materials: well-characterized materials used as references against which batches of biological products are assessed. These materials remain fundamental to ensuring the quality of biological products as well as the consistency of production and are essential for the establishment of appropriate clinical dosing.

Safety and efficacy change: a change that has an impact on the clinical use of the biotherapeutic product in relation to safety, efficacy, dosage and administration, and that requires data from clinical or post-marketing studies, and in some instances clinically relevant nonclinical studies, to support the change.

Secondary packaging facility: site involved in packaging activities using a packaging component that is not, and will not be, in direct contact with the dosage form (for example, putting the primary container in the outer container or affixing labels).

Shelf-life: the period of time during which a drug substance or drug product, if stored under the conditions defined on the container label, is expected to comply with the specification, as determined by stability studies on a number of batches of the product. The expiry date is assigned to each batch by adding the shelf-life period to the date of manufacture.

Similar biotherapeutic product (SBP): a biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product, and which was developed and approved based on the principles outlined in relevant WHO guidelines

Source material/starting material: material from a biological source that marks the beginning of the manufacturing process of a drug as described in a marketing authorization or license application and from which the active ingredient is derived either directly (for example, plasma derivatives, ascitic fluid or bovine lung) or indirectly (for example, cell substrates, host/vector production cells, eggs or viral strains).

Specification: a list of tests, references to analytical procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by the regulatory authorities.

Supplement: a written request submitted to the NAFDAC to approve a change in the original application for the marketing authorization (or product license) or any other notification to add to (that is, to supplement) the information in the original marketing authorization or product license file. A prior approval supplement (PAS) is a supplement requiring approval from the NAFDAC prior to implementation of the change. Also referred to as “change application dossier” in other documents.

Validation: the demonstration, with documentary evidence, that any procedure, process, equipment, material, activity or system will consistently produce a result meeting predetermined acceptance criteria.

Working cell bank (WCB): the working cell bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the master cell bank under defined culture conditions.

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 biotherapeutic product, and the potential impact of this on the safety or efficacy of the biologic, 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 biologic. 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 biologic. 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 biologic. 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 biologic lot release protocol, the MA holder should inform the institution responsible for reviewing the release of biologic 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 NAFDAC 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 biologic, but is not included in Appendix 1 or 2, NAFDAC may be consulted for the correct classification.

4.4 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance but must be notified to NAFDAC immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change. It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

4.4.1 Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification, but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to NAFDAC within 12 months of implementation of the changes. For convenience, applicants may group several AN change as a single submission.

4.4.2 Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission, and they can be considered

accepted if an objection is not issued by NAFDAC within 30 working days of the date of acknowledgement of receipt of the application.

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 biologic, 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 biologic 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 biologic 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 biologic, 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 biologics 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 biologic attributes and the disease that the biologic is designed to prevent. Other considerations include:

- Robustness of the immune response elicited by the biologic 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.
- Biologic attributes (for example, live as opposed to inactivated biologics).

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 biologic's safety or efficacy.
- Amended product labelling information.

- Clinical studies (protocol, statistical analysis plan and clinical study report);
- Clinical assay methods (including SOPs) and validations.
- The pharmacovigilance plans.

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 biologic 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 biologic concerned.
- Identification of subgroups for which the benefit-to-risk profile of the biologic 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 labeling 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 biologic. MA holders should consult with 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 to any of the labelling items which are not expected to have an impact upon the safe and efficacious use of the biotherapeutic product. In some cases, these changes may need to be reported to NAFDAC, and approval received prior to implementation, while in other cases reporting may not be required.

- Examples of product labelling information changes that require approval by the NRA prior to implementation are changes in the proper/nonproprietary name or trade name of the biotherapeutic product. Changes in this category are considered important for reasons of liability and monitoring.
- Examples of product labelling information changes that do not require approval by the NRA prior to implementation are administrative changes such as those related to labelling (for example, minor changes in format without any negative effect on 201 WHO Expert Committee on Biological Standardization Sixty-eighth report readability). These changes should be reported to the NRA as part of a subsequent PAS for safety and efficacy changes or product labelling information changes when updated product labelling information is included.

Manufacturers are encouraged to consult with the NRA regarding the appropriate reporting category for labelling changes to approved products.

Administrative Changes

1. Change in the brand name (proprietary name) of a registered product
2. Change in the name and/or corporate address of the supplier of the FPP
3. Change in the name or address of a manufacturer of an API that is not a supplier of a pre-qualified API or that is not supported by a CEP
4. Change in the name and/or address of a manufacturer of the FPP
5. Deletion of a manufacturing site or manufacturer

6. Guidance for Submission of Variation Applications

Variation applications can be submitted for Minor or Major Variations.

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

1. Applicants should download the application form: Variation Application form: [Biologic Variation Application Form Major Moderate Minor.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 Biologic 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 uploaded via our e-submission portal
5. Information on the contact person should be provided. The primary contact person should be the local representative authorized by the Biotherapeutic 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.

The reason for the proposed change should be provided under section 2.3.

1. All supporting documentation attached to the application should be indicated on the checklist provided under section 3.
2. Please note that there is no need to state the name of each document. The check boxes provided should be used.
3. 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.

6.1 Further Notes:

- a) The supporting documents should be provided in line with the CTD structure.
- b) Applicant is to send an email to vb.vbmrr@nafdac.gov.ng requesting for a link to upload all supporting documents including the filled NAFDAC variation form.
- c) Variation applications should be specific for one biologic product (i.e., separate applications 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 biologic component change may necessitate a

change in specification. For submissions that include multiple changes, the MA holder should clearly specify which data support for each change.

Multiple major or moderate quality changes for the same biologic 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 drug substance 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 biologic

7. Appendix 1: Changes to the Drug substance

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information for a biologic 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 biologic. In addition, MA holders should contact the NAFDAC if a change not included in the antigen table below has the potential to impact upon biologic quality.

8. Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
1. Change to a drug substance manufacturing facility:			
<i>Note: For the purpose of this change, manufacturing refers to unit operations in the manufacturing process of the drug substance and is not intended to refer to quality control testing, storage or transportation</i>			
a. Replacement or addition of a manufacturing facility for the bulk drug substance or any intermediate	None	1–4, 6–8	Major
	1–3	1–8	Moderate
b. Conversion of a drug substance manufacturing facility from single-product to multi-product	4	9, 10	Moderate
c. Deletion of a manufacturing facility or manufacturer of an intermediate drug substance, or bulk	5, 6	None	Minor

Conditions

1. The proposed facility is an approved drug substance facility for biotherapeutics (for the same company/marketing authorization holder).
2. Any changes to the manufacturing process and/or controls are considered either moderate or minor (for example, duplication of product line).
3. The new facility/suite is under the same quality assurance/quality control oversight.
4. The proposed change does not involve additional containment requirements.
5. There should remain at least one site/manufacturer, as previously authorized, performing the same function as the one(s) to be deleted.
6. The deletion should not be due to critical deficiencies in manufacturing (for example, recurrent out-of-specification events, environmental monitoring failures, etc.).

Supporting data

1. Evidence of GMP compliance with the facility.
2. Name, address, and responsibilities (for example, fermentation, purification) of the proposed facility.
3. Summary of the process validation studies and results.
4. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may be required if quality data alone are insufficient to establish comparability. The

extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality comparability findings,

the nature and level of the knowledge of the product, existing relevant nonclinical and clinical data, and aspects of their use.
5. Justification for the classification of any manufacturing process and/or control changes as moderate or minor.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified and agreed by the NAFDAC.
7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to

- undertake real-time stability studies to confirm the full shelf-life/hold- time of the drug substance under its normal storage conditions and to report to the NAFDAC any failures in these ongoing long-term stability studies. Matrixing, bracketing, use of smaller-scale batches and/or use of fewer than three batches of drug substance for stability testing may be acceptable where justified (6).
- Updated post-approval stability protocol.
 - Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If no revisions, the manufacturer should state that no changes were made to the change-over procedures.
 - Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
2. Change to the cell banks:			
<i>Note: New cell substrates that are unrelated to the licensed master cell bank (MCB) or pre-MCB material may require a new application for marketing authorization or license application.</i>			
a. Adaptation of an MCB into a new culture medium	None	1, 2, 5–8, 10	Major
b. Generation of a new MCB	1	1, 2, 5–8	Moderate
c. Generation of a new working cell bank (WCB)	2–4	1, 2	Minor
3. Change in the cell bank manufacturing site	None	1, 2, 9	Moderate
4. Change in the cell bank testing/storage site	5, 7	9	Minor
5. Change in the cell bank qualification protocol	None	3, 4	Moderate
	6	4	Minor

Conditions

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

Supporting data

1. Qualification of the cell bank according to guidelines considered acceptable by the NAFDAC.
2. Information on the characterization and testing of the MCB/WCB, and cells from the end-of-production passage or post-production passage.
3. Justification of the change to the cell bank qualification protocol.
4. Updated cell bank qualification protocol.
5. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case- by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the product, existing relevant nonclinical and clinical data, and aspects of its use.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the drug substance derived from the new cell bank. Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified

representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.

7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold- time of the drug substance under its normal storage conditions and to report to the NAFDAC any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified (6).
 8. Updated post-approval stability protocol.
 9. Evidence that the new company/facility is GMP-compliant.
 10. Supporting nonclinical and clinical data or a request for a waiver of in vivo studies with justification
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Description of change	Conditions to be fulfilled	Supporting data	Reporting category
6. Change to the fermentation or cell culture process:			
a. A critical change (a change with high potential to have an impact on the quality of the drug substance or drug product; for example, incorporation of disposable bioreactor technology)	None	1–7, 9, 11	Major
b. A change with moderate potential to have an impact on the quality of the drug substance or drug product (for example, extension of the in vitro cell age beyond validated parameters)	1, 3	1–6, 8, 10	Moderate
c. A noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product, such as: • a change in harvesting and/ or pooling procedures which does not affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of detection of adventitious agents or production scale; • duplication of a fermentation train; or • addition of similar/ comparable bioreactors	1–5, 7–10	1, 2, 4, 8	Minor

ccc

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
7. Change to the purification process, involving the following:			
a. A critical change (a change with high potential to have an impact on the quality of the drug substance or drug product, for example, a change that could potentially have an impact on the viral clearance capacity of the process or the impurity profile of the drug substance)	None	1, 2, 5–7, 9, 11, 12	Major
b. A change with moderate potential to have an impact on the quality of the drug substance or drug product (for example, a change in the chemical separation method, such as ion-exchange HPLC ¹ to reversed-phase HPLC)	1, 3	1, 2, 5–7, 10 - 12	Moderate
c. A noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product (for example, addition of an in-line filtration step equivalent to the approved filtration step)	1–4	1, 2	Minor
8. Change in scale of the manufacturing process:			
a. At the cell culture stage	3, 9–11	2, 3, 5–7, 9, 11	Moderate
b. At the purification stage	1,2,4,6	2,5-7,9,11	Moderate
9. Introduction of reprocessing steps	12, 13	8, 10, 11, 13	Minor
10. Addition of a new holding step or change in the parameters of an approved holding step	None	5,14	Moderate

Table continued

Conditions

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

Supporting data

1. Justification for the classification of the change(s) as critical, moderate or noncritical in terms of its impact on the quality of the drug substance.
2. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).

3. If the change results in an increase in the number of population doublings or subcultivations, information on the characterization and testing of the post- production cell bank for recombinant product or of the drug substance for non- recombinant product.
4. For drug substance obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/ transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues

from which the material is a derivative, country of origin of the source animals, use and previous acceptance of the material) (7).

5. Process validation results.
6. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality– comparability findings, the nature and level of knowledge of the product, existing relevant nonclinical and clinical data, and aspects of its use.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative 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 marketing authorization holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and.

