GUIDELINES ON VARIATION OF REGISTERED[1] BIOTHERAPEUTIC PRODUCTS

National Drug Authority
Head Office
NDA Tower
Plot 93, Buganda Road
P. O. Box 23096
Kampala, Uganda.
Tel: +256-417788100
Toll Free: 0800101999
E-mail: ndaug@nda.or.ug
Website: http://www.nda.or.ug

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*[1] In line with the National Drug Policy and Authority Act, Cap. 198 and the National Drug Policy and Authority (Registration) Regulations, 2014, the terms **"Registration" and "Holder of a Certificate of Registration"** as used in these guidelines are synonymous with the universally accepted term **"Marketing Authorization"** and **"Marketing Authorization Holder"**.*

Citation

These guidelines shall be cited as the *"Professional Guidelines on Variation of Registered Biotherapeutic Products, Doc. No. PAR/GDL/033 Revision No.: 2"*

Adoption and approval of these professional guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 198 of the Laws of Uganda (2024 Edition), the Drug Authority hereby ADOPTS and ISSUES these Professional Guidelines on **Variation of Registered Biotherapeutic Products**, Doc. No. 033, Revision No.:2, made this 15th day of September 2025, that take effect on 17th September 2025.

Signature

Dr. Medard Bitekyerezo
CHAIRPERSON
National Drug Authority
Kampala, Uganda

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ACRONYMS AND ABBREVIATIONS

BSE	Bovine Spongiform Encephalopathy
DNA	Deoxyribonucleic Acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice(s)
GMP	Good Manufacturing Practice(s)
HPLC	High-Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IQ	Installation Qualification
MCB	Master Cell Bank
NDA	National Drug Authority
NRA	National Regulatory Authority
OQ	Operational Qualification
PDA	Parenteral Drug Association
PK/PD:	Pharmacokinetic/Pharmacodynamic
PQ	Performance Qualification
SBP	Similar Biotherapeutic Product
SRA:	Stringent Regulatory Authority
TSE	Transmissible Spongiform Encephalopathy
WCB	Working Cell Bank
WHO-PQP	World Health Organisation Prequalification Programme

Introduction

Post approval changes/variations to a registered biotherapeutic product are essential for the continual improvement of the manufacturing process and for maintaining state-of-the-art control of the biotherapeutic product. The term “biotherapeutic products” as used in this document collectively includes the originator biotherapeutic products and Similar Biotherapeutic Products (SBPs) also called “biosimilars”.

The holder of the certificate of registration for registered biotherapeutic products should recognise that any change to a biotherapeutic product has a potential impact on;

a) the quality, safety and/or efficacy of that product;

b) any change to the information associated with the product (that is, product labelling information) may have an impact on its safe and effective use.

The regulation of changes to approved biotherapeutic products is key to ensuring that products of consistent quality, safety and efficacy are marketed after are registered.

Guidance for the implementation of the different types of variations is set out in this document to facilitate the task of both the holder of the certificate of registration and National Drug Authority and to guarantee that variations to the biotherapeutic product do not give rise to public health concerns.

The Guideline is therefore, intended to provide guidance to applicants on the conditions to be fulfilled and the type of documentation to be submitted before a variation can be approved by National Drug Authority. Three possible reporting categories of changes to biotherapeutic products have been provided in this guideline. These include; minor changes, major changes and changes that make a new registration application necessary.

Changes are classified as major (Major Variations) only in those instances where the level of risk is considered to be high and it is deemed necessary to provide National Drug Authority with adequate time for an assessment of the supporting documentation.
In circumstances where the risk of a change to the quality, safety and efficacy of the product is considered minimal or minor, the change can be reported as a notification or minor variation.

The change categories are organized according to the structure of the Common Technical Document (CTD). Specific CTD sections have been identified for individual data requirements in order to assist in the filing of documentation.
In addition, the guideline assists in understanding the possible consequences of the listed changes, and may be useful as a risk management tool to promote or enhance best practices within organizations.

The Guideline is an administrative instrument and, as such, allows for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with National Drug Authority to avoid the possible finding that applicable regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that National Drug Authority reserves the right to request information or material, or define conditions not specifically described in this guideline, in order to allow for adequate assessment of safety, efficacy or quality of the biotherapeutic product. National Drug Authority is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

2.0 Background

Following the approval of Professional Guidelines on Registration of Biotherapeutic Products, *Doc. No. PAR/GDL/016* and Professional Guidelines on Registration of SBPs, *Doc No. PAR/GDL/017* in 2019, the number of approved biotherapeutic products on the Ugandan market has been on the rise. It has become necessary to develop guidelines on making post-approval changes to biotherapeutic products in order to help address the complexity and other challenges associated with the life-cycle management of these products. These guidelines have been adapted from the WHO guidelines on procedures and data requirements for changes to approved biotherapeutic products.

2.1 Objectives

This guideline is intended to:

a) assist applicants with the classification of changes made to a registered biotherapeutic products;

b) provide guidance on the technical and other general data requirements to support changes to the quality, safety and efficacy attributes of the biotherapeutic product.

2.2 Policy

These guidelines are developed in accordance with the National Drug Policy and Authority Act Cap 198, Section 35 and National Drug Policy and Authority (Registration) Regulations, 2014, Regulation 39.

2.3 Scope

This guideline applies to applicants intending to make changes to a registered biotherapeutic product. This guideline should be read in conjunction with other applicable guidelines including Professional Guidelines on Registration of Biotherapeutic Products, *Doc. No. PAR/GDL/016* and Professional Guidelines on Registration of SBPs, *Doc No. PAR/GDL/017*.

The guideline applies in principle to all biologically active protein products used in the treatment of human diseases (for example, plasma fractionated products) and those intentionally modified by, for example, fusion proteins, PEGylation, conjugation with a cytotoxic drug or modification of rDNA sequences. The guideline also applies to protein products used for in vivo diagnosis (for example, monoclonal antibody products used for imaging).

While these guidelines apply to products that are registered, the principles described herein may also apply to quality changes that occur during development of a product and where comparability needs to be demonstrated.

However, the amount and type of data submitted for such products will be limited and will vary according to the nature of each product and its stage of development. The principles set out in this document may apply to low molecular weight heparins. Vaccines, gene and cell therapy products are not covered by these guidelines.

2.4 General Guidance

Whenever a biotherapeutic product is registered following abridged assessment on the basis of approval by a Stringent Regulatory Authority (SRA) or WHO prequalification programme (WHO PQP), subsequent applications for variations which are not country specific should also be approved by the same SRA or WHO PQP, and NDA be notified of the changes with proof of approval from the responsible SRA or WHO.

