SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

AMENDMENTS GUIDELINE FOR BIOLOGICAL MEDICINES

This guideline is intended to provide recommendations to applicants wishing to submit amendments for registered BIOLOGICAL medicines. It represents SAHPRA's current thinking on ensuring the safety, quality and therapeutic efficacy of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, quality and therapeutic efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used, but these should be scientifically and technically justified. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

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1. ABBREVIATIONS

CP Comparability Protocol
CTD Common Technical Document (ICH)
eCTD Electronic Common Technical Document
GCP Good Clinical Practice
GLP Good Laboratory Practice
GMP Good Manufacturing Practice
HCR Holder of the Certificate of Registration
MCB Master Cell Bank
NRA National Regulatory Authority
PAA Prior Approval Amendment to CTD
QC Quality Control
SAHPRA South African Health Products Regulatory Authority
SOP Standard Operating Procedures
WHO World Health Organization

2. INTRODUCTION AND SCOPE

2.1 Introduction

Often changes to the manufacturing process or labelling information need to be implemented after a biological medicine has been submitted for registration or approved (i.e. Registered). Changes may be made for a variety of reasons: e.g to improve the quality and/or the efficiency of manufacture (e.g., changes in the manufacturing process, equipment, facility), or to update safety and efficacy changes and/or product labelling information (e.g. add a new indication, improve the management of risk by adding a warning, limiting the target population or changing the dosage regime).It is accepted that

a) any change to the process or packaging of a biological medicine may impact the quality, safety, and therapeutic efficacy of a registered medicine; and
b) any change to the labelling information of a registered medicine may impact the safe and effective use of the same.

SAHPRA has a responsibility to evaluate and approve any post registration change that may affect the quality, safety or therapeutic efficacy of a registered medicine.

The Holder of the Certificate of Registration (HCR) is responsible for submitting an application for SAHPRA approval or to notify, ensuring that the manufacturer applies for SAHPRA approval, or notifies SAHPRA of all manufacturing or labelling changes to a registered biological medicine. Prior to implementing the change, the HCR or manufacturer should assess the effects of the change and demonstrate through appropriate studies (validation and/or analytical and/or clinical or non-clinical laboratory studies) the lack of an adverse effect of the change on the quality, safety and therapeutic efficacy of the medicine.

Regulation of changes to medicines is one of the most important elements in ensuring that medicines of constant quality, safety and therapeutic efficacy are distributed post authorisation. It is difficult to provide a set of guidelines that apply to all situations. An attempt has been made to cover a range of possible changes on manufacture, quality control, safety, therapeutic efficacy, and product labelling information.
The categories of changes and reporting procedures are provided in the main body of the document and the data requirements to support the proposed changes are provided in the appendices.
This guideline has been informed by the existing SAHPRA Amendments Guideline (2012) and the WHO Guideline for procedures and data requirements for changes to approved vaccine (TRS 993 Annex-4 2015).

2.2 Scope

This document provides guidelines for HCRs who intend to make changes to the original product license for an approved biological medicine on:

a) procedures and criteria for the appropriate categorization and reporting of changes; and
b) the data required to enable SAHPRA to evaluate the impact of the change on the quality, safety and efficacy of the medicine.

This guidance will form the basis for procedures for evaluation of post approval changes.

3. DEFINITIONS

Some of the definitions below were modified (compared to those provided in other documents) to reflect the meanings as used in this guidance.

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

Amendment: A written application submitted to SAHPRA to approve a change in the original registration application

Antigen (vaccine): The following definitions apply in this document:

- The active ingredient in a vaccine against which the immune response is raised. It may be a live attenuated preparation of bacteria, viruses or parasites; inactivated (killed) whole organisms; crude cellular fractions or purified active biological ingredients, including recombinant proteins (i.e., those derived from recombinant DNA expressed in a host cell); polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids; synthetic active biological ingredients; polynucleotides (such as plasmid DNA vaccines); or living vectored cells expressing specific heterologous immunogens. It may also be a combination of the antigens or immunogens listed above.
- Intermediate or component that may undergo chemical change or processing in the manufacture of the final product (drug product) and is present in the final product in a modified form intended to furnish the specified activity or effect. Also referred as **Drug Substance, Active Ingredient,** or **Active Substance** in other documents.

Biological Medicine: all medicines that contain a living organism, or are derived from a living organism or biological processes. They include, but are not limited to the following:

i. Plasma-derived and animal products e,g Clotting factors, immunosera, antivenoms;
ii. Vaccines;
iii. Biotechnology-derived medicines (recombinant DNA products) e,g rHu-antihaemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids;
iv. Products developed for Human Gene therapy

Well-characterised, low-molecular mass, medicinal biological compounds, may be excluded by specific regulatory decision from biological medicine status, and in that case, will not be reviewed through the biological medicines review process.

Change: Refers to any change made to an approved marketing authorisation in product composition, manufacture process, quality controls, equipment, facilities or product labelling information by the marketing authorisation holder. This is also referred to as **variation** in other documents.

Comparability Exercise: The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable. In addition to routine analyses performed during production and control of the active biological ingredient or final product, these evaluations typically include further characterisation studies. In some cases, non-clinical or clinical data might contribute to the conclusion

Comparability Protocol (CP): Establishes the tests to be done and acceptable limits to be achieved to demonstrate comparability of the pre-amendment and post-amendment products following specific quality change(s). A CP is a highly specific, well-defined plan for the future implementation of a quality (e.g., manufacturing-related changes, change of analytical method and site transfer change. It is also referred to as Post Approval Change Management Protocol in other documents.

Container Closure System: Refers to the following components:

- Primary container closure system is a packaging component that is or may be in direct contact with the final product dosage form (e.g., vial, pre-filled syringe). (Container closure systems for the active biological ingredients or intermediates of medicines normally only include primary container closure systems.)
- Secondary container closure system is a packaging component that is not and will not be in direct contact with the dosage form (e.g. carton, tray).

Dosage Form: means the pharmaceutical form in which the active ingredients, excipients and physical formulation of a medicine is presented.

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

Final Product: A finished dosage form (e.g., tablet or solution) that contains an active ingredient generally, but not necessarily, in association with inactive ingredients. It is also referred as **Finished Product** or **Drug Product** in other documents.

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

Holder of the Certificate of Registration (HCR): means a person in whose name a registration certificate has been granted and who is responsible for all aspects of the medicine, including quality, safety and compliance with conditions of registrations.

Intermediate: A material produced during steps in the manufacturing of a medicine that must undergo further processing before it becomes a final product.

Manufacturer: means a person manufacturing a medicine and includes a manufacturing pharmacy.

Product Labelling Information: Printed materials that accompany a prescription medicine and refers to all labelling items (SAHPRA Regulation # 10, #11 and # 12):

- Package Information (PI), including prescribing information: that provides product information on indication, dosage and administration, safety and efficacy results, contra-indications, warnings, and a description of the product for health care providers
- Inner label or container label
- Outer label or carton
- Patient information Leaflet (PIL)

Prior approval amendment (PAA): an amendment requiring approval from the SAHPRA prior to implementation of the amendment. Also referred to as **Change Application Dossier** in other documents.

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

Quality change: In the context of this document, quality change refers to a change in the manufacturing process, product composition, quality control testing, equipment or facility.

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.

Registration Application: A formal application to SAHPRA for approval to register and market a new medicine. The purpose of the Registration Application is to determine whether the medicine meets the statutory standards for safety, effectiveness, product labelling information and manufacturing.

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

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.

V**accine:** Preparations containing antigens capable of including a specific and active immunity in humans against an infecting agent or toxin

Vaccine Efficacy: Relative reduction in disease incidence in vaccinated people compared to unvaccinated people measured in a randomised, placebo-controlled clinical trial. In the context of this guidance document, medicine efficacy relates to all clinical data obtained to ensure medicine efficacy, immunogenicity or its effectiveness.

4. GENERAL CONSIDERATIONS

For each change the HCR should decide if the information in the original application or product registration application needs to be amended and requires an official submission to SAHPRA (i.e., an amendment application) based on the recommendations in this guideline. The HCR is responsible for the assessment of the effects of any change before implementing the change.

Amendments requiring approval prior to implementation of a change are referred to as Prior Approval Amendments (PAA). In general, no change should be implemented without approval of SAHPRA unless it is exempted in this guideline.

Changes to approved biological medicines are categorised based on a risk analysis. When the change affects the manufacturing process, this assessment should include evaluation of the effect of the change on the quality (i.e. identity, strength, quality, purity, and potency) of the final product as it may relate to the safety or efficacy of the medicine.

Changes that may potentially have a major or moderate impact require submission of a prior approval amendment to SAHPRA.

For each change, the HCR's amendment application should contain information determined by SAHPRA to be appropriate and should include the information developed by the HCR in assessing the effects of the change.
When changes are deemed to have potentially minimal impact or no impact, they should be recorded and retained by the manufacturer or the HCR and listed in the Annual Product Review/Report.

A manufacturer making a change to a biological medicine should also conform to other applicable laws and regulations, including good manufacturing practices (GMP), good laboratory practices (GLP), good clinical practices (GCP) and other applicable regulations.

For example, manufacturers should comply with relevant GMP validation and record keeping requirements and ensure that relevant records are readily available for examination by authorised SAHPRA personnel during

inspections. Inspections may occur routinely or may be triggered by major manufacturing changes (e.g., substantial change in production capacity, move to a new facility).

An assessment of the extent to which the quality change (also referred to as manufacturing change) affects the quality attributes (i.e., identity, strength, quality, purity, potency) of a biological medicine, is typically accomplished by comparing manufacturing steps test results from in-process, release and characterisation testing of pre-change (e.g historical data) and post-change material and determining if the test results are comparable (i.e., active ingredients, intermediate or final product made after the change should be shown to be comparable to and/or to meet the acceptance criteria of the active ingredients, intermediates or final product made before the change). In the case that minor differences are acceptable provided they are shown not to have an adverse impact on quality, safety and therapeutic efficacy of the product

Certain changes, such as changes in the composition of active ingredients, the introduction of new vaccine antigens (except for the annual influenza virus strain update of influenza vaccines), the use of new cell substrates (i.e. use of cells unrelated to the established master cell bank (MCB) or pre-master cell bank material or changes in the composition of key excipients are generally considered to be a new product and as such require the submission of a new registration application.

Cell substrate-related changes, such as re-derivation of the MCB, may require the submission of a new registration application, whether the cells are used as a substrate for propagation or organisms or constitute the active biological ingredient itself (e.g. a new MCB generated from a different isolate).