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

11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the drug product manufactured using the post- change drug substance into the stability programme.
12. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) (7).
13. Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times, resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the drug substance.
14. Demonstration that the new or revised holding step has no negative impact on the quality of the drug substance (data from commercial-scale or scientifically justified representative drug substance batch should be provided).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
11. Change in equipment used in the drug substance manufacturing process, involving the following:			
<i>Note: New bioreactor technology (for example, a change from stainless steel bioreactor to disposable bioreactor) is excluded from this table and should be filed according to change 6a.</i>			
a. Introduction of new equipment with different operating principles and different product contact material	None	1-5	Moderate
	3,4	1,2,5	Minor
b. Introduction of new equipment with the same operating principles but different product contact material	None	1, 3-5	Moderate
	3,4	1,4,5	Minor
c. Introduction of new equipment with different operating principles but the same contact material	None	1-3, 5	Moderate
	4	1,2,5	Minor

d.	Replacement of product-contact equipment with equivalent equipment	None	3	Minor
e.	Change of product-contact equipment from dedicated to shared	1,2	1,6	Minor
f.	Relocation of major equipment to another room in the same facility/suite/premises	2,4,5	None	Minor

Conditions

- 1. The site is approved as a multi-product facility.
- 2. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.
- 3. The manufacturing process is not impacted by the change in product-contact equipment.
- 4. The change has no impact on product quality.
- 5. Re-qualification of the equipment follows the original qualification protocol.

Supporting data

- 1. Information on the in-process control testing.
- 2. Process validation study reports.
- 3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the drug substance produced with the approved and proposed product contact equipment/material. Batch data on the next two full-production batches should be made available on request and reported by the marketing authorization holder if outside
- 4. Information on leachables and extractables.
- 5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
- 6. Information describing the change-over procedures for the shared product- contact equipment.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
12. Change in specification for the materials, involving the following:			
a. Narrowing of the approved specification limits for starting materials/ intermediates	1-4	1-3, 5	Minor
b. Widening of the approved specification limits for starting materials/intermediates	None	1-3, 5, 7	Moderate
	3-7	3-6	Minor
13. Change in supplier of raw materials of biological origin (for example, fetal calf serum, insulin, trypsin)	None	4,6,9,10	Moderate
	8	4,6	Minor
14. Change in source of raw materials of biological origin (for example, bovine trypsin to porcine trypsin)	None	4,7,9,10	Moderate
	8	4,7	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. There is no change in the drug substance specification outside the approved limits.
4. There is no change in the impurity profile of the drug substance outside the approved limits.
5. The change has no significant effect on the overall quality of the drug substance and/or drug product and there are no changes to the cell banks.
6. The change is not necessitated by recurring events arising during manufacture or because of stability concerns
7. The test does not concern a critical attribute (for example, content, impurity, any critical physical characteristics or microbial purity).

8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).
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Supporting data

1. Revised information on the quality and controls of the materials (for example, raw materials, starting materials, solvents, reagents and catalysts) used in the manufacture of the post-change drug substance.
2. Updated drug substance specification, if changed.
3. Copies or summaries of analytical procedures if new analytical procedures are used.
4. For drug substance obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/ transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, use and previous acceptance of the material) (7).
5. Comparative table or description, where applicable, of pre-change and post- change in-process tests/limits.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative pre- change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the marketing authorization holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
8. Justification/risk assessment showing that the attribute is non-significant.

9. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) (7).
10. Information demonstrating suitability of the auxiliary materials/reagents of both sources through the comparability of the drug substance.

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 drug substance, involving the following:			
a. Narrowing of approved in-process limits	1, 3, 6, 7	1, 4	Minor
b. Addition of new in-process test and limits	2, 3, 6	1–5, 8	Minor
c. Deletion of a non-significant in-process test	1–4, 6	1, 4, 7	Minor
d. Widening of the approved in process limits	None	1-4,6,8	Moderate
	1-4	1,4,5,8	Minor
a. Deletion of an in-process test which may have a significant effect on the overall quality of the drug substance	None	1, 4, 6, 8	Moderate
b. Addition or replacement of an in-process test as a result of a safety or quality issue	None	1–4, 6, 8	Moderate
16. Change in the in-process controls testing site	1–3, 5, 6	9	Minor

Note: Transfer of in-process control testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and is reviewed during inspections

Conditions

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

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
2. Updated drug substance specification, if changed.
3. Copies or summaries of analytical procedures if new analytical procedures are used.
4. Comparative table or description, where applicable, of pre-change and post- change in-process tests/limits.
5. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative pre- change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the

- marketing authorization holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
- Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
 - Justification/risk assessment showing that the attribute is non-significant.
 - Justification for the new in-process test and limits.
 - Evidence that the new company/facility is GMP-compliant.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
17. Change in the approved design space, involving the following:			
a. Establishment of a new design space	None	1	Major
b. Expansion of the approved	None	1	Major
c. Reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space)	1	1	Minor

Conditions

- The reduction in design space is not necessitated by recurring problems arising during manufacture.

Supporting data

1. Manufacturing development data to support the establishment of, or changes to, the design space.
-

Control of the drug substance

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
18. Change affecting the quality control (release and stability) testing of the drug substance, involving the following:			
<i>Note: Transfer of testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and is reviewed during inspections.</i>			
a. Transfer of the quality control testing activities for a non-pharmacopeial assay to a new company not approved in the current marketing authorization or license, or to a different site within the same company	None	1, 2	Moderate
	1-3	1,2	Minor
b. Transfer of the quality control testing activities for a pharmacopeial assay to a new company not approved in the current marketing authorization or license	None	1,2	Moderate
	1	1,2	Minor

Conditions

1. The transferred quality control test is not a potency assay or bioassay.
2. No changes are made to the test method.
3. The transfer is within a facility approved in the current marketing authorization for the performance of other tests.
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Supporting data

1. Information demonstrating technology transfer qualification for the non-pharmacoepial assay or verification for the pharmacoepial assay.

2. Evidence that the new company/facility is GMP-compliant.
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Description of change	Conditions to be fulfilled	Supporting data	Reporting category
19. Change in the standard/monograph (that is, specifications) claimed for the drug substance, involving the following:			
a. A change from a pharmacoepial standard/monograph to an in-house standard	None	1-5	Moderate
b. A change from an in-house standard to a pharmacoepial standard/monograph or from one pharmacoepial standard/monograph to a different pharmacoepial standard/monograph	1-4	1-3	Minor
20. Change in the specifications for the drug substance in order to comply with an updated pharmacoepial standard/monograph	1,2	1,2	Minor

Conditions

1. The change is made exclusively in order to comply with a pharmacoepial monograph.

- 2. There is no change in drug substance specifications outside the approved ranges.
- 3. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopeial standard/monograph.
- 4. There are no deletions or changes to any analytical procedures, except to comply with a pharmacopeial standard/monograph.