When a variation leads to a revision of the Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), package insert or product labelling, updated product information has to be submitted as part of the application.

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

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

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation, but can be included as an M1 change together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the substance of the variation submitted.

For the purpose of this document 'test procedure' has the same meaning as 'analytical procedure' and 'limits' have the same meaning as 'acceptance criteria'. 'Specification parameter' means the quality attribute for which a test procedure and limits are set, e.g.

assay, identity and water content. The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

3.0 Glossary

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

"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.

"Authority"
Refers to the National Drug Authority

"Biotherapeutic product"
a biological product with the indication of treating human disease. For the purpose of these 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, the product composition, manufacturing process, quality controls, analytical methods, equipment, facilities or product labelling information made to a registered product by the holder of a certificate of registration. May be referred to as "variations" or "post-notice of compliance change"

"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). May also be referred to as "post-approval change management protocol". 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) 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.

b) 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).

c) 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 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.

"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.

"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.

"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). May also be referred to as "pharmaceutical form".

"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. May also be referred to as "inactive ingredient".

"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 licensure. A manufacturer may also refer to any person or legal entity that is an applicant or holder of a product licence where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

"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:

a) 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);

i. patient labelling or consumer information;

ii. inner label or container label;

iii. 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. May also be referred to a "chemistry manufacturing and control (CMC) change".

"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 registered reference biotherapeutic product.

"Source material/starting material"
material from a biological source that marks the beginning of the manufacturing process of a drug as described in a registration 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.

"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.

4.0 Guidance for Implementation

4.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of administrative, quality, safety and efficacy-related changes. Specific change examples are provided in this guideline. However, it is to be noted that a change not cited in this guideline, shall be decided on by NDA on a case-by-case basis. Whenever the applicant is unclear about the classification of a particular change, National Drug Authority should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and efficacy of the product.

Individual changes normally require submission of separate variation applications. Grouping of variations is acceptable under the following circumstances;

a) when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;

b) when the same change affects multiple finished biotherapeutic products, e.g. addition of a new drug substance manufacturing site for multiple finished biotherapeutic products;

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

Applicants are also advised to exercise caution whenever several changes to the same finished biotherapeutic product are envisaged. Although individual changes may be classified under a lower reporting type, classification at a higher risk category may be warranted as a result of the composite effect of grouped changes. In all such cases, applicants are advised to always contact National Drug Authority prior to submission of the variation application in order to obtain guidance on classifying such changes.

4.2 Notifications

This guidance outlines the following types of changes that can be made to a registered biotherapeutic product on the NDA Drug Register and are considered to have minimal effects on safety, efficacy and quality of a registered biotherapeutic product.

M1 change (Annual Notification)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The indicated documentation is not required to be submitted. The documentation indicated for M1 change should be available on request or at the time of inspection. M1 changes do not require prior approval from NDA and should be submitted to NDA within 12 months of implementation of the changes.

M2 change (Immediate Notification)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application. M2 changes do not require prior approval from NDA for implementation but should be notified to NDA immediately after implementation.

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

4.3 Minor Variation (M3)

This is also referred to as an M3 change. This refers to changes that could have minor effects on the overall safety, efficacy and quality of the biotherapeutic product. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application. Prior acceptance by National Drug Authority is required before the changes can be implemented.

4.4 Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by National Drug Authority is required before the changes can be implemented.

4.5 New applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. For these cases a new dossier must be submitted. Examples of such changes are listed in Appendix 1.

4.6 Labelling information

For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, National Drug Authority must be notified and revised labelling information be submitted. The product should be labelled as prescribed in the Professional Guidelines on Submission of Documentation for Registration of a Pharmaceutical Product for Human Use, *Doc.No. PAR/GDL/004*.

4.7 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (M1, M2 or M3) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a major variation (Vmaj).

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

4.8 Documentation required

For each variation type, certain documents have been identified and the change categories are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation. Applicants should also submit;

a) a covering letter

b) filled and signed variation application form (the form can be downloaded from the NDA website: https://www.nda.or.ug/). Electronic version of the filled application form (scanned signed PDF file) shall be provided;

c) replacement of the relevant sections of the dossier as per CTD format;

d) an updated quality information summary (QIS) (if applicable);

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

It should be noted that NDA reserves the right to request further information not explicitly described in these guidelines.

5.0 Special Considerations

5.1 Comparability exercise

The need for and extent of a comparability exercise depends upon the potential impact of the change(s) on the quality, safety and efficacy of the biotherapeutic product. Comparability exercises can range from analytical testing alone (for example, where process changes have no impact on any quality attribute) to a comprehensive exercise requiring nonclinical and clinical bridging studies. For example, a change in the culture conditions or in the purification process may cause the alteration of the glycosylation profile of the product, including site directed glycosylation. Alteration of glycosylation profiles may cause a change in the pharmacokinetic/pharmacodynamic (PK/PD) profile of the product. If comparability can be demonstrated through analytical studies alone, nonclinical or clinical studies with the post change product are not necessary. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and/ or differences are observed between some critical quality attributes of the pre-change and post-change product, it may be necessary to include a combination of quality, nonclinical and/or clinical studies in the comparability exercise.

5.2 Bridging studies

Nonclinical and clinical bridging studies are studies in which a parameter of interest (such as a manufacturing process or formulation) is directly compared with a changed version of that parameter with respect to the effect of the change on the product's clinical performance. If the physicochemical properties, biological activity, purity and/or level of impurities of the pre-change and post-change product are comparable, the safety and efficacy of the biotherapeutic product can be inferred. However, nonclinical and/or clinical bridging studies may be required when analytical data alone either do not establish comparability or are insufficient to do so. The comparison of efficacy responses and safety outcomes (for example, PK/PD profile, or rates of common adverse events and serious adverse events) is often the primary objective. For ethical reasons, it is desirable to apply the 3R principles (Replacement, Reduction, Refinement) to the use of animals where scientifically appropriate. The following are examples of changes that are likely to require nonclinical and/or clinical bridging studies:

a) generation of a new MCB derived from a different host cell line;
b) a new formulation (for example, a new excipient);
c) a new presentation (for example, addition of pre-filled pens to vials);
d) a new dosing schedule.

For these and comparable changes, any proposed use of alternative approaches to a bridging study must be justified and discussed with NDA.

5.3 Similar Biotherapeutic Products

Following approval, an SBP is considered to be independent from the reference biotherapeutic product and has its own life-cycle. The manufacturer is not required to re-establish similarity to the reference product when comparability exercises are conducted. A major change in clinical use for an SBP that relies on the previously demonstrated similarity provided in the original approval of the SBP may be considered by the NDA on a case-by-case basis. For example, a new indication given to the reference product after approval of an SBP should not automatically be given to the SBP. However, when new safety information on the reference product is added after the original approval of the SBP, the labelling information changes of the SBP should follow the changes made for the reference product unless it can be demonstrated that the new information on the reference product is not relevant to the SBP.