Administrative changes related to acquisitions and mergers, company names, or contact information should be submitted directly to SAHPRA as a general correspondence to the registration certificate and evaluated by SAHPRA Inspectorate. [See Section 6, *Reporting Categories for Safety, Efficacy and/or Product Labelling Information Changes* for information on changes to the labelling items.]

In the case where a change has been approved by any of the regulatory authorities with which SAHPRA aligns itself, SAHPRA may choose to recognise the decision or make an independent decision based on their assessment. Foreign approval documentation may accompany the required information to support the change as outlined in this document. The responsibility of the final regulatory decision on the approval of the change still lies with SAHPRA. SAHPRA may consider establishing procedures on the recognition of approvals for the same changes by any of the regulatory authorities with which SAHPRA aligns itself.

Descriptions of the reporting categories for quality changes are provided for in section 5 and for safety, therapeutic efficacy and product labelling information changes in section 6. Proposed recommendations on the regulatory procedures for the reporting of changes to SAHPRA are described in section 7. Examples of suggested review timelines for changes in the various categories will be included in future under Appendix 1. A comprehensive list of quality changes and the type of information that should be included in an amendment application are provided in Appendix 2 for the active biological ingredient and intermediates and in Appendix 3 for the final product.

Examples of changes that affect clinical use and product labelling information (safety, therapeutic efficacy, dosage, administration, active components, and expiry date) are provided in Appendix 4.

5. REPORTING CATEGORIES FOR QUALITY CHANGES

Based on the potential effect of the quality change (e.g. manufacturing change) on the quality attributes (i.e. identity, strength, quality controls, purity, potency) of the medicine and on their potential impact on the quality, safety or efficacy, changes are categorised into major, moderate and minor and are identified as:

- Major Quality Changes,
- Moderate Quality Changes, or
- Minor Quality Changes.

The implementation of changes in the major or moderate category requires reporting to SAHPRA in order to amend the information in the original registration application. The Major and Moderate Quality Changes must be reviewed and approved by SAHPRA prior to implementation of the change.

Minor Quality Changes that are expected to potentially have a minimal or no effect on the quality, safety or efficacy of the medicine do not require submission of an amendment. The changes included in this category may be implemented by the HCR without prior review and approval by SAHPRA. However, these changes should be listed in the Annual Product Review and all the supporting information retained as part of the product's record by the manufacturer or HCR, should comply with GMP requirements, and should be available for review during inspections.

At any point when an amendment application is submitted for a product, all Minor Quality Amendments pertaining to the product should also be included in the CTD Module 1.2.1 f Amendment history and also be clearly addressed in the Amendment Schedule, and the latest amendments to any particular aspect should be submitted.

Further information on each category is provided below.
Appendices 2 and 3 provide an extensive list of Major, Moderate and Minor Quality Changes and the information required to support each change.
Appendix 2 includes changes to the active biological ingredient or intermediates and Appendix 3 includes changes to the final product. Quality changes listed in Appendices 2 and 3 should be reported in one of the reporting categories described in this section. If a quality change may have a potential impact on the quality, safety and therapeutic efficacy of the medicine and is considered to be major, moderate or minor, but is not included in Appendix 2 or 3, then SAHPRA should be consulted for proper classification. SAHPRA will establish a mechanism that allows for the update of this guideline when new regulatory category classifications are needed.

5.1 Major Quality Changes

Major Quality Changes are changes to the product composition, manufacturing process, quality controls, facilities, or equipment that have a potential to have a significant negative or positive impact on the quality, safety or efficacy of the biological medicine. The HCR should submit an application for amendment and receive an approval notification from SAHPRA before implementation of the change by the manufacturer. For a change under this category, the amendment should specify the products involved and include a detailed description of the proposed change. Additional supportive information is also needed as per Appendix 2 for the active ingredient and Appendix 3 for the final product and may include information such as: a description of the methods used and studies performed to evaluate the effect of the change on the product's safety or efficacy; the data derived from those studies; relevant validation protocols and results; updated product labelling information; and summaries of relevant standard operating procedure(s) (SOP) or a list referencing previously approved relevant SOP. In some cases Major Quality Changes may also require non-clinical and/or clinical data.

The recommendations in the World Health Organisation (WHO) *Guidelines on nonclinical evaluation of vaccines* [4], *Guidelines on clinical evaluation of vaccines: regulatory expectations* [5], *Guidelines on stability evaluation of vaccines* [6], other related guidelines [7-10] and recommendations for specific products and adjuvants, e.g WHO's Guidelines on the quality, safety and efficacy of bio-therapeutic protein products prepared by recombinant DNA technology (16), should apply.

5.2 Moderate Quality Changes

Moderate Quality Changes are changes to the product composition, manufacturing process, quality controls, facilities, or equipment, that have a moderate potential to have an impact on the quality, safety or therapeutic efficacy of the medicine.

The HCR should submit an amendment and receive an approval notification from SAHPRA before implementation of the change. The requirements for the amendment content of the Moderate Quality Changes are the same as

for the Major Quality Changes (see Section 5.1). However, the amount of required supportive data will be generally less than that for major changes and the review time is shorter.

5.3 Minor Quality Changes

Minor Quality Changes are changes to the product composition, manufacturing process, quality controls, facilities, or equipment that have a minimal potential to have an impact on the safety or efficacy of the medicine. The changes included in this category may be implemented by the manufacturer without prior review by SAHPRA (i.e. these changes do not require reporting and approval by SAHPRA).

For each product, the HCR or manufacturer should maintain a chronological comprehensive list of all quality changes, including Minor Quality Changes that occur in all production areas. Additionally, this list should include a description of the manufacturing and quality control changes including: the manufacturing site(s) or area(s) involved, the date each change was made and references of relevant validations and SOPs. The data to support Minor Quality Changes listed in Appendices 2 and 3 should be available upon request from SAHPRA or during inspections. SAHPRA requires that a list of the minor quality changes be reported either as part of subsequent amendments for prior approval or by annual notification amendments. When Minor Quality Changes are related to a major or moderate change, they should be included as part of the amendment for the Major or Moderate Quality Change.

6. REPORTING CATEGORIES FOR SAFETY, EFFICACY AND/OR PRODUCT LABELLING INFORMATION CHANGES

After assessing the effect of a change related to the clinical use or to the product labelling information, on the safe and effective use of a biological medicine, HCRs should report this change in one of the following categories:

- **Safety and Therapeutic Efficacy Changes**
- **Product Labelling Information Changes**
- **Administrative Product Labelling Information Changes**

The product labelling information includes the following labelling items: prescribing information (or Professional Information) for health care providers or patients, outer label (i.e. carton), and inner label (i.e. container label). After approval, a HCR should **promptly** revise all promotional and advertising items to make them consistent with implementation of the product labelling information change. Further information on each category is provided below. See Appendix 4 for examples of therapeutic efficacy, safety and product labelling information changes considered to be appropriate for each category.

6.1 Safety and Efficacy Changes

Safety and Efficacy Changes are changes that impact the clinical use of the biological medicine and relate to safety, therapeutic efficacy, dosage, and administration, and require data from clinical studies to support the change. For biosimilar medicines, references may be made to the clinical data generated for the reference product (e.g. in the case of a safety related PI update to add new adverse events, warnings or precautions) Safety and Efficacy Changes are major changes and require amendment application submission and approval prior to implementation of the change.

Generally, Safety and Efficacy Changes affect the product labelling information and have the potential to increase or decrease the exposure levels of the medicine, either by expanding the population that is exposed, or by changing dosage or dosing. These changes may be related to clinical use of the medicine such as:

a) addition or expansion of a safety claim or efficacy claim, including expansion of the population that is exposed;
b) change in strength or a route of administration*;
c) change in the recommended dose and/or dosing range or schedule;
{including for a vaccine, the addition of a booster dose;)
d) co-administration with other medicines; or
e) deletion or reduction of existing risk management measures (e.g. contraindications, adverse events, warnings or cautionary text/statements, in the product labelling information).

It is possible that SAHPRA may consider that these changes require a new Registration application, e.g. changes in route of administration or strength. Furthermore, in some cases, changes involving the subcutaneous and intramuscular administration routes may not require a new application, while others such as changes from intramuscular to intranasal administration routes may require a new application.

The type and scope of the required supportive non-clinical and/or clinical safety and efficacy data are determined case-by-case based on risk-benefit considerations related to the impact of the changes, the medicine attributes and the disease it is designed to prevent or treat and may be based on considerations such as:

- Robust nature of the therapeutic (or immune) response elicited by the medicine and availability of a correlate of efficacy.
- Availability of animal models; and
- Medicine attributes (i.e., live vs. inactivated vaccines).

HCRs are encouraged to consult with SAHPRA, on the adequacy of the clinical data needed to support a safety and efficacy change if deemed necessary. Additionally, changes in dosage form (i.e., change from lyophilised to

liquid) and delivery device (i.e. change from needle and syringe to jet injector) may require clinical data and SAHPRA should also be consulted on the data required to support such changes.

For non-clinical and clinical studies, the recommendations given in the WHO Guidelines on non-clinical evaluation of vaccines [4], Guidelines on clinical evaluation of vaccines: regulatory expectations [5], Guidelines on the quality, safety and therapeutic efficacy of biotherapeutic protein products prepared by recombinant DNA technology [16] and other related guidelines [7-10] should apply. Guidance on approaches to the non-clinical and clinical comparability exercise can also be found in WHO's guidelines on evaluation of similar biotherapeutic products [19,20]

For a change under this category, the HCR should submit a CTD application to SAHPRA that includes the following:

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

6.2 Product Labelling Information Changes

Product Labelling Information Changes are changes to the labelling items that have the potential to improve the management of risk to the population currently indicated for use of the medicine (or in any other way exposed to the medicine) by:

a) the identification or characterisation of any adverse event, addition or strengthening of risk management measures for the adverse event;
b) the identification of subgroups for which the benefit to risk profile of the medicine has the potential to be less favourable; and
c) the addition or strengthening of risk management measures, including instructions on dosing or any other conditions of use.

Product Labelling Information Changes require amendment submission and approval prior to the distribution of the product. Often amendments for Product Labelling Information Changes related to clinical use require data from pharmacovigilance reports (i.e. Periodic Safety Update Reports, PSUR).Changes supported by large clinical or non-clinical studies usually are not considered as Product Labelling Information Changes but as Safety and Efficacy Changes.

6.3 Administrative Product Labelling Information Changes

Administrative Product Labelling Information Changes (e.g. change of distributor's address, minor format change) require reporting to SAHPRA prior to implementation by the HCR, but do not require prior approval by SAHPRA. They are changes that are not expected to impact the safety, therapeutic efficacy, and/or effective use of the product. In addition, these changes should be reported to SAHPRA as part of subsequent amendments for Safety and Efficacy Changes or Product Labelling Information Changes when updated product labelling information is included.