Supporting data

- 1. Revised drug product labelling information, as applicable.
- 2. Updated copy of the proposed drug substance specifications.
- 3. Where an in-house analytical procedure is used and a pharmacopeial standard/ monograph is claimed, results of an equivalency study between the in-house and pharmacopeial methods.
- 4. Copies or summaries of validation reports if new analytical procedures are used.
- 5. Justification of specifications with data.

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

Conditions

None

Supporting data

1.

Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
2.

Updated copy of the proposed drug substance specifications.
3.

Copies or summaries of analytical procedures if new analytical procedures are used.
4.

Copies or summaries of validation reports if new analytical procedures are used to monitor the new CQA at release.
5.

Justification and supporting data for each proposed change to the control strategy.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
22. Change in the specification/analytical procedure used to release the drug substance, involving the following:			
a. Deletion of a test	None	1, 5, 6	Moderate
b. Addition of a test	1-3	1-3, 5	Minor
c. Replacement of an analytical procedure	None	1-5	Moderate
	5,6,8	1,4,5	Minor
d. Changes from an approved analytical procedure	None	1-5	Moderate
	2,4-6	1,4,5	Minor
e. Change from an in-house analytical procedure to a recognized compendial/pharmacopeial analytical procedure	None	1-5	Moderate
	2, 6	1-3	Minor
f. Widening of an approved acceptance criterion	None	1, 5, 6	Moderate

g. Narrowing of an approved acceptance criterion	1, 4, 7	1	Minor
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Conditions

1. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits).
2. There is no change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability.
3. The addition of the test is not intended to monitor new impurity species.
4. The method of analysis is the same and is based on the same analytical technique or principle (for example, change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. The modified analytical procedure maintains or improves performance parameters of the method.
6. The change does not concern potency-testing.
7. Acceptance criteria for residual solvent are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
8. The change is from one pharmacopoeial assay to another pharmacopoeial assay or the marketing application holder has demonstrated an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies.

Supporting data

1. Updated drug substance specifications.
2. Copies or summaries of analytical procedures if new analytical procedures are used.
3. Validation/qualification results if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification for the proposed drug substance specification (for example, tests, acceptance criteria or analytical procedures).

6. Documented evidence that consistency of quality is maintained.
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9. Reference Standard or Materials

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
23. Replacement of a primary reference standard	None	1, 2	Moderate
24. Change of the reference standard from pharmacopeial or international standard to in- house (no relationship with international standard)	None	1, 2	Moderate
25. Change of the reference standard from in-house (no relationship with international standard) to pharmacopeial or international standard	3	1,2	Minor
26. Qualification of a new batch of reference standard against the approved reference standard (including qualification of a new batch of a secondary reference standard against the approved primary standard)	1	1,2	Minor
27. Change to reference standard qualification protocol	None	3,4	Moderate
28. Extension of the reference standard shelf-life or re-test period	2	5	Minor

Conditions

1. Qualification of the new reference standard is in accordance with an approved protocol.
2. The extension of the shelf-life of the reference standard is in accordance with an approved protocol.
3. The reference standard is used for a physicochemical test

Supporting data

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

Drug substance container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
29. Change in the primary container closure system(s) for the storage and shipment of the drug substance	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 (including results of transportation or compatibility studies, if appropriate)

Supporting data

1. Updated dossier sections describing information on the proposed container closure system (for example, description, composition, materials of construction of primary packaging components, specifications).

2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing) and compliance with pharmacopeial standards, if applicable.

3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (for example, results of transportation or compatibility studies, and extractable/leachable studies).

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

5. Comparative table of pre-change and post-change specifications of the container closure system.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
30. Change in the supplier for a primary container closure, involving the following:			
a. Replacement or addition of a supplier	None	1-3	Moderate
	1,2	None	Minor
b. Deletion of a supplier	None	None	Minor

Conditions

1.

There is no change in the type of container closure, the materials of construction or the sterilization process for a sterile container closure component.
2.

There is no change in the specifications of the container closure component outside the approved ranges.

Supporting data

1.

Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
2.

Information on the proposed container closure system (for example, description, materials of construction of primary packaging components, specifications).
3.

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
31. Change in the specification/analytical procedure of the primary container closure system for the drug substance, involving the following:			
a. Deletion of a test	1, 2	1, 2	Minor

b.	Addition of a test	3	1–3	Minor
c.	Replacement of an analytical procedure	6, 7	1–3	Minor
d.	Minor changes to an analytical procedure	4–7	1–3	Minor
e.	Widening of an acceptance criterion	None	1, 2	Moderate
f.	Narrowing of an acceptance criterion	8	1	Minor

Conditions

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopeial requirement.
2. The change to the specification does not affect the functional properties of the container closure component and does not result in a potential impact on the performance of the drug substance.
3. The change is not necessitated by unexpected recurring events arising during manufacture of the primary container closure system or because of stability concerns.
4. There is no change in the acceptance criteria outside the approved limits.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity or sensitivity.
8. The change is within the range of approved acceptance criteria.

Supporting data

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

Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
32. Change in the shelf-life of the drug substance or for a stored intermediate of the drug substance, involving the following:			
a. Extension	None	1–5	Moderate
	1–4	1, 2, 5	Minor
b. Reduction	None	1–5	Moderate
	5	2–4	Minor

Conditions

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

Supporting data

1. Summary of stability testing and results (for example, studies conducted, protocols used, results obtained).
2. Proposed storage conditions and shelf-life, as appropriate.
3. Updated post-approval stability protocol and stability commitment.
4. Justification for the change to the post-approval stability protocol or stability commitment.