5.4 Comparability protocol

A comparability protocol (also referred to as "Post-approval Change Management Protocol") establishes a framework for a well-defined plan for future implementation of a quality change. This will include the tests to be done and acceptable limits to be achieved when assessing the effect of specific changes on the quality, safety or efficacy of a biotherapeutic product or SBP. For some changes, the routine quality tests performed to release the drug substance or drug product are not considered sufficient for assessing the impact of the change, and additional in-process tests and characterization tests may be needed. Comparability protocols are often used for the routine replenishment of WCBs and reference standards used in quality control tests when the remaining aliquots of reference standards expire or diminish. The purpose of a comparability protocol is to provide transparency in the data requirements for changes and increase the predictability of the effects of changes. This allows for the more expedient distribution of a product by permitting the holder of a certificate of registration to submit a protocol for a change which, if approved, may justify a reduced reporting category for the change when the comparability data are obtained and the change is implemented.

6.0 Reporting categories for quality changes

A quality change may be reported as major variation or minor variation based on the impact of the change on the quality attributes (that is, identity, strength, purity and potency) of the biotherapeutic product, and on the potential impacts of this on the safety or efficacy of the product.

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 biotherapeutic product or SBP should be reported as major variations. Major quality changes should be approved by NDA before their implementation.

Changes to the product composition, manufacturing process, quality controls, facilities or equipment that have minimal or no potential to have an impact on the quality, safety or efficacy of the biotherapeutic product or SBP should be reported as notifications or minor

variations. For each approved product, the holder of a certificate of registration or manufacturer should maintain a comprehensive chronological list of all quality changes. Additionally, this list should include a description of the quality changes, including the manufacturing site(s) or area(s) involved, the date each change was made, and references to relevant validations and standard operating procedures.

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

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

a) safety and efficacy change;

b) product labelling information change;

c) urgent product labelling information change; or

d) 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 (that is, carton) and inner label (that is, container label). After approval, the holder of a certificate of registration should promptly revise all promotional and advertising items relating to the biotherapeutic product to make them consistent with implementation of the product labelling information change. In addition, examples of efficacy, safety and product labelling information changes considered to be appropriate for each category are provided in Appendix 2.

7.1 Safety and efficacy changes

Safety and efficacy changes are changes that have an impact on the clinical use of the biotherapeutic product in relation to safety, efficacy, dosage and administration. To support such changes, data are required from clinical studies and, in some cases, from clinically relevant nonclinical studies. Safety and efficacy changes also require approval prior to implementation of the change.

In general, safety and efficacy changes affect the product labelling information and have the potential to increase or decrease the exposure levels of the biotherapeutic product either by expanding the population that is exposed or by changing dosage or dosing. These changes may be related to clinical use of the biotherapeutic product, and can include:

a) addition or expansion of a safety claim or efficacy claim, including expansion of the population that is exposed;

b) change in the recommended dose and/or dosing schedule;

c) co-administration with other biotherapeutic products or medicines;

d) deletion or reduction of existing risk-management measures (for example, contraindications, adverse events, warnings or cautionary text/statements in the product labelling information).

The type and scope of the required 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 biotherapeutic product attributes and the disease that the biotherapeutic product is designed to prevent.
Other considerations include:

a) the nature of the disease treated (that is, morbidity and mortality, acute or chronic disease, current availability of disease therapy, and size and nature of patient population);

b) safety considerations (for example, adverse drug reactions observed, adverse events in specific patient populations, management of adverse reactions and change in rates of adverse reactions);

c) the availability of animal models.

Holders of a certificate of registration are encouraged to consult with NDA on the adequacy of the clinical and/or nonclinical data needed to support a safety and efficacy change, if deemed necessary. Additionally, some changes such as content of excipients or residual components, or delivery device may require clinical data as well as revision of the product labelling information. The Authority should be consulted on the data required to support such changes.

For nonclinical and clinical studies, the recommendations given in Professional Guidelines on Registration of Biotherapeutic Products, *Doc. No. PAR/GDL/016* and Professional Guidelines on Registration of Similar Biotherapeutic Products, *Doc. No. PAR/GDL/017,* should apply.

For a change under this category, the holder of a certificate of registration should submit an application to NDA that includes the following where applicable:

a) a detailed description of and rationale for the proposed change;

b) a summary of the methods used and studies performed to evaluate the effect of the change on the safety or efficacy of the biotherapeutic product;

c) amended product labelling information;

d) information on clinical studies (protocol, statistical analysis plan and clinical study report);

e) information on clinical assay methods (standard operating procedures) and validations; and

f) the pharmacovigilance plan.

7.2 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 for which use of the biotherapeutic product is approved through:

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

Product labelling information changes require the filing of an application to NDA and a notification of approval should be given prior to distribution of the product.
An application for product labelling information changes related to the clinical use of a product often require data from pharmacovigilance reports (that is, 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 holder of a certificate of registration should submit to NDA an application that includes the following where applicable:

a) a detailed description of and rationale for the proposed change;
b) pharmacovigilance reports and statistical analysis of results; and
c) amended product labelling information.

7.3 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 in which the biotherapeutic product is approved for use. The holder of a certificate of registration should consult with the authority and agree on the required supporting documentation and time frames for the labelling changes.

Note: A letter of acceptance will be issued to a Holder of certificate of registration when a variation is considered acceptable.

8.0 Summary of Changes

Different examples of changes to the quality, safety and efficacy of the biotherapeutic product are listed below with conditions to be fulfilled and the required supporting data for each given reporting category.