7.PROCEDURES

The establishment of procedures and criteria for adequate oversight of changes is the responsibility of SAHPRA.

SAHPRA has established this guideline regarding the submission procedures and time lines with action dates to be considered by HCRs when preparing to submit an amendment for a change.

Because Major Quality or Efficacy and Safety Change amendments require extensive documentation and data, the review times should be longer than for Moderate Quality Change or Product Labelling Information Change amendments. Furthermore, SAHPRA may establish different timelines for reviews of Major Quality Changes not requiring clinical data, compared to Safety and Efficacy Changes requiring clinical data.

See Appendix 1 for examples of regulatory categories and review timelines.

In the case where SAHPRA decides to recognise the approval of any of the regulatory authorities with which SAHPRA aligns itself, timelines may not apply. HCRs may contact SAHPRA to determine the adequate category of amendments prior to submission of the information in support of a change especially if the change is not included in Appendices 2 to 4.

HCRs may also consult with SAHPRA on the adequacy of clinical data required to support a Safety, Efficacy or Product Labelling Information Change. HCRs are encouraged to contact SAHPRA regarding plans for future changes and proposed filing dates for changes to existing products to aid SAHPRA in planning the allocation of review resources.

All communication with SAHPRA must be through the office of the CEO.

To aid in the acceptance of submissions for review, the cover letter to an amendment for a manufacturing change should specify that the amendment is being reported in the selected category by labelling the submission as:

- Major Quality Change, or
- Moderate Quality Change.

The cover letter to an amendment application for a safety, efficacy or product labelling information change should specify that the change is being reported in the selected category by labelling the submission as:

- Safety and Efficacy Change,
- Product Labelling Information Change, or
- Administrative Product Labelling Information Change.

Major Quality Change amendments that contain both, quality data and revised product labelling information but no clinical data should be labelled **Major Quality Change and Product Labelling Information Change** and the cover letter should specify that the submission includes both, quality changes and revised product labelling information items**.** Major Quality Change amendments that contain both, quality and safety and efficacy data (from clinical studies) and revised product Labelling information, should be labelled **Major Quality Change and Safety and Efficacy Change** and the cover letter should specify that the submission includes quality changes and revised product labelling information items**.**

All amendment applications should include a list of all the changes contained in the submission. The list should describe each change with sufficient detail to allow SAHPRA to speedily determine whether the appropriate reporting category has been used and should be part of the cover letter. If the submission has been inappropriately classified, the HCR will be notified.

Minor Quality Changes that are related to a Moderate or Major Quality Change, should be included in the prior approval amendment if they were implemented after the submission of a previous amendment for a Moderate or

Major Quality Change (e.g. a minor change such as tightening of a specification, should be included in an amendment for a moderate or major change which includes updated quality control release information).

7.1 Procedures for Prior Approval Amendments

The procedures in this section apply to all changes requiring approval prior to implementation: Major Quality Changes, Moderate Quality Changes, Safety and Efficacy Changes, and Product Labelling Information Changes.

The following common items should be included, where applicable, in the submission package for post approval changes:

a) A cover letter that includes:
   I. the type of submission (e.g., Major Quality Change, Moderate Quality Change);
   II. a narrative of the change(s) and a rationale for the change(s);
   III. any other information relevant to the submission; and
   IV. an indication of the general type of supporting data.
b) Completed documents or forms based on SAHPRA requirements such as: Medicines Submission Application Form signed and dated;
c) GMP documentation information, as applicable;
d) Where relevant, a side-by-side comparison showing the differences between the approved manufacturing process (including quality control tests) compared to the proposed ones.

In addition to the above common information, the specific information to support the various quality changes is outlined in Appendices 3, 4 and 5. It should be noted that the common information is not repeated for the various changes outlined in the appendices. All data recommended to support a change should be provided with the submission.

When recommended supporting data cannot be submitted, a detailed rationale should be provided. For submissions that include multiple changes, the applicant should clearly specify which supporting data support each change.

If the same change is applicable to multiple products, a separate submission is generally required for each product but the data may be cross-referenced. When cross-references are made to previously submitted information, details on the cross-referenced information should be indicated in the covering letter (e.g., brand name of the product, manufacturer's/HCR's name, submission type, application number, date approved).

Submission filed in electronic format (ZA eCTD) or paper (ZA CTD) should be based on the current requirements of SAHPRA. The submitted data should be well organised and should be provided in the format defined by SAHPRA. A CD-ROM/USB that includes all the documentation relating to an amendment application can be useful.

If SAHPRA determines that the information submitted in an amendment fails to demonstrate the continued quality, safety or efficacy of the product made with the change, it will try to resolve the problems with the HCR. In such cases SAHPRA will issue an information request letter for additional documentation, information and clarification to be submitted by the HCR. If the identified deficiencies are not resolved and may have a negative impact on the product, SAHPRA may decide to issue a written non-compliance notification by which the change cannot be implemented and product made with the amendments cannot be distributed.

If the information in the amendment is adequate and all identified deficiencies are resolved in a satisfactory manner, SAHPRA will issue a written approval notification. Regarding the resolution of conflicts or disputes between SAHPRA and the HCR, the Act 101 (1965) provides procedures for review and appeal of decisions.

The following points should be considered when submitting changes:

- **Comparability Protocol:**

A comparability protocol (also referred to as post approval change management protocol in other documents)

establishes a framework for a well-defined plan for the future implementation of a quality change, the tests

to be done and acceptable limits to be achieved to demonstrate the lack of negative effect for specific manufacturing changes on the quality, safety or therapeutic efficacy of the medicine. A comparability protocol is a highly specific, well-defined plan for the future implementation of a quality change. For some changes the routine quality tests performed to release active biological ingredient or final product are not considered adequate to assess the impact of the change and additional in-process tests and characterisation tests may be needed (e.g., addition of bioburden and endotoxin tests to support the removal of preservatives from the manufacturing process).

The purpose of a comparability protocol is to allow for a more expedient distribution of product by permitting MA holders to submit a protocol for a change, which if approved, may justify a reduced reporting category for the particular change at the time the comparability data are obtained and the change is implemented. This concept is not included in this guidance as the use of the comparability protocol is not currently harmonised amongst NRAs. It is the decision of the NRA whether or not to include the review and approval of comparability protocols in their approach to regulating changes to approved medicines. Currently SAHPRA does not have a mechanism for reviewing and approving a comparability protocol. Nonetheless this may change in the future. For those NRAs currently taking this approach, a new comparability protocol, or a change to an existing one, requires submission of an amendment and approval prior to implementation because it may result in a decreased reporting category for the changes covered in the comparability protocol after the actual comparability data are submitted. The change of reporting category for the comparability protocol vs. the comparability data should be established by the NRA at the time the comparability exercise is approved.

- **Multiple Changes**:
  Multiple related changes involving various combinations of individual changes may be submitted in the same amendment application. For example, a site change may also involve equipment and manufacturing process changes or a medicine component change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, the submission should be in accordance with the most restrictive of the categories recommended for the individual changes. For submissions that include multiple changes, the HCR should clearly specify which supporting data support which change.

  Multiple Major or Moderate Quality Changes for the same medicine may be filed in a single submission provided those changes are related and/or supported by the same information. Any other category of changes (e.g. Minor Quality Changes and Administrative Product Labelling Information Changes) may be filed together with other submissions whether or not they are related and/or support the same information. If the changes are related, the HCR should indicate the association between the proposed changes. Such changes could affect both the active biological ingredient and the final product. If there are too many changes filed within the same submission or major issues are identified with a change which would require extensive time to review, SAHPRA may ask the HCR to divide the changes into separate submissions and resubmit the file. As indicated above, if the recommended reporting categories for the individual changes differ, the submission should be in accordance with the most restrictive of the categories recommended for the individual changes. In case of numerous changes of the same category, SAHPRA may reclassify the submission to the next higher level based on the potential impact of the sum of the changes on the quality, safety and efficacy of the medicine. This reclassification should be communicated to the HCR at the start of the assessment.

- **Production Documents:**
  Production documents (executed lot records) are not required at the time of filing to support post- approval changes. However, these may be requested during review and should be available upon request and during inspections

7.2 Procedures for Minor Quality Changes

Minor Quality Changes do not require notification and prior approval from SAHPRA for implementation. However, any minor changes that have been implemented should be annotated in the affected documents (e.g. SOPs, batch records). Minor Quality Changes should be listed in a single document and related supportive data as recommended in Appendices 2 and 3 should be adequately recorded and filed and should be available to SAHPRA upon request or inspections. Additionally, Minor Quality Changes that were previously implemented and are related to a Major or Moderate Quality Change should be included when submitting a prior approval amendment for the related change.

SAHPRA may audit minor quality changes by requesting and reviewing the supporting data as deemed appropriate. If the classification of the change or the supportive data is not considered to be acceptable, the HCR may be requested to file a Major or Moderate Quality Change amendment. In cases where the change has already been implemented, the HCR may continue to distribute the medicine until such time as any issues are resolved. However, if SAHPRA considers that the changed medicine may impact the safety, therapeutic efficacy, quality and/or effective use, SAHPRA may request the HCR to withdraw the medicine from the market.

For changes that are not reported, if SAHPRA determines (during an inspection) that the information for the change fails to demonstrate the continued safety or efficacy of the product made using the changes, it will try to resolve the problems with the HCR. If SAHPRA finds that the product in distribution poses a danger to public health, or if it determines that there are unresolved issues, it may require the HCR to cease distribution of the product made using the changes or to remove the product from distribution pending resolution of the issues related to the changes.

7.3 Procedures for Administrative Product Labelling Information Changes

For Administrative Product Labelling Information Changes, a copy of the most recent revised product Labelling information should be submitted to SAHPRA as an amendment to the registration application, but do not require approval prior to implementation.

Additionally, Administrative Product Labelling Information changes should be included when submitting amendments for Safety and Efficacy Changes or Product Labelling Information Changes, for minor changes that have been implemented from the time of the last approved product Labelling information to the time of the amendment submission. For minor changes, the product Labelling information should be annotated when filing the next prior approval amendment to indicate those administrative changes that have been implemented.
These amendment procedures must follow current SAHPRA Guidelines for amendments to Professional Information and Patient Information Leaflets.

8.1. Adjuvants

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

There is substantial diversity among vaccine adjuvants, antigens and the diseases they are designed to prevent. Therefore, the supportive information needed for adjuvant-related changes will depend on product-specific features, the clinical indications, and the impact of the change. The recommendations in the WHO *Guidelines on the non-clinical evaluation of vaccine adjuvants and adjuvanted vaccines* [12] should be followed.