Table continued

5. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on stability testing of at least three commercial-scale batches unless otherwise justified). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the drug substance. Under special circumstances, interim stability-testing results and a commitment to notify the NAFDAC of any failures in the ongoing long-term stability studies may be provided. In such cases, the extrapolation of shelf-life should be made in accordance with ICH Q1E guidelines (8).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
33. Change in the post-approval stability protocol of the drug substance, involving the following:			
a. Substantial 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	1–5	Moderate
	1	1, 2, 4, 5	Minor
b. Addition of test(s) into the post-approval stability protocol	2	1, 2, 4, 5	Minor
c. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 5	Minor

Table continued

Conditions

- 1. In the case of replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
- 2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
- 3. Deletion of time point(s) is made in accordance with relevant guidelines (for example, (6)).

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
34. Change in the storage conditions for the drug substance, involving the following:			
a. Addition or change to storage conditions for the drug substance (for example, widening or narrowing of a temperature criterion)	None	1–4	Moderate
	1,2	1-3	Minor
	None	1, 3, 4	Moderate

b. Addition of a cautionary Statement	1	1,3,4	Minor
Table continued			
c. Deletion of a cautionary statement	None	1, 3, 5	Minor

Conditions

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

Supporting data

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

Description and composition of the drug product

Note: Changes in dosage form and/or presentation may, in most cases, necessitate the filing of a new application for marketing authorization or licensure. Marketing authorization holders are encouraged to contact the NAFDAC for further guidance.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
35. Change in the description or composition of the drug product, involving the following:			
a. Addition of a dosage form or change in the formulation (for example, lyophilized powder to liquid, change in the amount of excipient, new diluent for lyophilized product)	None	1–10	Major
b. Change in fill volume (same concentration, different volume)	None	1, 5, 7, 9, 10	Major
	1,2	1,5,7,9	Moderate
	1–3	5, 7, 9	Minor
c. Change in the concentration of the active ingredient (for example, 20 units/ml versus 10 units/ml)	None	1, 5, 7, 9, 10	Major
	2, 4, 5	1, 5, 7	Moderate
d. Addition of a new presentation (for example, addition of a new pre-filled syringe where the approved presentation is a vial for	None	1, 5, 7–10	Major

a biotherapeutic in a liquid
dosage form)

Conditions

1. No changes are classified as major in the manufacturing process to accommodate the new fill volume.
 2. No change in the dose is recommended.
 3. The change involves narrowing the fill volume while maintaining the lower limit of extractable volume.
 4. The new concentration is bracketed by existing approved concentrations.
 5. More than two concentrations are already approved (that is, linear PK/PD profile of the product from at least three different concentrations over the bracketed range has been demonstrated and the two extreme concentrations of the bracketed range have been shown to be bioequivalent or therapeutically equivalent).
-

Supporting data

-
1. Revised drug product labelling information, as applicable.
 2. Characterization data demonstrating comparability of the new dosage form and/ or formulation.
 3. Description and composition of the dosage form if there are changes to the composition or dose.
 4. Discussion of the components of the drug product, as appropriate (for example, choice of excipients, compatibility of drug substance and excipients, leachates, compatibility with new container closure system).
 5. Information on the batch formula, manufacturing process and process controls, controls of critical steps and intermediates, process validation results.
 6. Control of excipients if new excipients are proposed (for example, specification).
 7. Information on specification, analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three consecutive commercial-scale batches should be provided).

- Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
- 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).
 - Comparative pre-change and post-change test results for the manufacturer’s characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/ hold-time of the drug product under its normal storage conditions and to report to the NAFDAC any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (6).
 - Supporting clinical data or a justification for why such studies are not needed.

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
36. Change to the diluent, involving the following:			
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	1–6	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. 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 drug product specification outside the approved limits.
3. The proposed diluent is commercially available in the country/jurisdiction of the NAFDAC.
4. The addition of the diluent filling line is in an approved filling facility

Supporting data

1. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
2. Updated copy of the proposed specification for the diluent.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the approved and proposed diluent. Comparative test results for the approved diluent do not need to be generated concurrently; relevant historical testing results are acceptable.
4. Updated stability data on the product reconstituted with the new diluent.
5. Evidence that the facility is GMP-compliant.
6. Revised drug product labelling information, as applicable.

Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
37. Change in the approved design space, involving the following:			
a. Establishment of a new design space	None	1	Major
b. Expansion of the approved design space	None	1	Major
c. Reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space)	1	1	Minor

Conditions

1. The reduction in design space is not necessitated by recurring problems that have arisen during manufacture.

Supporting data

1. Pharmaceutical development data to support the establishment or changes to the design space.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
38. Change involving a drug product manufacturer/ manufacturing facility, involving the following:			
a. Change in manufacturing process	None	1–7	Major
	1–5	1–3, 5–8	Moderate

b.	Conversion of a drug product manufacturing facility from single-product to multi-product facility	None	9, 10	Moderate
c.	Replacement or addition of a secondary packaging facility, including secondary functional packaging (that is, assembly) facility	2, 3	1–3	Minor
d.	Deletion of a drug product manufacturing facility or packaging site	6, 7	None	Minor

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/marketing authorization holder).
2. There is no change in the composition, manufacturing process and drug product specification.
3. There is no change in the container/closure system and storage conditions.
4. The same validated manufacturing process at critical steps (that is, compounding and filling) is used.
5. The newly introduced product is in the same family of product(s), or in the same therapeutic classification, as the products already approved at the site, and also uses the same filling process/equipment.
6. There should remain at least one site/manufacturer, as previously authorized, performing the same function as the one(s) to be deleted.
7. The deletion should not be due to critical deficiencies in manufacturing (for example, recurrent out-of-specification events, environmental monitoring failures, etc.).

Supporting data

1. Name, address and responsibilities (for example, formulation, filling, primary/ secondary packaging) of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP-compliant.
3. Confirmation that the description of the manufacturing process of the drug product has not changed (other than the change in facility), or submission of supporting data on the revised description of the manufacturing process if the process has changed.
4. Comparative description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
5. Summary of the process validation studies and results.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/ hold-time of the drug product under its normal storage conditions and to report to the NAFDAC any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (6).
8. Rationale for considering the proposed formulation/filling facility as equivalent.

9. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If there are no revisions, the manufacturer should state that no changes were made to the change-over procedures.
 10. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.
-

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
39. Change in the drug product manufacturing process, involving the following:			
a. Scale-up of the manufacturing process at the formulation/filling stage	None	1–6	Major
	1–4	1–6	Moderate
b. Addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, lyophilizer)	None	1–7	Moderate
	5	2, 7, 8	Minor
c. Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	None	1, 3–5	Moderate
	1–4, 8	1, 4	Minor
d. Addition of a new step (for example, filtration)	3	1-6	Moderate
e. Product-contact equipment changes from dedicated to shared (for example, formulation tank, filter housing, filling line and head, lyophilizer)	6,7	2,9	Minor

Conditions

- The proposed scale uses similar/comparable equipment to the approved equipment.
Note: Change in equipment size is not considered as using similar/ comparable equipment.

2. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch size (for example, the same formulation, controls and standard operating procedures are utilized).
 3. The change should not be a result of recurring events that have arisen during manufacture or because of stability concerns.
 4. There is no change in the principle of the sterilization procedures of the drug product.
 5. Replacement of equipment with equivalent equipment; the change is considered “like for like” (that is, in terms of product contact material, equipment size and operating principles).
 6. The site is approved as a multi-product facility.
 7. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.
 8. The change does not affect the lyophilization step.
-

Supporting data

1. Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed drug product.
2. Information on the in-process control testing, as applicable.
3. Process validation results (for example, media fills), as appropriate.
4. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
5. Comparative pre-change and post-change test results for the manufacturer’s characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if

present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/ hold-time of the drug product under its normal storage conditions and to report to the NAFDAC any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (6).

- 6. Information on leachables and extractables, as applicable.
- 7. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
- 8. The rationale for regarding the equipment as similar/comparable, as applicable.
- 9. Information describing the change-over procedures for the shared product- contact equipment

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
40. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, involving the following:			
a. Narrowing of approved in-process limits	2, 3, 7	1, 4	Minor
b. Addition of new in-process test and limits	2, 3, 6	1–5, 8	Minor
c. Deletion of a non-significant in-process test	2–4	1, 4, 7	Minor
d. Widening of the approved in-process limits	None	1–4, 6, 8	Moderate
	1–3	1, 4, 5, 8	Minor
e. Deletion of an in-process test which may have a significant	None	1, 4, 6, 8	Moderate

effect on the overall quality of the drug product				
f.	Addition or replacement of an in-process test as a result of a safety or quality issue	None	1-4, 6, 8	Moderate
41. Change in in-process controls testing site		1-3,5,6	9	Minor

Note: Transfer of in-process control testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections

Conditions

1. There is no change in drug product specification outside the approved limits.
2. There is no change in the impurity profile of the drug product outside the approved limits.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. The test does not concern a critical attribute (for example, content, impurities, any critical physical characteristics or microbial purity).
5. The replaced analytical procedure maintains or improves precision, accuracy, specificity and sensitivity, if applicable.
6. There is no change in the in-process control limits outside the approved limits.
7. The test procedure remains the same, or changes in the test procedure are minor

Supporting data

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
2. Updated drug product specification if changed.
3. Copies or summaries of analytical procedures if new analytical procedures are used.

4.

Comparative table or description, where applicable, of current and proposed in-process tests.
5.

Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for one commercial- scale batch of the pre-change and post-change drug product (certificates of analysis should be provided). Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the marketing authorization holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified.
6.

Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product (certificates of analysis should be provided). Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable.
7.

Justification/risk assessment showing that the attribute is non-significant.
8.

Justification for the new in-process test and limits.
9.

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
42. Change in the specification/analytical procedure used to release the excipient, involving the following:			
a. Deletion of a test	5, 8	1, 3	Minor
b. Addition of a test	4	1–3	Minor
c. Replacement of an analytical procedure	1–3	1, 2	Minor
d. Minor changes to an approved analytical procedure	None	1, 2	Minor

e. Change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1, 2	Minor
f. Widening of an approved acceptance criterion	None	1, 3	Moderate
g. Narrowing of an approved 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 improves precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient.
4. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements).
5. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
6. The analytical procedure remains the same, or changes in the test procedure are minor.
7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits).
8. An alternative test analytical procedure is already authorized for the specification attribute/test and this procedure has not been added through a minor change submission.

Supporting data

1. Updated excipient specification.
2. Where an in-house analytical procedure is used and a recognized compendial standard is claimed, results of an equivalency study between the in-house and compendial methods.

3. Justification of the proposed excipient specification (for example, demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
43. Change in the standard/monograph (that is, specifications) claimed for the excipient	None	1-4	Moderate
	1-5	1-4	Minor

Conditions

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

Supporting data

1. Updated excipient specifications.
2. Where a House analytical procedure is used and a pharmacopoeial/compendial standard/monograph is claimed, results of an equivalency study between the House and compendial methods.
3. Justification of the proposed excipient specifications (for example, demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).
4. A declaration that consistency of quality and of the production process of the excipient is maintained.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
44. 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
45. 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
46. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source (for example, different animal source, different country of origin)	5,6	2-7	Major
47. Change in manufacture of a biological excipient	None	2–7	Major
	2	2–7	Moderate
	1, 2	2–7	Minor
48. Change in supplier for a plasma-derived excipient (for example, human serum albumin	None	3-8	Major
	3,4	5,6,9	Moderate
49. Change in supplier for an excipient of non-biological origin	None	2,3,5-7	Moderate

or of biological origin (excluding plasma-derived excipient)	1,5,6	3	Minor
50. Change in excipient testing site	1	10	Minor
<i>Note: Transfer of testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and is reviewed during inspections</i>			

Conditions

1. There is no change to the specification of the excipient or drug 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 NAFDAC.
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 (7).
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 (7).
3. Information demonstrating comparability in terms of physicochemical properties, and the impurity profile of the proposed excipient compared to the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed excipient.