9.0 Administrative Changes

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
1	Change of the of the holder of a certificate of registration of the finished biotherapeutic product			
a)	Change in the name and/or corporate address of the Holder of a certificate of registration of the biotherapeutic product	1	1,3,4	M2
b)	Change of Holder of Certificate of Registration from one company to another	2	2-4	M2
Conditions to be fulfilled				
1) Confirmation that the supplier of the product remains the same legal entity 2) All legal requirements for change of Holder of Certificate of Registration have been met & Legal transfer of change has been completed				
Documentation required				
1) A formal document from a relevant official body (e.g. the national medicines regulatory authority (NMRA)) in which the new name and/or address is mentioned. 2) Notarized transfer documents 3) Company registration certificate from the relevant jurisdiction 4) Revised product labelling				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
2	Change in the name and/or address of a manufacturer of the drug substance	1	1	M2
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
3	Change in the name and/or address of a manufacturer of the finished biotherapeutic product	1	1,2	M2
Conditions to be fulfilled				
1) No change in the location of the manufacturing site and in the manufacturing operations.				
Documentation required				
1) Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned. 2) Two (2) commercial samples of the product				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
4	Deletion of a manufacturing site or manufacturer involving: production, packaging or testing of the drug substance, intermediate product or finished biotherapeutic product	1,2	1,2	M2
Conditions to be fulfilled				
1) At least one other site continues to perform the same function(s) as the site(s) intended to be deleted. 2) The deletion of site is not a result of critical deficiencies in manufacturing.				
Documentation required				
1) Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application. 2) Two (2) commercial samples of the finished biotherapeutic product if the deleted manufacturing site appears on the approved product label.				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
5	Change of Local Technical Representative (LTR)	1	1-3	M2
Conditions to be fulfilled				
1) Proposed LTR should have a wholesale license from NDA				
Documentation required				

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

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
6	Change of proprietary product name (brand or trade name)	1	1,2	M3
Conditions to be fulfilled				
1) The proposed brand name should not have been accepted for another product.				
Documentation required				
1) Revised product information 2) Two (2) commercial samples of the product				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
7	Submission of a new or updated transmissible spongiform encephalopathy (TSE) CEP for an excipient (addition or replacement)	None	1	M1
Conditions to be fulfilled				
None				
Documentation required				
1) Copy of the up to date TSE CEP.				

10.0 Quality changes

10.1.0 Drug Substance

10.1.1 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
8	Change to a drug substance manufacturing facility:			

	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.			
a)	Replacement or addition of a manufacturing facility for the bulk drug substance or any intermediate	None	1–4, 6–8	Vmaj
		1-3	1–8	M3
b)	Conversion of a drug substance manufacturing facility from single-product to multi-product	4	9,10	M3
Conditions to be fulfilled				
1) The proposed facility is an approved drug substance facility for biotherapeutics (for the same company/holder of certificate of registration). 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.				
Documentation required				

1) Evidence of GMP compliance of 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 NDA.
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 NDA any failures in these ongoing long-term stability studies. Matrixing, bracketing, use of smaller-scale batches and/or use of fewer than three batches of drug substance for stability testing may be acceptable where justified.
8) Updated post-approval stability protocol.
9) Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If no revisions, the manufacturer should state that no changes were made to the change-over procedures.
10) Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.

Description of change	Conditions to be fulfilled	Documentation required	Reporting type

9	Change to the cell banks: *Note: New cell substrates that are unrelated to the licensed master cell bank (MCB) or pre-MCB material may require a new licence/registration application.*			
a)	Adaptation of MCB into a new culture medium	None	1, 2, 5–8, 10	Vmaj
b)	Generation of a new MCB	1	1, 2, 5–8	M3
c)	Generation of a new working cell bank (WCB)	2-4	1, 2	M2
10	Change in the cell bank manufacturing site	None	1, 2, 9	M3
11	Change in the cell bank testing/storage site	5, 7	9	M2
12	Change in the cell bank qualification protocol	None	3,4	M3
		6	4	M2

Conditions to be fulfilled

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 licence.
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.

Documentation required

1) Qualification of the cell bank according to guidelines considered acceptable by the Authority.
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 NDA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified.
8) Updated post-approval stability protocol.
9) Evidence that the new company/facility is GMP-compliant.
10) Supporting nonclinical and clinical data or a request for a waiver of in vivo studies with justification.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
13	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	Vmaj
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	M3
c)	A noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product, such as: i. 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; ii. duplication of a fermentation train; or iii. addition of similar/comparable bioreactors	1–5, 7–10	1, 2, 4, 8	M2
14	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	Vmaj
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 to reversed-phase HPLC)	1,3	1, 2, 5–7, 10–12	M3

c)	A noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product (for example, to the approved filtration step)	1–4	1,2	M2
15	Change in scale of the manufacturing process			
a)	At the cell culture stage	3, 9–11	2, 3, 5–7, 9, 11	M3
b)	At the purification stage	1, 2, 4, 6	2, 5–7, 9, 11	M3
16	Introduction of reprocessing steps	12,13	8, 10, 11, 13	M2
17	Addition of a new holding step or change in the parameters of an approved holding step	None	5, 14	M3

Conditions to be fulfilled addition of an in-line filtration step equivalent

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.

Documentation required

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 sub-cultivations, information on the characterization and testing of the postproduction 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).
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 holder of a certificate of registration if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified
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 Authority any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified.

10) Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes with at least one commercial-scale drug substance batch produced with the proposed changes under real-time/ real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report to NDA 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).
13) Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times, resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the drug substance.
14) Demonstration that the new or revised holding step has no negative impact on the quality of the drug substance (data from one commercial-scale or scientifically justified representative drug substance batch should be provided).

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
18	Change in equipment used in the drug substance manufacturing process, involving the following: *Note: New bioreactor technology (for example, a change from stainless steel bioreactor to disposable bioreactor) is excluded from this table and should be filed according to change 13a.*			
a)	Introduction of new equipment with different operating principles and different product contact material	None	1-5	M3
		3, 4	1, 2, 5	M2

b)	Introduction of new equipment with the same operating principles but different product contact material	None	1, 3–5	M3
		3, 4	1, 4, 5	M2
c)	Introduction of new equipment with different operating principles but the same product contact material	None	1–3, 5	M3
		4	1, 2, 5	M2
d)	Replacement of product contact equipment with equivalent equipment	None	3	M2
e)	Change of product-contact equipment from dedicated to shared	1, 2	1, 6	M2
f)	Relocation of major equipment to another room in the same facility/suite/ premises	2, 4, 5	None	M2

Conditions to be fulfilled

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.

Documentation required

1) Information on the in-process control testing.
2) Process validation study reports.
3) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one 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 holder of a certificate of registration if outside specification (with proposed action).
4) Information on leachables and extractables.
5) Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
6) Information describing the change-over procedures for the shared product contact equipment.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
19	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	M2
b)	Widening of the approved specification limits for starting materials/ intermediates	None	1–3, 5, 7	M3
		3–7	3–6	M2
20	Change in supplier of raw materials of biological origin (for example, fetal calf serum, insulin, trypsin)	None	4, 6, 9, 10	M3
		8	4, 6	M2
21	Change in source of raw materials of biological origin (for example, bovine trypsin to porcine trypsin)	None	4, 7, 9, 10	M3
		8	4, 7	M2

Conditions to be fulfilled

1) The change in specification for the materials is within the approved limits.
2) The grade of the materials is the same or is of higher quality, where appropriate.
3) 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).