8.2. Annual Viral Strain Changes for Influenza Vaccines

To ensure that influenza vaccines are effective against circulating influenza virus strains, the WHO reviews global epidemiological data twice annually and if necessary, recommends new vaccine strain(s) in accordance with the available evidence for the northern and southern hemispheres [13, 14]. The WHO and NRAs usually recommend the use of certain virus strains based on the antigenic characteristics of the influenza virus hemagglutinin (HA) and neuraminidase (NA) glycoproteins. Influenza vaccine viruses usually are derived from isolates obtained from laboratories in the WHO influenza network.

For seasonal influenza vaccines, annual changes in the vaccine strain composition are considered Moderate Quality Changes because of the extensive experience with such changes and to maximise flexibility and brevity of the review process as needed. HCRs of approved seasonal vaccines are expected to submit a Moderate Quality Change amendment to support annual changes in the influenza strain composition.

To allow for timely distribution of vaccines SAHPRA reviews the amendment in a speedy process. The supportive quality information generally consists of information on the source of the viruses, passage history until establishment of working seeds, and results of quality release tests performed on working virus seeds (including identity confirmation). In addition, updated product Labelling information items (Professional Information and inner and outer labels with relevant strain composition and formula year) should also be provided.
This information is detailed in the SAHPRA Amendment Guideline 2012 for seasonal strain change of influenza vaccines.

Changes to manufacturing processes, posology, and product Labelling information of influenza vaccines that are not related to the annual update should follow the normal categorisation as described in Appendices 2 to 4 and should not be included in the strain change amendments to avoid delays in the approval process. Due to the time constraints related to the seasonality of influenza vaccines, changes that are not related to vaccine strain composition should be timed such that approval would allow manufacture of vaccines made with the change to be distributed prior to the start of the influenza season (i.e. the fall of the southern and northern hemispheres).

8.2.1. Introduction

There are several influenza vaccines registered and marketed in South Africa, all of which contain three influenza strains: usually two of type A and one of type B. Each year the manufacturer changes the viral strain composition to conform to those deemed most likely to cause outbreaks during the next influenza season [May to October] in the Southern Hemisphere.

The WHO, via the International Influenza Centres assisted by National Laboratories, studies the isolates, incidence and virulence of influenza viral strain around the world and generates strain recommendations, prior to the influenza season for each hemisphere. The WHO recommendations are intended for worldwide use and therefore need to be adapted to the epidemiological situation of each country.

The influenza vaccine manufacturers obtain viral strains that conform to the characteristics of the strains recommended by the WHO and develop manufacturing processes to incorporate these into their respective products. These formulations are then submitted for approval from the regulatory authority to amend the formula, the manufacturing processes (where applicable), the Professional Information and the Patient Information Leaflet.

This guideline outlines the process to be followed when submitting an annual viral strain change to ensure standardised and adequate evaluation for quality, safety and therapeutic efficacy, and to expedite the approval process.

This process is solely for routine annual vaccine viral strain changes and any related safety information to be included in the Professional Information and the Patient Information Leaflet. No other amendments may be included in the process.

8.2.2. Time for submission

The application must be submitted to SAHPRA as soon as the required information is available. Submission of the application by the end of October of the year preceding the intended Influenza season will allow for comprehensive and diligent review.

The intention is to have routine annual vaccine strain changes approved by the end of February of the year of the relevant influenza season. Late or incomplete submissions will lead to delays in the review and approval process.

8.2.2.1. Information and documentation required

The application to change viral strain involves changes to the Registration Certificate and therefore the relevant amendment fee should be paid and proof of such payment be included in the submission.

The following information and the relevant documents must be included:

1) WHO recommended strain list for the relevant hemisphere.
2) Manufacturer's choice of strains for inclusion.
3) Details of manufacturing procedure (declaration if unchanged).
4) The source, history and master/working seed characterisation of each strain included.
5) Egg/cell culture: Safety specifications and tests. (Declaration if unchanged.)
6) Final product release specifications and results. This must include Endotoxin release limit.
7) Retrospective data about the "efficacy or performance" of influenza vaccines (preceding year / season).
8) Stability data (accelerated or from the most recent, or most similar batch of approved vaccine).
9) Copy of the approved Professional Information.
10) Copy of the proposed Professional Information indicating: The year/season for which the vaccine will be used.

8.3. Bridging Studies

Clinical and non-clinical bridging studies are trials in which a parameter of interest (e.g. manufacturing process, formulation, dosing schedule) is directly compared with a changed version of that parameter with respect to the effect of the change on the product's clinical performance. If the physicochemical properties, biological activity, purity, level of impurities and contaminants of the pre-amendment and post-amendment product are comparable, the safety and efficacy of the biological medicine can be inferred. However, non-clinical and/or clinical bridging studies may be required when analytical data alone are insufficient to establish comparability. Comparison of therapeutic or immune responses and safety outcomes [e.g., rates of common adverse events (AEs) and serious AEs (SAEs)] are often the primary objectives. If the immune response and safety profiles are similar, then efficacy and safety of the changed medicine can be inferred.

In some cases safety and efficacy data comparing the medicine before the change to the medicine produced with the change (bridging studies), may be required. The following are examples of manufacturing changes that may require non-clinical and/or clinical bridging studies:

- Use of a new or re-derived virus seed or bacterial cell bank or host cell line (i.e. re-derived master cell bank).
- New agents used for inactivation or purification of the active ingredient with major impact on the quality of the active ingredient.
- New dosage form.
- New formulation (e.g., amount and composition of ingredients, adjuvants, or preservatives, amount of reactogenic residual components from the manufacturing process).

9. REFERENCES

1. Guidelines for national authorities on quality assurance for biological products. Annex 2, in: *WHO Expert Committee on Biological Standardization. Forty-second report*. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 822).
2. *Regulation of vaccines: building on existing medicines regulatory authorities*. Annex 2, in: *WHO Expert Committee on Biological Standardization,. Forty-fifth report*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 858).
3. WHO NRA assessment tools/indicators. Geneva, World Health Organization, 2008 (http://www.who.int/immunization_standards/national_regulatory_authorities%20/vaccine_indic ators/en/index.html/).
4. Guidelines on nonclinical evaluation of vaccines. Annex 1, in: *WHO Expert Committee on Biological Standardization. Fifty-fourth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927).
5. Guidelines on clinical evaluation of vaccines: regulatory expectations. Annex 1, in: *WHO Expert Committee on Biological Standardization. Fifty-second report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 924).
6. Guidelines on stability evaluation of vaccines. Annex 3 in: *WHO Expert Committee on Biological Standardization. Fifty-seventh report.* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 962).
7. Handbook: good laboratory practice (GLP). Quality principles for regulated non-clinical research and development, 2nd edition. Geneva, World Health Organization, 2009.
8. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. Annex 3 in: *The use of essential drugs. Sixth report of the WHO Expert Committee*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850).
9. Good Manufacturing Practices for pharmaceutical products: main principles. Annex 4, in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization 2003 (WHO Technical Report Series, No. 908).
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11. Guidelines for independent lot release of vaccines by regulatory authorities. *WHO Expert Committee on Biological Standardization. Sixty-first report*. Geneva, World Health Organization (in press).
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13. Recommendations for the production and control of influenza vaccine (inactivated). *WHO Expert Committee on Biological Standardization. Fifty-fourth report*. Geneva, World Health Organization 2005 (WHO Technical Report Series, No. 927).
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15. *WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (document WHO/BCT/QSD/03.01). Geneva, World Health Organization, 2003.
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17. WHO Guidelines on procedure and data requirements for changes to approved biotherapeutic products, proposed guidelines WHO/BS/2017.2311)
18. WHO Guideline for procedures and data requirements for changes to approved vaccine (TRS 993 Annex-4 2015)
19. Guidelines on evaluation of similar biotherapeutic products (SBPs). In: WHO Expert Committee on Biological Standardization: sixtieth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 977
20. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs). In: WHO Expert Committee on Biological Standardization: Sixty-seventh report. Geneva: World Health Organization; 2017: Annex 2 (WHO Technical Report Series, No. 1004.
21. Health Canada Guidelines
22. EMA guidelines
23. United States Food and Drug Administration regulations and guidance. 21 Code of Federal Regulations, Parts: 601.12 *Changes to an approved application*; 610.9 *Equivalent methods and processes*. FDA *Guidance for Industry: Changes to an Approved Application: Biological Products* (July, 1997).
24. Pharmaceutical and Analytical CTD/ guideline, 2.25 PA CTD Aug 14 v6
25. Amendments guideline, 2.08 Amendments Jul12 v6
26. Biosimilar Medicines: Quality, Non-Clinical and Clinical Requirements Guideline, 2.30 Biosimilars Aug14 V3

APPENDIX 1 - Reporting Categories

It is recommended that NRAs establish review timelines to allow HCRs to plan the implementation of changes. The review times are established based on the capabilities of the NRAs, the impact of the change, and the amount of required supportive data. Therefore, the review time frames for major changes should be longer than for moderate changes. The suggested review times for SAHPRA will be included at a later stage. The review time would start when the application has been accepted for review and found to be complete and end at the time when the initial assessment is shared with the HCR either in an approval or as a request for supplementary documentation. In case of the latter the shorter timelines may apply for the secondary assessment following reception of HCR answers. In case of need of minor clarifications, the NRA may communicate with the HCR during the initial assessment period without stopping the clock to be able to finalise the assessment within the proposed time line.

Table 1. Examples Prior Approval Amendments

Category	**Amendment**
Quality Changes	
Major Quality Changes	Prior Approval Amendment
Moderate Quality Changes	Prior Approval Amendment
Minor Quality Changes	Do not require notification to SAHPRA [1]
Safety, Efficacy and Product Labelling Information Changes	
Safety and Efficacy Changes	Prior Approval Amendment
Product Labelling Information Changes	Prior Approval Amendment
Administrative Product Labelling Information Changes	Require notification to SAHPRA, but do not require approval prior to implementation[2]

N/A – not applicable

[1]Minor Quality Changes that are related to a Moderate or Major Quality Change, should be included in the prior approval amendment if they were implemented after the submission of a previous amendment for a Moderate or Major Quality Change (e.g. a minor change such as tightening of a specification, should be included in an amendment for a moderate or major change which includes updated quality control release information).

[2]Notification of Administrative Product Labelling Information Changes may involve the submission of annotated and clean copies of the product labelling information items as general correspondence to the MA or product licence.