5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three commercial-scale batches of the proposed excipient.
-
6. Comparative pre-change and post-change test results for the manufacturer’s characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug product under its normal storage conditions and to report to the NAFDAC any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (6).
7. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, or BSE/TSE risk (7)), including viral safety documentation where necessary.
8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
9. A letter from the supplier certifying that no changes were made to the plasma- derived excipient compared to the currently approved corresponding medicinal product.
10. Evidence that the new company/facility is GMP-compliant.
-

Control of the drug product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
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51. Change affecting the quality control testing of the drug product (release and stability), involving the following:

Note: Transfer of testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and is reviewed during inspections

a.	Transfer of the quality control testing activities for a non-pharmacopoeial assay (in-house) to a new company not approved in the current marketing authorization or license or to a different site within the same company	None	1, 2	Moderate
b.	Transfer of the quality control testing activities for a pharmacopoeial assay to a new company not approved in the current marketing authorization or license	1-3	1,2	Minor
b.	Transfer of the quality control testing activities for a pharmacopoeial assay to a new company not approved in the current marketing authorization or license	None	1, 2	Moderate
		1	1, 2	Minor

Conditions

1. The transferred quality control test is not a potency assay or bioassay.
2. There are no changes to the test method.
3. The transfer is within a facility approved in the current marketing authorization for the performance of other tests.

Supporting data

1. Information demonstrating technology transfer qualification for the non-pharmacopoeial assays or verification for the pharmacopoeial assays.
2. Evidence that the new company/facility is GMP-compliant.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
52. Change in the standard/monograph (that is, specifications) claimed for the drug product, involving the following:			
a. A change from a pharmacopoeial standard/ monograph to an in-house standard	None	1-5	Moderate
b. A change from an in-house standard to a pharmacopoeial standard/monograph or from one pharmacopoeial standard/monograph to a different pharmacopoeial standard/monograph	1-4	1-3	Minor
53. Change in the specifications for the drug product to comply with an updated pharmacopoeial standard/monograph	1,2	1-3	Minor

- Conditions**
1. The change is made exclusively to comply with a pharmacopoeial monograph.
 2. There is no change in drug product specifications outside the approved ranges.
 3. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph.
 4. There is no deletion or change to any analytical procedures, except to comply with a pharmacopoeial standard/monograph

- Supporting data**
1. Revised drug product labelling information, as applicable.
 2. An updated copy of the proposed drug product specifications.
 3. Where an in-house analytical procedure is used and a pharmacopoeial standard/ monograph is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.

4. Copies or summaries of validation reports if new analytical procedures are used.
5. Justification of specifications with data.

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

Conditions

None

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
55. Change in the specification/analytical procedure used to release the drug product, involving the following:			
a. Deletion of a test analytical procedure and/or an acceptance criterion	None	1, 6, 7	Moderate
b. Addition of a test	1, 2, 7	1–3, 5	Minor
c. Replacement of an analytical procedure	None	1–5	Moderate
	4, 5, 8	1, 4, 5	Minor
d. Changes to an approved analytical procedure	None	1–5	Moderate
	1, 3–5	2, 4, 5	Minor
e. Change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1-5	Moderate
	1,5	1-3	Minor
f. Widening of an approved acceptance criterion	None	1,5,7	Moderate
g. Narrowing of an approved acceptance criterion	1,3,6,7	1	Minor

Conditions

- There is no change to the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability.
- The additional test is not intended to monitor new impurity species.
- 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.
- The modified analytical procedure maintains or improves the performance parameters of the method.

5. The change does not concern potency-testing.
 6. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
 7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, or impurity content outside the approved limits).
 8. The change is from a pharmacopoeial assay to another pharmacopoeial assay or the marketing application holder has demonstrated an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies
-

Supporting data

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

Reference Standards

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
56. Replacement of a primary reference standard	None	1, 2	Moderate
57. Change of the reference standards from a pharmacopoeial or international standard to in-house (no relationship with international standard)	None	1, 2	Moderate
58. Change of the reference standard from in-house (no relationship with international standard) to a pharmacopoeial or international standard	3	1, 2	Minor
59. Qualification of a new batch of reference standard against the approved reference standard (including qualification of a new batch of a secondary reference standard against the approved primary standard)	1	2	Minor
60. Change to the reference standard qualification protocol	None	3, 4	Moderate
61. Extension of the reference standard shelf-life or re-test period	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.
 3. The reference standard is used for a physicochemical test.
-

Supporting Data

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

Drug product container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
62. Modification of a primary container closure system (for example, new coating, adhesive, stopper, type of glass)	None	1-7	Moderate
	4	3,7	Minor
	1-3	3	Minor
<i>Note: The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation (see change 35d)</i>			
63. 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
64. Deletion of a container closure system	None	1	Minor
<i>Note: The NAFDAC should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate)</i>			

Conditions

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

Supporting data

1. Revised product labelling information, as appropriate.
2. For sterilized products, process validation results, unless otherwise justified.
3. Update dossier containing information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary packaging components).
4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and biological reactivity tests.
5. Summary of release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
6. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced (unless otherwise justified) with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real- temperature conditions should also be provided. A possibility of 3 months of real- time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the

manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug product under its normal storage conditions and to report to the NAFDAC any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (6).

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
65. Change in the supplier for a primary container closure component, involving the following:			
a. Replacement or addition of a supplier	1,2	1,2	Minor
<i>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 62 on modification of a primary container closure system.</i>			
b. Deletion of a supplier	None	None	Minor

Conditions

1. There is no change in the type of container closure, materials of construction, shape and dimensions, or in the sterilization process for a sterile container closure component.
2. There is no change in the specification of the container closure component outside the approved acceptance criteria.

Supporting data

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

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

Conditions

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeia requirement.
2. The change to the specification does not affect the functional properties of the container closure component and does not have a potential impact on the performance of the drug product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. There is no change to the acceptance criteria outside the approved limits.

- 5. The new analytical procedure is of the same type.
- 6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
- 7. The new or modified analytical procedure maintains or improves precision, accuracy, specificity and sensitivity.
- 8. The change is within the range of approved acceptance criteria.