Documentation required

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

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
22	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	M1
b)	Addition of new in-process test and limits	2, 3, 6	1–5, 8	M1
c)	Deletion of a non-significant in-process test	1–4, 6	1, 4, 7	M2

d)	Widening of the approved in-process limits	None	1–4, 6, 8	M3
		1–4	1, 4, 5, 8	M2
e)	Deletion of an in-process test which may have a significant effect on the overall quality of the drug substance	None	1, 4, 6, 8	M3
f)	Addition or replacement of an in-process test as a result of a safety or quality issue	None	1–4, 6, 8	M3
23	Change in the in-process controls testing site *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.*	1–3, 5, 6	9	M2

Conditions to be fulfilled

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 minor.

Documentation required

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

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
24	Change in the approved design space, involving the following:			
a)	Establishment of a new design space	None	1	Vmaj
b)	Expansion of the approved design space	None	1	Vmaj
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	M2

Conditions to be fulfilled
1) The reduction in design space is not necessitated by recurring problems arising during manufacture.
Documentation required
1) Manufacturing development data to support the establishment of, or changes to, the design space.

10.1.2 Control of the drug substance

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
25	Change affecting the quality control (release and stability) testing of the drug substance, 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 to a new company not approved in the registration, or to a different site within the same company	None	1, 2	M3
		1–3	1, 2	M2
b)	Transfer of the quality control testing activities for a pharmacopoeial assay to a new company not approved in the registration	None	1, 2	M3
		1	1, 2	M2
Conditions to be fulfilled				
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 product registration for the performance of other tests.				
Documentation required				
1) Information demonstrating technology transfer qualification for the non-pharmacopoeial assay or verification for the pharmacopoeial assay. 2) Evidence that the new company/facility is GMP-compliant.				

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
26	Change in the standard/monograph (that is, specifications) claimed for the drug substance, involving the following:			

a)	A change from a pharmacopoeial standard/ monograph to an in-house standard	None	1–5	M3
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	M2
27	Change in the specifications for the drug substance in order to comply with an updated pharmacopoeial standard/monograph	1, 2	1, 2	M2
Conditions to be fulfilled				
1) The change is made exclusively in order to comply with a pharmacopoeial monograph. 2) There is no change in drug substance specifications outside the approved ranges. 3) There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph. 4) There are no deletions or changes to any analytical procedures, except to comply with a pharmacopoeial standard/monograph.				
Documentation required				
1) Revised drug product labelling information, as applicable. 2) Updated copy of the proposed drug substance specifications. 3) Where an in-house analytical procedure is used and a pharmacopoeial standard/monograph is claimed, results of an equivalency study between the in-house and pharmacopoeial method. 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**	**Documentation required**	**Reporting type**
28	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)	None	1–3, 5	Vmaj
b)	Addition of a new critical quality attribute in the control strategy.	None	1–5	M3
c)	Deletion of a critical quality attribute from the control strategy	None	1–5	M3
Conditions to be fulfilled				
None				

Documentation required
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	Documentation required	Reporting type
29	Change in the specification/analytical procedure used to release the drug substance, involving the following:			
a)	Deletion of a test	None	1, 5, 6	M3
b)	Addition of a test	1–3	1–3, 5	M2
c)	Replacement of an analytical procedure	None	1–5	M3
		5, 6, 8	1, 4, 5	M2
d)	Changes to an approved analytical procedure	None	1–5	M3
		2, 4–6	1, 4, 5	M2
e)	Change from an in-house analytical procedure to a recognized compendial/ pharmacopoeial analytical procedure	None	1–5	M3
		2, 6	1–3	M2
f)	Widening of an approved acceptance criterion	None	1, 5, 6	M3
g)	Narrowing of an approved acceptance criterion	1, 4, 7	1	M1

Conditions to be fulfilled
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 holder of a certificate of registration has demonstrated an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies.
Documentation required
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.

10.1.3 Reference standards or materials

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
30	Replacement of a primary reference standard	None	1, 2	M3
31	Change of the reference standard from pharmacopoeial or international standard to in-house (no relationship with international standard)	None	1, 2	M3
32	Change of the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	3	1, 2	M2
33	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	M2
34	Change to reference standard qualification protocol	None	3, 4	M3
35	Extension of the reference standard shelf-life or re-test period	2	5	M2

Conditions to be fulfilled
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.
Documentation required
1) Justification for the change in reference standard. 2) Information demonstrating qualification of the proposed reference standards or materials (for example, source, characterization, certificate of analysis, 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.

10.1.4 Drug substance container closure system

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
36	Change in the primary container closure system(s) for the storage and shipment of the drug substance	None	1, 2, 4, 5	M3
		1	1, 3, 5	M2
Conditions to be fulfilled				
1) The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (including results of transportation or compatibility studies, if appropriate).				
Documentation required				

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

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
37	Change in the supplier for a primary container closure, involving the following:			
a)	Replacement or addition of a supplier	None	1–3	M3
		1, 2	None	M2
b)	Deletion of a supplier	None	None	M2

Conditions to be fulfilled

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.

Documentation required
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 NDA 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.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
38	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	M2
b)	Addition of a test	3	1–3	M2
c)	Replacement of an analytical procedure	6, 7	1–3	M2
d)	Minor changes to an analytical procedure	4-7	1–3	M2
e)	Widening of an acceptance criterion	None	1, 2	M3
f)	Narrowing of an acceptance criterion	8	1	M2

Conditions to be fulfilled
1) The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement. 2) The change to the specification does not affect the functional properties of the container closure component and does not result in a potential impact on the performance of the drug substance. 3) The change is not necessitated by unexpected recurring events arising during manufacture of the primary container closure system or because of stability concerns. 4) There is no change in the acceptance criteria outside the approved limits. 5) The new analytical procedure is of the same type.

6) Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure. 7) The new or modified analytical procedure maintains or tightens precision, accuracy, specificity or sensitivity. 8) The change is within the range of approved acceptance criteria.
Documentation required
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.

10.1.5 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
39	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	M3
		1–4	1, 2, 5	M2
b)	Reduction	None	1–5	M3
		5	2–4	M2

Conditions to be fulfilled

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)*.