APPENDIX 2 - Post Approval changes to the active biological ingredient

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information for an active ingredient. The information summarised in the table provides recommendations for:

(a) the *conditions to be fulfilled* for a given change to be classified as either a major, moderate, or minor change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for a Moderate Quality Change are not fulfilled, the change is considered a Major Quality Change;

(b) the *supporting data* for a given change, either to be submitted to SAHPRA and/or maintained by the HCR. If any of the supporting data outlined for a given change are not provided, is different or is not considered applicable, adequate scientific justification should be provided; and

(c) the *reporting category* (e.g. Major, Moderate or Minor Quality Change).

It is important to note that SAHPRA reserves the right to request additional information or material as it deems appropriate, or to define conditions not specifically described in this document in order to allow SAHPRA to adequately assess the quality, safety and therapeutic efficacy of a vaccine. HCRs should contact SAHPRA if a change is not included in the table and if it may have the potential to impact on product quality.

Supporting data should be provided according to the submission format accepted by SAHPRA. This is ZACTD and/or ZA eCTD formatted submissions, the supporting data should be provided in the appropriate sections of the CTD Modules (not as separate documents).

Quality Changes to Comply with Updated Compendia and/or Pharmacopeia

SAHPRA recognises certain compendia and/or pharmacopeia (i.e British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopoeia
Quality changes to approved compendial/pharmacopoeial materials (e.g. raw materials, reagents, etc.), analytical procedures or assays solely to comply with updated compendial/pharmacopoeial requirements are considered a minor change as long as the change is made within six (6) months of the implementation of the updated compendial/pharmacopoeial requirements. Otherwise, the HCR is required to file a moderate change for approval by SAHPRA.

General Information

Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Category**
1. Change in the name of the active biological ingredient	1	1-2	Minor
Conditions			
1. Confirmation that information on the active biological ingredient has not changed as a result of the submission (e.g. cross reference(s) should be provided to the previously approved medicine submission, including brand name of the final product, manufacturer's / applicant' s name, date approved).			
Supporting Data			

1. Revised product information including Labelling.
2. Information on the proposed nomenclature of the active biological ingredient and evidence that the proposed name for the active biological ingredient is recognised (e.g. proof of acceptance by WHO,

Manufacture

Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Category**
2. Change to an Active biological ingredient manufacturing facility:			
a. replacement or addition of a manufacturing facility for the active bulk, or any intermediate of the active biological ingredient	None	1-4,6-8	Major
	1-4	2, 4-8	Moderate
b. deletion of a manufacturing facility or manufacturer for an intermediate, active biological ingredients , or bulk	5-6	None	Minor
Conditions			
1. This is an addition of a manufacturing facility/suite to an approved active manufacturing site. 2. Any changes to the manufacturing process and/or controls are considered either moderate or minor. 3. The new facility/suite is under the same QA/QC oversight. 4. The proposed change does not involve additional containment requirements. 5. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. 6. The deletion should not be due to critical deficiencies concerning manufacturing (e.g. recurrent deviations, recurrent out-of-specification events, environmental monitoring failures, etc.)			
Supporting Data			

1. Evidence of facility GMP compliance.
2. Name, address, and responsibility of the proposed facility.
3. Summary of the process validation and/or evaluation studies. The complete report with all raw data could be requested during review.
4. Comparability of the pre and post-change active biological ingredient with respect to physico-chemical characterisation, biological activity, and impurity profile. Occasionally, bridging non- clinical and/or clinical studies may be required when quality data are insufficient to establish comparability. The extent and nature of non-clinical 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 medicine, existing relevant non-clinical and clinical data, and aspects of medicine use.
5. Justification for the classification of any manufacturing process and/or control changes as moderate.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the pre and post-change active biological ingredient. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller scale batches, and/or the use of less than 3 batches and/or leveraging data from scientifically justified representative batches or batches not necessary manufactured consecutively may be acceptable where justified and agreed upon by SAHPRA.
7. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least 3 commercial scale batches of active biological ingredient produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life /hold-time of the active biological ingredient under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than 3 batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
8. Updated post-approval stability protocol.

Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Category**
3. Change to the active biological ingredient fermentation, viral propagation or cellular propagation process:			
a. a critical change (e.g. incorporation of disposable bioreactor technology)	None	1-7, 9, 11	Major
b. a change with moderate potential to adversely Impact quality of the active biological ingredient or final product (e.g. extension of the *in vitro* cell age beyond validated parameters)	2,4	1-6, 8, 10	Moderate

c. a non-critical change, such as: change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of detection of adventitious agents, or production scale; or duplication of a fermentation train; or addition of similar/comparable bioreactors	1-6, 9-11	1-4	Minor
4. Change to the active biological ingredient purification process involving:			
a. a critical change (e.g. change that could potentially impact negatively the viral clearance capacity of the process or the impurity profile of the active)	None	1-2, 5-7, 9, 11, 12	Major
b. a change with moderate potential to impact quality of the active or final product (e.g. change in the chemical separation method, for example ion- exchange HPLC to reverse phase HPLC)	2,4	1-2,5-7,10-11	Moderate
c. a non-critical change with minimal potential to impact the quality of the active biological ingredient or final product (e.g. addition of an in-line filtration step equivalent to the approved filtration step)	1-5	1-2	Minor
5. Change in scale of the manufacturing process:			
a. at the fermentation or viral propagation or cellular propagation stage	12-13	3, 6-7, 9, 11	Moderate
b. at the purification stage	1,3,5,7	6-7, 9, 11	Moderate

6.Change in supplier of raw materials/reagents of biological origin (e.g. production eggs, foetal calf serum, human serum albumin)	None	4, 8, 12-	Moderate
	8	4, 8	Minor
7. Change in source of raw materials/reagents of biological origin	None	4, 7, 12-13	Moderate
	8	4, 7	Minor
8. Introduction of reprocessing steps	14	8, 10-11, 14	Moderate
Conditions			

1. No change in the principle of the sterilisation procedures of the active biological ingredient.
2. The change does not impact the viral clearance data or the chemical nature of an inactivating agent.
3. No change in the active biological ingredient specifications outside of the approved ranges.
4. No change in the impurity profile of the active biological ingredient outside of the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The change in scale is linear.
8. The change is for compendial raw materials/reagents of biological origin (excluding human plasma-derived materials).
9. The new fermentation train is identical to the approved fermentation train(s), if applicable.
10. No change in the approved *in vitro* cell age.
11. The change is not expected to have an impact on the quality, safety or efficacy of final product.
12. No change in the proportionality of the raw materials (i.e. the change in scale is linear).
13. The change in scale involves the use of the same bioreactor (i.e. does not involve the use of a larger bioreactor).

14 The need for reprocessing is not due to recurrent deviations from the validated process and the root cause triggering reprocessing is identified.

Supporting Data

1. Justification for the classification of the change(s) as critical, moderate or non-critical as it relates to the impact on the quality of the active biological ingredient.
2. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
3. If the change results in an increase in the number of population doublings or subcultivations, information on the characterisation and testing of the post-production cell bank for recombinant product, or of the active biological ingredient for non-recombinant product.
4. For active biological ingredients obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g. ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g. name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance).
5. Process validation and/or evaluation studies
6. Comparability of the pre and post-change active biological ingredient with respect to physico-chemical characterisation, biological activity, and impurity profile. Occasionally, bridging non-clinical and/or clinical studies may be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis taking into consideration the quality comparability findings, the nature and level of the knowledge of the medicine, existing relevant nonclinical and clinical data, and aspects of medicine use
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the pre- and post-change active biological ingredient. Matrixing, bracketing, the use of smaller scale batches, and/or the use of less than 3 batches may be acceptable where justified and agreed upon by SAHPRA.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the pre- and post- change active biological ingredient. Batch data on the next two full production batches should be made available upon request and reported by the HCR if outside specification (with proposed action). The use of a smaller scale batch may be acceptable where justified and agreed upon by SAHPRA.

9. Comparative pre and post-change test results for the manufacturer's characterised key stability indicating parameters with at least 3 commercial scale active biological ingredient batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the active biological ingredient under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than 3 batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
10. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least one commercial scale active biological ingredient batch produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the active biological ingredient under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller scale batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
11. Updated post-approval stability protocol and stability commitment to place the first commercial scale batch of the final product manufactured using the post-change active biological ingredient into the stability program.
12. Information assessing the risk with respect to potential contamination with adventitious agents (e.g. impact on the viral clearance studies, BSE/TSE risk).
13. Information demonstrating comparability of the auxiliary materials/reagents of both sources.
14. Data describing the root cause triggering the reprocessing as well as validation data (e.g. extended hold times, resistance to additional mechanical stress) to support that the reprocessing does not have an impact on the active biological ingredient.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
9. Changes to the cell banks:			
a. generation of a new Master Cell Bank (MCB)	1	1-2,5,7-9	Moderate
b. generation of a new Working Cell Bank (WCB)	None	1-2	Moderate
	2-4	1-2	Minor
c. Extension of shelf life of the MCB or WCB	5	1-2	Minor
10. Changes to the seed lots:			

a. a new Master Seed Lot (MSL); or a Working Seed Lot (WSL) extended beyond an approved passage level	None	5-9, 11	Major
b. generation of a new WSL	2-3	5-9, 11	Moderate
	2-4	5-6, 11	Minor
11. Change in cell bank/seed lot testing site	6	10	Minor
12. Change in cell bank/seed lot qualification protocol	None	3-4	Moderate
	7	4	Minor

Conditions

1. The new MCB is generated from a pre-approved MCB or WCB.
2. The new cell bank/seed lot is generated from a pre-approved MCB/MSL.
3. The new cell bank/seed lot is at the pre-approved passage level.
4. The new cell bank/seed lot is released according to a pre-approved protocol/ process or as described in the original license
5. The testing to support the extension of shelf life is performed according to the pre-approved protocol or as described in the original licence
6. No changes have been made to the tests/acceptance criteria used for the release of the cell bank/seed lot.
7. The protocol is considered more stringent (i.e. addition of new tests or tightening of acceptance criteria).

Supporting Data

1. Qualification of the cell bank according to guidelines considered acceptable by SAHPRA.
2. Information on the characterisation and testing of the MCB /WCB, and cells from the end-of-production (EPC) passage or post-production passage.
3. Justification of the change to cell bank/seed lot qualification protocol.
4. Updated cell bank/seed lot qualification protocol
5. Comparability of the pre and post-change active biological ingredient with respect to physico-chemical characterisation, biological activity, and impurity profile. Occasionally, bridging non-clinical and/or clinical studies may be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case

basis taking into consideration the quality comparability findings, the nature and level of the knowledge of the medicine, existing relevant non-clinical and clinical data, and aspects of medicine use.