Supporting data

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

Stability

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
67. Change in the shelf-life of the drug product, involving the following:			
a. Extension (includes extension of shelf-life of the drug product as packaged for sale, and hold-time after opening and after dilution or reconstitution)	None	1-5	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 commercial-scale batches unless otherwise justified.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
68. Change in the post-approval stability protocol of the drug product, involving the following:			
a. Substantial 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	1-5	Moderate
b. Addition of test(s) into the post-approval stability protocol	1	1,2,4,5	Minor
c. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4,5	Minor
d. Replacement of sterility testing by the container	None	1,2,4,5	Moderate
	3	4,5	Minor

Conditions

1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities.
2. Deletion of time point(s) is done according to relevant guidelines (for example, (6)).

3. The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application related to the drug product.

Supporting data

1. Copies or summaries of analytical procedures if new analytical procedures are used.
2. Validation results if new analytical procedures are used.
3. Proposed storage conditions and or shelf-life, as appropriate.
4. Updated post-approval stability protocol, including justification for the change, and stability commitment.
5. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
69. Change in the labelled storage conditions for the drug product or the diluted or reconstituted biotherapeutic products, involving the following:			
a. Addition or change of storage condition(s) for the drug product, diluted or reconstituted drug product (for example, widening or narrowing of a temperature criterion, addition of or change to controlled temperature chain conditions)	None	1-4, 6	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
Table continued
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 commercial-scale batch unless otherwise justified. 6. Results of stability testing under appropriate conditions covering the proposed shelf-life, generated on at least three commercial-scale batches unless otherwise justified

10. Administrative Changes

Description of change	Conditions to be fulfilled	Documentation Required	Reporting type
1. Change in the pack design of a registered product	1-3	1-3	Vmin

Conditions to be fulfilled

- 1. Application should be initiated by the marketing authorization holder (applicant) on NAPAMS.
- 2. Valid product registration status.
- 3. The proposed pack design is not a pass-off which could lead to dispensing errors (e.g. similar design for two different API’s).

Documents required

- 1. Letter Application stating purpose and signed by the responsible officer (e.g. Managing Director or Superintendent Pharmacist).
- 2. Evidence of valid product registration certificate(s) for the products concerned.
- 3. Copy of coloured artwork of product labelling in the proposed brand name.

Description of change	Conditions to be fulfilled	Documentation Required	Reporting type
2. Change in the brand name (proprietary name) of a registered product	1-5	1-5	Vmin

Conditions to be fulfilled

- 1. Application should be initiated by the marketing authorization holder (applicant)
- 2. Valid product registration status
- 3. The proposed brand name is not a pass-off which could lead to medication errors (e.g. similar sounding brand names of two different API’s)
- 4. Confirmation of registration of trademark for the proposed name
- 5. NAFDAC treasury receipt showing payment of applicable fees.

Documents Required

- 1. Letter Application stating purpose and signed by the responsible officer (e.g. Managing Director or Superintendent Pharmacist).
- 2. Copy of valid product registration certificate(s) for the products concerned

- 3. Copy of trademark registration certificate
- 4. Copy of coloured artwork of product labelling in the proposed brand name
- 5. NAFDAC treasury receipt showing payment of applicable fees.

Description of change	Conditions to be fulfilled	Documentation Required	Reporting type
3. Change in the name and/or corporate address of the applicant of the FPP involving:			
3a. Change in the name and/or address of the applicant	1	1	IN
3b. Change of Agencyship for products registered based on power of Attorney	2-7	1,3,4,5,6,7-9	Vmin
3c. Change of Agencyship for product registered based on Contract Manufacturing Agreement	2,3-8	1,3,4,5,9,10	Vmin

Conditions to be fulfilled

- 1. Confirmation that the applicant of the product remains the same legal entity.
- 2. Application should be initiated by the new applicant/receiving party.
- 3. Product registration is still valid.
- 4. Revocation of power of attorney from existing applicant and transferred to the new applicant/receiving party.
- 5. Confirmation of ‘No Objection’ from the existing applicant.
- 6. Assignment of the trademark for the products concerned to the new applicant/receiving party.
- 7. Payment of applicable fees.
- 8. Confirmation of new Contract Manufacturing Agreement (CMA).

Documentation required

- 1. Letter Application stating purpose and signed by the responsible officer (e.g. Managing Director or Superintendent Pharmacist).

- 2. A formal document from a relevant official body (e.g. the national medicines regulatory authority (NMRA)) in which the new name and/or address is mentioned.
- 3. Copy of Product Registration Certificate or valid Product Notification.
- 4. Trademark registration certificate.
- 5. Deed of assignment of trademark.
- 6. Letter of ‘No Objection’.
- 7. Evidence of revocation of existing power of attorney.
- 8. New Power of Attorney issued in the name of the new applicant/receiving party.
- 9. NAFDAC treasury receipt showing payment of applicable fees.
- 10. A signed and dated Contract Manufacturing Agreement stating the roles of all parties involved.
- 11. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.

Description of change	Conditions to be fulfilled	Documentation Required	Reporting type
4. Change in the name or address of a manufacturer of an API that is not a supplier of a prequalified API or that is not supported by a CEP	1	1-2	IN

Conditions to be fulfilled

- 1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

- 2. A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.
- 3. An updated Letter of Access in case of change in the name of the holder of the APIMF.

Description of change	Conditions to be fulfilled	Documentation Required	Reporting type
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5. Change in the name and/or address of a manufacturer of the FPP.	1	1	Vmin
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Conditions to be fulfilled

1. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation required

1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.

Description of change	Conditions to be fulfilled	Documentation Required	Reporting type
6. Deletion of a manufacturing site or manufacturer involving:			
6a. production of the API starting material	1	1	AN
6b. production or testing of the API intermediate or API	1-2	1	IN
6c. production, packaging or testing of the intermediate or FPP	1-2	1	IN

Conditions to be fulfilled

1. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.
2. The deletion of the site is not a result of critical deficiencies in manufacturing.

Documentation required

1. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.

Examples of changes that make a new application or extension application necessary

1. Change of the API to a different API
2. Inclusion of an additional API in a multicomponent product
3. Removal of one API from a multicomponent product
4. Change in the dose and/or strength of one or more APIs
5. change from a liquid to a powder for reconstitution or vice versa
6. Changes in the route of administration
7. Additional presentation volumes

Conditions to be fulfilled

None

Document Required

New application/extension application