Documentation required
1) Summary of stability testing and results (for example, studies conducted, protocols used, results obtained). 2) Proposed storage conditions and shelf-life, as appropriate. 3) Updated post-approval stability protocol and stability commitment. 4) Justification for the change to the post-approval stability protocol or stability commitment. 5) Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on stability testing of at least three commercial-scale batches unless otherwise justified). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the drug substance. Under special circumstances, interim stability-testing results and a commitment to notify NDA 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.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
40	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	M3
		1	1, 2, 4, 5	M2
b)	Addition of test(s) into the post-approval stability protocol	2	1, 2, 4, 5	M2
c)	Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 5	M2
Conditions to be fulfilled				
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.				
Documentation required				

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**	**Documentation required**	**Reporting type**
41	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	M3
		1, 2	1–3	M2
b)	Addition of a cautionary statement	None	1, 3, 4	M3
		1	1, 3, 4	M2
c)	Deletion of a cautionary statement	None	1, 3, 4	M2

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

11.0 Drug Product

11.1.0 Description and composition of the drug product

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
42	Change in the description or composition of the drug product, involving the following:			
a)	Change in the formulation of a finished biotherapeutic product (for example, new excipient, change in the amount of excipient, new diluent for lyophilized product)	None	1–10	Vmaj
b)	Change in fill volume (same concentration, different volume)	None	1, 5, 7, 9, 10	Vmaj
		1, 2	1, 5, 7, 9	M3
		1–3	5, 7, 9	M2
c)	Addition of a new presentation (for example, addition of a new pre-filled syringe where the approved presentation is a vial for a biotherapeutic in a liquid dosage form)	None	1, 5, 7–10	Vmaj
Conditions to be fulfilled				
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.				
Documentation required				

1) Revised drug product labelling information, as applicable.
2) Characterization data demonstrating comparability of the new formulation.
3) Description and composition of the biotherapeutic product if there are changes to composition.
4) Discussion of the components of the drug product, as appropriate (for example, choice of excipients, compatibility of drug substance and excipients, leachates, compatibility with new container closure system).
5) Information on the batch formula, manufacturing process and process controls, controls of critical steps and intermediates, process validation results.
6) Control of excipients if new excipients are proposed (for example, specification).
7) Information on specification, analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three consecutive commercial-scale batches should be provided). Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
8) Information on the container closure system and leachables and extractables, if any of the components have changed (for example, description, materials of construction and summary of specification).
9) Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug product under its normal storage conditions and to report to NDA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified.
10) Supporting clinical data or a justification for why such studies are not needed.

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
43	Change to the diluent, involving the following:			
a)	Change in manufacturing process	None	1–5	M3
		1, 3	1–4	M2
b)	Replacement of or addition to the source of a diluent	None	1–6	M3

		1–3	1–3	M2
c)	Change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5	M2
d)	Addition of a diluent filling line	1, 2, 4	1, 3, 5	M2
e)	Deletion of a diluent	None	None	M2

Conditions to be fulfilled

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

Documentation required

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

11.1.1 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
44	Change in the approved design space, involving the following:			
a)	Establishment of a new design space	None	1	Vmaj
b)	Expansion of the approved design space	None	1	Vmaj
c)	Reduction in the approved design space (any change that reduces or limits the range of parameters used to	1	1	M2

	define the design space)			
Conditions to be fulfilled				
1) The reduction in design space is not necessitated by recurring problems that have arisen during manufacture.				
Documentation required				
1) Pharmaceutical development data to support the establishment or changes to the design space.				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
45	Change involving a drug product manufacturer/manufacturing facility, involving the following:			
a)	Replacement or addition of a manufacturing facility for the drug product (including formulation/filling and primary packaging)	None	1–7	Vmaj
		1–5	1–3, 5–8	M3
b)	Conversion of a drug product manufacturing facility from single-product to multiproduct facility	None	9, 10	M3
c)	Replacement or addition of a secondary packaging facility, including secondary functional packaging (that is, assembly) facility	2, 3	1–3	M2
Conditions to be fulfilled				
1) The proposed facility is an approved formulation/filling facility (for the same company/ holder of a certificate of registration). 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.				

Documentation required
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 Authority any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified. 8) Rationale for considering the proposed formulation/filling facility as equivalent. 9) Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If there are no revisions, the manufacturer should state that no changes were made to the change-over 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	Documentation required	Reporting type
46	Change in the drug product manufacturing process, involving the following:			
a)	Scale-up of the	None	1–6	Vmaj

	manufacturing process at the formulation/filling stage	1–4	1–6	M3
b)	Addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, lyophilizer)	None	1–7	M3
		5	2, 7, 8	M2
c)	Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	None	1, 3–5	M3
		1–4, 8	1, 4	M2
d)	Addition of a new step (for example, filtration)	3	1–6	M3
e)	Product-contact equipment change from dedicated to shared (for example, formulation tank, filter housing, filling line and head, lyophilizer)	6, 7	2, 9	M2

Conditions to be fulfilled

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

Documentation required
1) Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed 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 NDA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified. 6) Information on leachables and extractables, as applicable. 7) Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment. 8) The rationale for regarding the equipment as similar/comparable, as applicable. 9) Information describing the change-over procedures for the shared product contact equipment.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
47	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	M1
b)	Addition of new in-process test and limits	2, 3, 6	1–5, 8	M1
c)	Deletion of a non-significant in-process test	2–4	1, 4, 7	M2
d)	Widening of the approved in-process limits	None	1–4, 6, 8	M3
		1–3	1, 4, 5, 8	M2
e)	Deletion of an in-process test which may have a significant effect on the overall quality of the drug product	None	1, 4, 6,8	M3
f)	Addition or replacement of an in-process test as a result of a safety or quality issue	None	1–4, 6, 8	M3
48	Change in in-process controls testing site *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.*	1–3, 5, 6	9	M2

Conditions to be fulfilled

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.

Documentation required
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 holder of a certificate of registration 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	Documentation required	Reporting type
49	Change in the specification/analytical procedure used to release the excipient, involving the following:			
a)	Deletion of a test	5, 8	1, 3	M2
b)	Addition of a test	4	1–3	M2
c)	Replacement of an analytical procedure	1–3	1, 2	M2
d)	Minor changes to an approved analytical procedure	None	1, 2	M2
e)	Change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1, 2	M2
f)	Widening of an approved acceptance criterion	None	1, 3	M3

g)	Narrowing of an approved acceptance criterion	3, 4, 6, 7	1	M1

Conditions to be fulfilled

1) Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2) The replaced analytical procedure maintains or 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.