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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
13. Change in product-contact equipment/material used in the active biological ingredient manufacturing process , such as:			
a. Introduction of new equipment having different operating principles and different product material	None 3-4	1-5 1,2,5	Moderate minor
b. introduction of new equipment with the same operating principles but different product contact material used in a critical step new	None 3-4	1, 3- 5 1,4-5	Moderate minor
c. Introduction of new equipment with different operating principles but the same product contact material	None 4	1–3, 5 1,2,5	Moderate Minor
d. Replacement of product-contact equipment with equivalent equipment	none	3	minor
e. Change of product-contact equipment from dedicated to shared	1,2	1, 6	minor
f. Relocation of equipment to another room in the same facility/suite/premises	2,4,5	none	minor
Conditions			

1. The site is approved as a multi-product facility.

2. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.

3. The manufacturing process is not impacted by the change in product-contact equipment.

4. The change has no impact on product quality.

5. Re-qualification of the equipment follows the original qualification protocol, if applicable.

Supporting Data

1. Information on the in-process control testing.
2. Process validation and/or evaluation studies.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial scale batches of the active biological ingredient produced with the approved and proposed product contact equipment/material). Batch data on the next two full production batches should be made available upon request and reported by the MAH 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	Supporting Data	Reporting Categories
14. Change in specifications for the starting materials, involving:			
a. Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active biological ingredient and/or final product.	None	1, 3-5, 7-8	Major
b. raw materials, starting materials	1,3-4, 11	1,3-6	Minor
c. solvents, reagents, catalysts	2-4	1,3-6	Minor
15. Change to in-process tests or limits applied during manufacture of the active biological ingredient, involving:			
a. Tightening of in-process limits	5, 9	2, 7	Minor
b. Addition of new in-process test and limits	4, 5, 10, 11	2, 4, 5, 7,8, 10	Minor
c. Deletion of a non-significant in-process test	4, 5, 6	2, 7, 9	Minor
d. Widening of the approved in-process limits, which may have a significant effect on the overall quality of the active biological ingredient	None	2, 4, 5, 7, 8, 10	Major
e. Deletion of an in-process test which may have a significant effect on the overall quality of the active biological ingredient	None	2, 4, 5, 7, 8,	Major

f. Addition or replacement of an in-process test as a result of a safety or quality issue	None	2, 4, 5, 7, 8, 10	Moderate
16. Change in in-process controls testing site	3-5, 7, 8	11	Minor

Conditions

1. The change in specifications for the materials is within the approved ranges.
2. The grade of the materials is the same or is of higher quality.
3. No change in active biological ingredient specifications outside of the approved ranges.
4. No change in the impurity profile of the active biological ingredient outside of the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The test does not concern a critical parameter, e.g. content, impurity, any critical physical characteristics or microbial purity.
7. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
8. No change in the in-process control limits outside of the approved ranges.
9. The test procedure remains the same, or changes in the test procedure are minor.
10. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
11. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)

Supporting Data

1. Revised information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the post-change active biological ingredient.
2. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed active biological ingredient
3. Updated active biological ingredient specifications if changed.
4. Copies or summaries of analytical procedures, if new analytical procedures are used.
5. Copies or summaries of validation reports, if new analytical procedures are used.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the approved and proposed active biological ingredient. Batch data on the next two full production batches should be made available upon request and reported by the HCR if outside specification (with proposed action). The use of a smaller scale batch may be acceptable where justified and agreed upon by SAHPRA
7. Comparative table or description where applicable of pre and post-change in-process tests/limits.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for three (3) commercial scale batch of the pre- and post-change active biological ingredient. Matrixing, bracketing, the use of smaller scale batches, and/or the use of less than 3 batches may be acceptable where justified and agreed upon by SAHPRA. Comparative pre-change test results need not be generated concurrently; relevant historical testing results are acceptable
9. Justification/risk assessment showing that the parameter is non-significant
10. Justification for the new in-process test and limits.
11. Evidence that the new company/facility is GMP compliant.

Control of the Active biological ingredient

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
17. Changes affecting the quality control (QC) (release and stability) testing of the active biological ingredient, involving:			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house)	2, 3	1-2	Minor
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not approved in the current market authorisation.	1	1-2	Minor
Conditions			
1. The transferred QC test is not a potency assay or a bioassay. 2. No changes to the test method 3. Transfer within a site approved in the current market authorisation.			
Supporting Data			
1. Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
18. Change in the specifications used to release the active biological ingredient , involving:			
a. deletion of a test	None	1,6	Moderate
b. addition of a test	1-3	1-3,6	Minor
c. replacement of an analytical procedure	None	1-3,4-5	Moderate
d. change in animal species/strains for a test (e.g. new species/strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)	None	6-7	Moderate
d. minor changes to an approved analytical procedure	4-7	1,4-5	Minor
e. a change from an in-house analytical procedure to a recognized compendial/pharmacopeial analytical procedure	4,7	1-3	Minor
f. widening of an acceptance criterion	None	1,5, 8	Moderate
g. tightening of an acceptance criterion	1, 8, 9	1	Minor

Conditions

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

Supporting Data

1. Updated active biological ingredient specifications.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification of the proposed active biological ingredient specifications (e.g. tests, acceptance criteria, or analytical procedures).
6. Data demonstrating that the change in animals/strains gives comparable results with those obtained using the approved animals/strains.
7. Copies of relevant certificate of fitness for use (e.g. veterinary certificate)
8. Declaration/evidences that consistency of quality and of the production process is maintained.

Reference Standards or Materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
19. Qualification of a new reference standard against a new primary international standard	None	1-2	Moderate
20. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1-2	Moderate
21. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	1-2	Minor
22. Change to reference standard qualification protocol	None	3-4	Moderate
23. Extension of reference standard shelf life	2	5	Minor
Conditions			
1. Qualification of the new reference standard is according to an approved protocol. 2. The extension of the shelf life is according to an approved protocol. 3. The reference standard is used for physicochemical test			
Supporting Data			
1. Justification for the change in reference standard 2. Information demonstrating qualification of the proposed reference standards or materials (e.g. source, characterisation, certificate of analysis). 3. Justification of the change to reference standard qualification protocol. 4. Updated reference standard qualification protocol. 5. Summary of stability testing and results to support the extension of reference standard shelf life.			

Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
24. Change in the primary container closure system(s) for the storage and shipment of the active biological ingredient	None	1-2,4, 5	Moderate
	1	1,3, 5	Minor
Conditions			
1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.			
Supporting Data			

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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
25. Change in the specifications of the primary container closure system for the active biological ingredient, involving:			
a. deletion of a test	1-2	1-2	Minor
b. addition of a test	3	1-3	Minor
c. replacement of an analytical procedure	6-7	1-3	Minor
d. minor changes to an analytical procedure	4-7	1-3	Minor
e. widening of an acceptance criterion	None	1-2	Moderate
f. tightening of an acceptance criterion	8	1	Minor
Conditions			

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

Supporting Data

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

Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
26. Change in the shelf life/hold-time for the active biological ingredient or for a stored intermediate of the active biological ingredient , involving:			
a. extension	None	1- 5	Moderate
	1-5	1-2,5	Minor
b. reduction	None	1-5	Moderate
	6	2-4	Minor

Conditions

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

Supporting Data

1. Summary of stability testing and results (e.g. 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 of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (i.e. full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches). For intermediates, data to show that the extension of shelf life has no negative impact on the quality of the active biological ingredient. Under special circumstances and with prior agreement with SAHPRA, interim stability testing results and a commitment to notify SAHPRA of any failures in the ongoing long term stability studies may be provided.

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

Conditions

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

Supporting Data

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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
28. Change in the storage conditions for the active biological ingredient , involving:			

a. addition or change of storage condition for the active biological ingredient (e.g. relaxation or tightening of a temperature criterion)	None	1-4	Moderate
	1-2	1-3	Minor

Conditions

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

Supporting Data

1. Proposed storage conditions and shelf life.
2. Updated post-approval stability protocol and stability commitment.
3. Justification of the change in the labeled storage conditions/cautionary statement.
4. Results of stability testing (i.e. full real time/real temperature stability data covering the proposed shelf life generated on one (1) commercial scale batch).

APPENDIX 3 - Post Approval Changes to the Final Product

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information of the final product. The information summarised in the final product table provides recommendations for:

(a) the *conditions to be fulfilled* for a given change to be classified as either a major, moderate, or minor change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for a Moderate Quality Change are not fulfilled, the change is considered a Major Quality Change;

(b) the *supporting data* for a given change, either to be submitted to SAHPRA; and/or maintained by HCR. If any of the supporting data outlined for a given change is not provided, is different or is not considered applicable, adequate scientific justification should be provided; and

(c) the *reporting category* (e.g. Major, Moderate or Minor Quality Change).

It is important to note that SAHPRA reserves the right to request additional information or material as deemed appropriate, or to define conditions not specifically described in this document in order to allow them to adequately assess the quality, safety or efficacy of a medicine. HCRs should contact SAHPRA, if a change is not included in the table and if it may have the potential to impact on medicine quality.

Supporting data should be provided according to the submission format accepted by SAHPRA. For example, for SAHPRA to accept ICH CTD and/or ICH eCTD formatted submissions, the supporting data should be provided in the appropriate sections of the CTD Modules (not as separate documents).

Quality Changes to Comply with Updated Compendia and/or Pharmacopeia

SAHPRA recognises the British Pharmacopoeia (BP), European Pharmacopoeia (Ph Eur) and United States Pharmacopoeia (USP). Quality changes to approved compendial/pharmacopoeial materials (e.g. raw materials, reagents, etc.), analytical procedures or assays solely to comply with updated compendial/pharmacopoeial requirements is considered a minor change as long as the change is made within six months of the implementation of the updated compendial/pharmacopoeial requirements.

Description and Composition of the Final Product

Note: Changes in dosage form and/or presentation in some cases may necessitate the filing of a new application for marketing authorisation. HCRs are encouraged to contact SAHPRA for further

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
29. Change in the description or composition of the final product , involving:			
a. addition of a dosage form or change in the formulation (e.g., lyophilised powder to liquid, change in the amount of excipient, new diluent for lyophilised product). *Note: change in formulation does not include changes in active biological ingredient(s) or adjuvants. A change in active biological ingredient(s) or adjuvants requires the filing of a new application for marketing authorization. HCRs are encouraged to contact the*	None	1-10	Major
b. change in fill volume (same concentration, different volume)	None	1,3,5,7,10	Major
	1-2 1-3	1,3,5,7 5,7	Moderate Minor
c. addition of a new presentation (e.g., addition of a new pre-filled syringe where the approved presentation is a vial for a medicine in a liquid dosage form)	None	1,5,7-10	Major
Conditions			
1. No changes classified as major in the manufacturing process to accommodate the new fill volume. 2. No change in the dose recommended. 3. Narrowing of fill volume while maintaining the lower limit of extractable volume.			
Supporting Data			

1. Revised final product labelling information (as applicable).
2. Characterisation data demonstrating that the conformation and immunogenicity of the active biological ingredient is comparable in the new dosage form and/or formulation.
3. Description and composition of the dosage form if there are changes to the composition or dose.
4. Discussion of the components of the final product, as appropriate (e.g. choice of excipients, compatibility of active biological ingredient and excipients, leachates, compatibility with new container closure system (as appropriate).
5. Information on the batch formula, manufacturing process and process controls, controls of critical steps and intermediates, process validation and/or evaluation studies.
6. Control of excipients, if new excipients are proposed (e.g. specifications).
7. Information on specification(s), analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three (3) consecutive commercial scale batches should be provided). Bracketing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.
8. Information on the container closure system and leachables and extractables, if any of the components have changed (e.g. description, materials of construction, summary of specifications).
9. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least 3 commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than three batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
10. Supporting clinical data or a justification why such studies are not needed.

Description and Composition of the Final Product: Change to an Adjuvant

Note: Change in type/structure of a chemical adjuvant, in the type of a biological adjuvant or in a component of a biological adjuvant may necessitate the filing of a new application for marketing authorisation. HCRs are encouraged to contact SAHPRA for further guidance.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
30. Change involving an approved chemical/synthetic adjuvant:			
a. change in supplier of a chemical/synthetic adjuvant	None	4-6,10	Moderate
	1-2	5	Minor
b. change in manufacture of a chemical/synthetic adjuvant	None	4-6,10	Moderate
c. change in specifications of a chemical/synthetic	None	6-10	Moderate

adjuvant (including the tests and/or the analytical procedures)	1,3	7-9	Minor

31. Change involving a biological adjuvant:

a. change in supplier of a biological adjuvant	None	1-7,10-11,12	Major
b. change in manufacture of a biological adjuvant	None	1-7,10-11	Major
	4	1-5,7	Moderate
c. change in specifications of a biological adjuvant (including the tests and/or the analytical procedures)	None	6-10	Moderate
	1,3	7-9	Minor
Conditions			
1. Any change in specifications of the adjuvant is within the approved ranges (i.e. tightening of acceptance criterion). 2. The adjuvant is an aluminum salt. 3. The change in specifications consists in the addition of a new test or in a minor change to an analytical procedure. 4. No change in the supplier of the adjuvant.			
Supporting Data			

1. Information assessing the risk with respect to potential contamination with adventitious agents (e.g. impact on the viral clearance studies, BSE/TSE risk).
2. Information on the quality and controls of the materials (e.g. raw materials, starting materials) used in the manufacture of the proposed adjuvant.
3. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.
4. Process validation and/or evaluation studies (e.g. for manufacturing of the adjuvant) unless justified.
5. Description of the general properties including stability, characteristic features and characterisation data of the adjuvant, as appropriate.
6. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least 3 commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of three months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than three batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
7. Updated copy of the proposed specifications for the adjuvant (and updated analytical procedures if applicable).
8. Copies or summaries of analytical procedures, if new analytical procedures are used.
9. Copies or summaries of validation reports, if new analytical procedures are used.
10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the final product with the approved and proposed adjuvant, as applicable.
11. Supporting non-clinical and clinical data, if applicable.
12. Evidence of facility GMP compliance

Description and Composition of the Final product: Change to a Diluent

Note: Changes to diluents containing adjuvants and/or active biological ingredients are considered final products and as such the corresponding changes to final product, not diluent, should be applied.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
32. Change to diluent, involving:			
a) Change in manufacturing process	**none** **1 , 3**	**1-5** **1-4**	**Moderate** **Minor**
b. replacement of or addition to the source of a diluent	None	1-5	Moderate
	1-3	1-3	Minor
c. change in facility used to manufacture a diluent (same company)	1-2	3, 5	Minor

d. addition of a diluent filling line	1-2,4	1-3,5	Minor
e. deletion of a diluent	None	None	Minor

Conditions

1. The diluent is water for injection (WFI) or a salt solution approved for parenteral human use (i.e. does not include an ingredient with a functional activity, e.g. a preservative).
2. After reconstitution, there is no change in the final product specifications outside of the approved ranges.
3. The proposed diluent is commercially available in the country/jurisdiction of SAHPRA.
4. The addition of the diluent filling line is in an approved filling facility.

Supporting Data

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

Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
33. Change involving a final product manufacturer/manufacturing facility, such as:			
a. replacement or addition of a manufacturing facility for the final product (including formulation/filling and primary packaging)	None	1-7	Major
	1-5	1-3, 5-8	Moderate
b. conversion of a drug product manufacturing facility from single-product to multiproduct facility	none	9-10	Moderate
c. replacement or addition of a secondary packaging facility; a labelling /storage facility; or a distribution facility	2-3	1-3	Minor
d. deletion of a final product manufacturing facility or packaging facility	None	1	Minor

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/HCR).
2. No change in the composition, manufacturing process and final product specifications.
3. No change in the container/closure system or storage condition.
4. The same validated manufacturing process is used.
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the one of those already approved at the site and uses the same filling process/equipment.

Supporting Data

1. Name, address, and responsibility of the proposed production facility involved in manufacturing and testing
2. Evidence of facility GMP compliance.
3. Confirmation that the description of the manufacturing process of the drug product has not changed as a result of the submission (other than the change in facility), or a revised description of the manufacturing process.
4. Comparative description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
5. 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- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least three commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of three months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than three batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
8. Rationale for considering the proposed formulation/filling suite 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, a signed attestation from the manufacturer that no changes were made to the change-over procedures.

10. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
34. Change in the final product manufacturing process, such as:			
a. scale-up of the manufacturing process at the formulation/filling stage	1-4	1,3 -4, 7, 8	Moderate
b. addition or replacement of equipment (e.g. formulation tank, filter housing, filling line and head, and lyophiliser) within the existing filling areas	None	1-3, 6, 8	Moderate
	5	3	Minor
c. addition or replacement of equipment (e.g., lyophiliser) in a new area (e.g., adjacent room)	None	1-3	Moderate
d. addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	1-4	1-4, 6, 8	Minor
e. addition of a new step (e.g. filtration)	3	1-4, 7	Moderate
Conditions			
1. The proposed scale uses similar/comparable equipment to that approved (N.B. 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 (e.g. the same formulation, controls, standard operating procedures (SOPs) are utilised). 3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns. 4. No change in the principle of the sterilisation procedures of the final product. 5. For product-contact equipment, the change is considered 'like for like' (i.e. in term of product-contact material/equipment size).			

Supporting Data

1. Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
2. Information on the in-process control testing, as applicable.
3. Process validation and/or evaluation studies (e.g. media fills, as appropriate). The proposed validation protocol is acceptable, but data could be requested.
4. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed final product. Bracketing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified. Comparative pre-change test results do not need to be generated concurrently
5. Summary of stability testing and results (e.g. studies conducted, protocols used, results obtained).
6. Commitment to place the first commercial scale batch of the final product manufactured using the proposed formulation/filling suite into the stability program, and to notify SAHPRA of any failures in the ongoing stability studies.
7. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least 3 commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than three batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
8. Rationale for regarding the equipment as similar/comparable, as applicable.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
35. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:			
a. Tightening of in-process limits	2,3,,7	1,4	Minor
b Addition of new in-process test and limits	2,3,6,	1-5, 8	Minor
c. Deletion of a non-significant in-process test	2- 4	1,4,7	Minor
d. Widening of the approved in-process limits,	None 1-3	1-4,6,8 1,4,5,8	Moderate Minor
e. Deletion of an in-process test which may have a significant effect on the overall quality of the final product	None	1-4,6,8	Moderate
f. Addition or replacement of an in-process test as a result of a safety or quality issue	None	1-4, 6, 8	Moderate

36. Change in in-process controls testing site *Note: Transfer of in-process control testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections*	1-3, 5-6	9	Minor

Conditions

1. There is no change in drug product specifications outside of the approved ranges.
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 parameter, e.g. content, impurities, any critical physical characteristics or microbial purity.
5. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
6. There is no change in the in-process control limits outside of the approved limits.
7. The test procedure remains the same, or changes in the test procedure are minor.

Supporting Data

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance.
2. Updated drug product specification if changed.
3. Copies or summaries of analytical procedures if new analytical procedures are used.
4. Comparative table or description, where applicable, of current and proposed in-process tests.
5. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug product (certificates of analysis should be provided). Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the marketing authorisation holder if outside specification (with proposed action).The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product (certificates of analysis should be provided). Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable.
7. Justification/risk assessment showing that the attribute is non-significant.
8. Justification for the new in-process test and limits.
9. Evidence that the new company/facility is GMP compliant.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
37. Change in the specifications used to release the excipient, involving: *Note: Excludes adjuvants, refer to adjuvant specific changes.*			

a. deletion of a test	5, 8	1,3	Minor
b. addition of a test	4	1-3	Minor
c. replacement of an analytical procedure	1-3	1-2	Minor
d. minor changes to an approved analytical procedure	None	1-2	Minor
e. a change from an in-house analytical procedure to a recognized compendial analytical procedure	None	1-2	Minor
f. widening of an acceptance criterion	None	1,3	Moderate
g. tightening of an acceptance criterion	3-4, 6, 7	1	Minor

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the excipient.
4. Acceptance criterion for residual solvents are within recognised or approved acceptance limits, e.g. within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements.
5. The deleted test has been demonstrated to be redundant with respect 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, e.g. new unqualified impurity; change in total impurity limits
8. An alternative test analytical procedure is already authorised for the specification parameter/test and this procedure has not been added through a minor change submission.