Documentation required

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

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
50	Change in the standard/monograph (that is, specifications) claimed for the excipient	None	1–4	M3
		1–5	1–4	M2

Conditions to be fulfilled

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.
Documentation required
1) Updated excipient specifications. 2) Where an in-house analytical procedure is used and a pharmacopoeial/compendial standard/monograph is claimed, results of an equivalency study between the in-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**	**Documentation required**	**Reporting type**
51	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	Vmaj
52	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	M3
53	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	M2
54	Change in manufacture of a biological excipient	None	2–7	Vmaj
		2	2–7	M3
		1, 2	2–7	M2
55	Change in supplier for a plasma-derived excipient (for example, human serum albumin)	None	3–8	Vmaj
		3, 4	5, 6, 9	M3
56	Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient)	None	2, 3, 5–7	M3
		1, 5, 6	3	M2

57	Change in excipient testing site *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.*	1	10	M2
Conditions to be fulfilled				
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 product and no manufacturing changes were made by the supplier of the new excipient since its last approval in Uganda. 4) The excipient does not influence the structure/conformation of the active ingredient. 5) The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material. 6) Any new excipient does not require the assessment of viral safety data.				
Documentation required				

1) Declaration from the manufacturer of the excipient that the excipient is entirely of vegetable or synthetic origin.
2) Details of the source of the excipient (for example, animal species, country of origin) and the steps undertaken during processing to minimize the risk of TSE exposure.
3) Information demonstrating comparability in terms of physicochemical properties, and the impurity profile of the proposed excipient compared to the approved excipient.
4) Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed excipient.
5) Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three 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 NDA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified.
7) Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, or BSE/TSE risk, including viral safety documentation where necessary.
8) Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
9) A letter from the supplier certifying that no changes were made to the plasma derived excipient compared to the approved corresponding product.
10) Evidence that the new company/facility is GMP-compliant.

11.1.2 Control of the drug product

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
58	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	None	1, 2	M3

	(in-house) to a new company not approved in the registration certificate or to a different site within the same company	1–3	1, 2	M2
b)	Transfer of the quality control testing activities for a pharmacopoeial assay to a new company not approved in the registration certificate	None	1, 2	M3
		1	1, 2	M2
Conditions to be fulfilled				
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 registration for the performance of other tests.				
Documentation required				
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**	**Documentation required**	**Reporting type**
59	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	M3
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	M2
60	Change in the specifications for the drug product to comply with an updated pharmacopoeial standard/ monograph	1, 2	1–3	M2
Conditions to be fulfilled				
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.
Documentation required
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**	**Documentation required**	**Reporting type**
61	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).	None	1–3, 5	Vmaj
b)	Addition of a new critical quality attribute to the control strategy	None	1–5	M3
c)	Deletion of a critical quality attribute from the control strategy	None	1, 5	M3
Conditions to be fulfilled				
None				
Documentation required				
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	Documentation required	Reporting type
62	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	M3
b)	Addition of a test	1, 2, 7	1–3, 5	M2
c)	Replacement of an analytical procedure	None	1–5	M3
		4, 5, 8	1, 4, 5	M2
d)	Changes to an approved analytical procedure	None	1–5	M3
		1, 3–5	2, 4, 5	M2
e)	Change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1–5	M3
		1, 5	1–3	M2
f)	Widening of an approved acceptance criterion	None	1, 5, 7	M3
g)	Narrowing of an approved acceptance criterion	1, 3, 6, 7	1	M1

Conditions to be fulfilled

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

Documentation required
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.

11.1. 3 Reference standards

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
63	Replacement of a primary reference standard	None	1, 2	M3
64	Change of the reference standards from a pharmacopoeial or international standard to in-house (no relationship with international standard)	None	1, 2	M3
65	Change of the reference standard from in-house (no relationship with international standard) to a pharmacopoeial or international standard	3	1, 2	M2
66	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	M2
67	Change to the reference standard qualification protocol	None	3, 4	M3

68	Extension of the reference standard shelf-life or re-test period	2	5	M2
Conditions to be fulfilled				
1) The qualification of a new standard is carried out in accordance with an approved protocol. 2) The extension of the shelf-life of the reference standard is carried out in accordance with an approved protocol. 3) The reference standard is used for a physicochemical test.				
Documentation required				
1) Revised product labelling to reflect the change in reference standard, as applicable. 2) Qualification data of the proposed reference standards or materials (for example, source, characterization, 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.				

11.1.4 Drug product container closure system

	Description of change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
69	Modification of a primary container closure system (for example, new coating, adhesive, stopper, type of glass) *Note: The addition of a new container closure system (for example, addition of a pre-filled syringe where the approved presentation is only a vial) is considered a change in presentation (see change 42c).*	None	1–7	M3
		4	3, 7	M2
		1–3	3	M2
70	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	M3
71	64. Deletion of a container closure system *Note: NDA should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate.*	None	1	M2

Conditions to be fulfilled
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.
Documentation required
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 NDA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified. 7) Information demonstrating the suitability of the proposed container/closure system with respect to its relevant properties (for example, results from last media fills; results of interaction studies demonstrating preservation of protein integrity and maintenance of sterility for sterile products; maintenance of sterility in multidose containers; user testing).

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
72	Change in the supplier for a primary container closure component, involving the following:			
a)	Replacement or addition of a supplier *Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data, such as is shown for change 69 on modification of a primary container closure system.*	1, 2	1, 2	M2
b)	Deletion of a supplier	None	None	M2
Conditions to be fulfilled				
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.				
Documentation required				
1) Letter from the holder of a certificate of registration 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	Documentation required	Reporting type
73	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	M2
b)	Addition of a test	3	1, 2	M2
c)	Replacement of an analytical Procedure	6, 7	1–3	M2
d)	Minor changes to an analytical procedure	4–7	1–3	M2
e)	Widening of an acceptance criterion	None	1, 2	M3
f)	Narrowing of an acceptance Criterion	8	1	M1

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

11.1.5 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
74	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	M3
b)	Reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1–5	M3
Conditions to be fulfilled				
None				

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

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
75	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	M3
b)	Addition of test(s) into the post-approval stability protocol	1	1, 2, 4, 5	M2
c)	Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 5	M2
d)	Replacement of sterility testing by the container/ closure system integrity testing	None	1, 2, 4, 5	M3
		3	4, 5	M2
Conditions to be fulfilled				
1) The addition of the test(s) is not due to stability concerns or to the identification of new impurities. 2) Deletion of time point(s) is done according to relevant guidelines. 3) The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application related to the drug product.				
Documentation required				
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	Documentation required	Reporting type
76	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	M3
b)	Addition of a cautionary statement (for example, “Do not freeze”)	None	1, 2, 4, 5	M3
c)	Deletion of a cautionary statement (for example, “Do not freeze”)	None	1, 2, 4, 6	M3
Conditions to be fulfilled				
None				
Documentation required				
1) Revised product labelling information, as applicable. 2) Proposed storage conditions and shelf-life. 3) Updated post-approval stability protocol and stability commitment. 4) Justification of the change in the labelled storage conditions/cautionary statement. 5) Results of stability testing under appropriate stability conditions covering the proposed shelf-life, generated on one 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.				

12.0 Safety, efficacy and product labelling changes

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
77	Change in the Summary of product Characteristics, Labelling or package leaflet of a similar biotherapeutic product following assessment of the same change for the reference originator biotherapeutic product.			
a)	Implementation of change(s) for which no new additional data are required from the Holder of Certificate of Registration	None	1	M3

b)	Implementation of change(s) which require to be further substantiated by new additional data from the Holder of Certificate of Registration (e.g. comparability data)	None	1,2	Vmaj
c)	i. Change of the layout/artwork without altering meaning. ii. Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts that do not imply an unapproved indication.	None	3-6	M3
Conditions to be fulfilled				
None				
Documentation required				
1) Revised product information 2) Applicable additional data 3) Approved product labelling. 4) Proposed product labelling, a clean and annotated version highlighting the changes made. 5) Letter of declaration from the holder of a certificate of registration stating that no other changes on the label except for the intended change. 6) Relevant document/reference to support the changes (where applicable).				

Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
78	Implementation of change(s) requested by National Drug Authority following assessment of an Urgent safety restriction, class labelling or periodic safety update report			
a)	Implementation of agreed wording change(s) for which no new additional data are required from the Holder of Certificate of Registration	None	1-2	M3
b)	Implementation of change(s) which require to be further substantiated by new additional data from the Holder of Certificate of Registration	None	1-3	Vmaj
Conditions to be fulfilled				
None				

Documentation required				
1) National Drug Authority request with attached relevant assessment report 2) Revised product information 3) Applicable additional data				
Description of change		**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
79	Variations related to significant modification of product information including prescribing information (SmPC and Patient Leaflet) and product label due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	None	1-5	Vmaj
Conditions to be fulfilled				
None				
Documentation required				
1) Approved product information. 2) Applicable additional data 3) Revised product information; a clean and annotated version highlighting the changes made. 4) Letter of declaration from the holder of a certificate of registration stating that no other changes have been made on the label except for the intended change. 5) Relevant document/reference to support the changes (where applicable).				

12.0 References

Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3 WHO TRS 1011.

Guidelines on Variation of Registered Pharmaceutical Products, Doc. No. PAR/GDL/005

Professional Guidelines on Registration of Biotherapeutic Products, Doc. No. PAR/GDL/016

Professional Guidelines on Registration of Similar Biotherapeutic Products, Doc. No. PAR/GDL/017

Professional Guidelines on Submission of Documentation for Registration of a Pharmaceutical Product for Human Use, Doc. No. PAR/DGL/004

Professional Guidelines on Variation of Registered Vaccines, Doc. No. PAR/GDL/018

Appendix 1: Examples of changes that make a new application necessary

These include the following:

a) Change of the drug substance in a biotherapeutic product to a different drug substance

b) Change in the route of administration

c) Change in the dosage form (such as replacement of a suspension for injection with a lyophilized cake

d) Change in the dose and/or strength of the drug substance in the biotherapeutic product

e) Inclusion or removal of a drug substance in a multicomponent biotherapeutic product.

In the event a variation application is submitted to NDA for a registered biotherapeutic product involving any of the changes listed in this appendix, the applicant will be requested to submit a registration application for a new product in line Professional Guidelines on Registration of Biotherapeutic Products, *Doc. No. PAR/GDL/016* and Professional Guidelines on Registration of SBPs, *Doc No. PAR/GDL/017* as appropriate.

Appendix 2: Safety, efficacy and product labelling information changes

The examples of safety and efficacy changes, product labelling information changes and administrative product labelling information changes given in this appendix are provided for clarification. However, such changes are not limited to those included in this appendix. They may also result in changes to the product labelling information for health care providers and patients, and inner and outer product labels.
The amount of safety and efficacy data needed to support a change may vary according to the impact of the change, risk–benefit considerations and product-specific characteristics (that is, there is no "one size fits all" approach).

Holders of Certificates of Registration or applicants are encouraged to contact NDA for guidance on the data needed to support major changes if deemed necessary.

Safety and efficacy changes

Safety and efficacy changes require approval prior to implementation of the change and are generally submitted for changes related to clinical practice, safety and indication claims.
Examples of safety and efficacy changes that require data from clinical studies, post-marketing observational studies or extensive post-marketing safety data include:

a) change to the indication;
    i. addition of a new indication
    ii. modification of an approved indication.
b) Change in the recommended dose and/or dosing schedule
c) Change to the use in specific at-risk groups (such as addition of information on use in pregnant women or immunocompromised patients).
d) Change to add information on co-administration with other medicines.
e) Change to add a new delivery device (such as adding a needle-free jet injector).
f) Change in existing risk-management measures:
g) Deletion of an existing route of administration
h) Deletion of a contraindication (such as use in pregnant women).

Product labelling information changes

Product labelling information changes should be submitted to NDA for approval before implementation. This includes changes which do not require clinical efficacy data, safety data or extensive pharmacovigilance (safety surveillance) data. Examples of product labelling information changes associated with changes that have an impact on clinical use include;

a) Addition of an adverse event identified as consistent with a causal association with use of the biotherapeutic product concerned.

b) Change in the frequency of occurrence of a given adverse reaction.

c) Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group).

d) Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions.

e) Revisions to the instructions for use, including dosage, administration and preparation for administration to optimize the safe use of the biotherapeutic product.

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 on the safe and efficacious use of the biotherapeutic product. Examples of these changes include;

a) Change in the name of the MA holder and/or manufacturer (such as change of name due to a merger).

b) Change in the trade name of the biotherapeutic product.

c) Minor changes to the layout of the product labelling information items, or revision of typographical errors without changing the content of the label.

d) Update of the MA holder's contact information (for example, customer service number or web site addresses) or the distributor's name.

e) Update of the existing information for referenced literature without adding or removing references.

f) Changes made to comply with an official compendium (such as change of common name).

g) Minor changes to the text to add clarity in relation to maintaining consistency with common label phrase standards (for example, a change from "not recommended for children" to "not for use in children").

DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
15 Feb 2023	0	PAR/GDL/033	Grant Munkwase Etuko Daniel	First Issue
07 Oct. 2024	1	PAR/GDL/033	Dora Namyalo	Revision of physical address of Head Office to NDA Tower, Plot 9, Buganda Road and reference to NDP&A act from Cap. 206 to Cap 198
15 Sep. 2025	2	PAR/GDL/033	Grant Munkwase Racheal Nabwami	i. Recategorization of LTR and MAH changes to immediate Notification. ii. Clarification on the need for prior NDA approval for M3 and Vmaj changes before implementation. iii. Deletion of section 7.4 on administrative product labelling information changes because it was ambiguous.

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