Supporting Data

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

Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Categories**
38. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk.	None	2-7	Major
39. Change in the source of an excipient from a TSE risk (e.g. animal) source to a vegetable or synthetic source	None	1,3,5,6	Moderate
40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5	2-7	Minor
41. Change in manufacture of a biological excipient Note: excludes biological adjuvants, refer to adjuvant specific changes.	None 1, 2	2-7 2-7	Major minor

	2	2-3,5-7	Moderate
42. Change in supplier for a plasma-derived excipient (e.g. human serum albumin)	None	4-8	Major
	3-4	5,6,9	Moderate

43. Change in supplier of an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient) Note: excludes chemical/synthetic adjuvants, refer to adjuvant specific changes.	None	2, 3,5-7	Moderate
	1,5	3	Minor
44. Change in excipient testing site	1	10	Minor

Conditions

1. No change in the specifications of the excipient or final product outside of the approved ranges.
2. The change does not concern a human plasma-derived excipient.
3. The human plasma-derived excipient from the new supplier is an approved medicinal product and no manufacturing changes were made by the supplier of the new excipient since its last approval in South Africa country/jurisdiction.
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 compared to the previously approved material.
6. Any new excipient does not require the assessment of viral safety data

Supporting Data

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Details of the source of the excipient (e.g. animal species, country of origin) and the steps undertaken in processing to minimise the risk of TSE exposure.
3. Information demonstrating comparability in term of physico-chemical characterisation and impurity profile of the proposed excipient with the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed excipient.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the proposed excipient.
6. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least three commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of three months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life /hold-time of the final product under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than three batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
7. Information assessing the risk with respect to potential contamination with adventitious agents (e.g. impact on the viral clearance studies, BSE/TSE risk) including viral safety documentation where necessary.
8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
9. Letter from the supplier certifying that no changes were made to the plasma derived excipient compared to the currently approved corresponding medicinal product.
10. Evidence that the new company/facility work under acceptable quality standards.

Control of Final Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
45. Changes affecting the quality control (QC) testing of the final product (release and stability), involving: *Note: Transfer of testing to a different facility within a GMP approved site is not considered to be a change and handled by GMP.*			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company or to a different facility within the same company	None	1-2	Moderate
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company	1	1-2	Moderate
Conditions			
1. The transferred QC test is not a potency assay or a bioassay.			
Supporting Data			
1. Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
46. Change in the specifications used to release the final product , involving:			
a			
a. deletion of a test analytical procedure and/or an acceptance criterion	None	1,6,7	Moderate
b. addition of a test	1-2, 7	1-3, 5	Minor
c. replacement of an analytical procedure	None 4,8	1-5 1,4,5	Moderate Minor
d. minor changes to an approved analytical procedure	none 1,3-5	1-5 2, 4-5	Moderate Minor
e. change from an in-house analytical procedure to a recognized compendial analytical procedure	none 1,5	1-5 1,5,7	Moderate Moderate
f. widening of an acceptance criterion	None	1,5,7	Moderate
g. tightening of an acceptance criterion	1,3,6,7	1	Minor
Conditions			

1. There is no change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The additional test is not intended to monitor new impurity species.
3. The method of analysis is the same (e.g. 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 tightens precision, accuracy, specificity and sensitivity.
5. The change does not concern potency testing.

6. Acceptance criterion for residual solvents are within recognized or approved acceptance limits, e.g. within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements.
7. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity in total impurity limits.
8. The change is from a pharmacopoeial assay to another pharmacopoeial assay.

Supporting Data

1. An updated copy of the proposed drug product specification.

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

3. Validation/qualification results if new analytical procedures are used.

4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.

5. Justification for the change to the analytical procedure (e.g. demonstration of the suitability of the analytical procedure in monitoring the drug product, including the degradation products) or for the change to the specification (e.g. demonstration of the suitability of the revised acceptance criterion to control the drug product).

6. Justification for the deletion of the test (e.g. 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 are maintained.

Reference Standards or Materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
47. Qualification of a new reference standard against a new primary international standard.	None	1-2	Moderate
48. Change the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1-2	Moderate
49. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	1-2	Minor
50. Change to reference standard qualification protocol	None	3-4	Moderate
51. Extension of reference standard shelf life	2	5	Minor

Conditions

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

Supporting Data

1. Revised product labelling to reflect the change in reference standard (as applicable)
2. Information demonstrating qualification of the proposed reference standards or materials (e.g. source, characterization, certificate of analysis).
3. Justification of the change to 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 reference standard shelf life.

Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
52. Modification of a primary container closure system (e.g. new coating, adhesive, stopper, type of glass)	None	1-6	Moderate
Note: the addition of a new container closure system (e.g. addition of a pre-filled syringe where the currently approved presentation is a vial only) is considered a change in presentation, see change #29 c.	1-3	3	Minor
53. Addition of a secondary functional container closure system (e.g., pre-filled autoinjector)	None.	1-3,6	Moderate
54. Change from a reusable container to a disposable container with no changes in product-contact material (e.g. change from reusable pen to disposable pen)	None	1,3,6	Moderate
55. Deletion of a container closure system	None	1	Minor

Conditions to be fullfilled

1. No change in the type of container closure or materials of construction.

2. No change in the shape or dimensions of the container closure.

3. The change is made only to improve the quality of the container and does not modify the product contact material (for example, increased thickness of the glass vial without changing interior dimensions).

Supporting Data

1. Revised product labelling information, as appropriate.
2. For sterile products, process validation and/or evaluation studies, or provide equivalency rationale. For a secondary functional container closure system, validation testing report.
3. Information on the proposed container closure system, as appropriate (e.g. description, materials of construction of primary/secondary packaging components, performance specifications).
4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity tests.
5. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least 3 commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of three months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life /hold-time of the final product under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than 3 batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.
6. Information demonstrating suitability of the proposed container/closure system with respect to its relevant properties (e.g. results from last media fills, results of transportation and/or interaction studies demonstrating preservation of protein integrity and maintenance of the sterility for sterile products, maintenance of the sterility in multi-dose container, user testing, etc.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
56. Change in the supplier for a primary container closure component , involving:			
a. replacement or addition of a supplier	None	1-3	Moderate
	1-2	None	Minor
b. deletion of a supplier	None	None	Minor

Conditions

1. No change in the type of container closure, materials of construction, shape, dimensions or in the sterilisation process for a sterile container closure component.
2. No change in the specifications of the container closure component outside of the approved ranges.

Supporting Data

1. Data demonstrating the suitability of the container closure system (e.g. extractable/leachable testing).
2. Information on the proposed container closure system (e.g. description, materials of construction of primary packaging components, specifications).
3. Comparative pre and post-change test results for the manufacturer's characterised key stability indicating parameters with at least three commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme is acceptable. The data should cover a minimum of three months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to SAHPRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than three batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
57. Change in the specifications used to release a primary container closure component or functional secondary container closure component, involving:			
a. deletion of a test	1-2	1-2	Minor
b. addition of a test	3	1-2	Minor
c. replacement of an analytical procedure	6-7	1-3	Minor
d. minor changes to an analytical procedure	4-7	1-3	Minor
e. widening of an acceptance criterion	None	1-2	Moderate
f. tightening of an acceptance criterion	8	1	Minor

Conditions

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

Supporting Data

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

Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
58. Change in the shelf life for the final product , involving:			
a. extension (includes extension of shelf life of the final product as packaged for sale, after opening and after dilution or reconstitution)	None	1-5	Moderate
	1-5	1-2,5	Minor
b. reduction (includes reduction as packaged for sale, after opening and after dilution or reconstitution)	None	1-5	Moderate
	6	2-4	Minor

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

Supporting Data
1. Summary of stability testing and results (e.g. studies conducted, protocols used, results obtained). **2.** Proposed storage conditions and shelf life, as appropriate. **3.** Updated, post-approval stability protocol. **4.** Justification of the change to the post-approval stability protocol or stability commitment. **5.** Results of stability testing under real time/real temperature conditions covering the proposed shelf life generated on at least three (3) commercial scale batches.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
59. Change in the post-approval stability protocol of the final product , involving:			

a. major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature	None	1-6	Moderate
b. addition of time point(s) into the post-approval stability protocol	None	4-5	Minor
c. addition of test(s) into the post-approval stability protocol	1	4-5	Minor
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf life	None	4-5	Minor
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf life	2	4-5	Minor
f. replacement of the sterility testing by the container/closure system integrity testing	None	1-2,4-5	Moderate
	3	4-5	Minor

Conditions

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

Supporting Data

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

Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Categories**
60. Change in the labeled storage conditions for the final product or the diluted or reconstituted medicine, involving:			
a. addition or change of storage condition(s) for the final product, diluted or reconstituted medicine (e.g. relaxation or tightening of a temperature criterion, addition or change of controlled temperature chain conditions)	None	1-4,6	Moderate
	1-2	1-4	Minor
b. addition of a cautionary statement (e.g. do not freeze)	1	1-2,4-5	Minor

c. deletion of a cautionary statement (e.g. do not freeze)	None	1-2,4,6	Moderate

Conditions

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

Supporting Data

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

APPENDIX 4

Safety, Efficacy and Product Labelling Information Post Approval

The examples of Safety and Efficacy, Product Labelling Information and Administrative Product Labelling Information in this appendix are provided for clarification, but are not limited to the ones included in this section and may affect changes to the product labelling information for health care providers and patients, and inner and outer medicine labels. Because the amount of safety and efficacy data needed to support a change may vary based on the impact of the change, risk/benefit considerations, and product specific characteristics (i.e. there is no "one size fits all"), this appendix provides a list of examples of changes in the various categories rather than a detailed table linking each change with the required data needed to support the change (such as those provided in Appendices 2 and 3 for quality changes). HCRs are encouraged to contact SAHPRA for guidance on the data needed to support major changes if deemed necessary.

Safety and Efficacy

Safety and Efficacy Change amendments requiring approval prior to implementation of the change should be submitted for changes in clinical practice, and changes in safety and indication claims. In some cases safety and efficacy data comparing the approved clinical use of a medicine with a new one, may be required. Such studies, often referred to as clinical bridging studies, are trials in which a parameter of interest (e.g. formulation, dosing schedule, population group) is directly compared with a changed version of that parameter with respect to the effect of the change on the product's clinical performance. Comparison of immune responses and safety outcomes [e.g. rates of common adverse events (AEs) and serious AEs (SAEs)] are often the primary objectives. If the immune response and safety profiles are non-inferior, then efficacy and safety of the medicine can be inferred.

The following list contains some examples of Safety and Efficacy Changes requiring clinical studies:

1. Expansion of safety claims: Change due to increase of risk based on updated data from post-marketing clinical studies (confirmatory safety and efficacy studies or studies conducted in new populations), post-marketing surveillance, or studies of shedding and transmission.
2. Expansion or contraction of efficacy claims: New indications and usage (including re-introduction of a withdrawn indication) based on clinical studies demonstrating efficacy or lack of efficacy in specific populations.
3. New route of administration*, new dosage form*, new strength*, new dose, new dosing regimen, including concomitant administration with other medicines.
4. Change in existing risk management measures, existing route of administration, dosage form and/or strength due to safety reasons.
5. Changes based on data from nonclinical studies.

*SAHPRA may consider that these changes require a new market authorisation or product license.

Product Labelling Information Changes

Product Labelling Information Change amendments should be submitted for changes which do not require clinical efficacy or safety data or extensive pharmacovigilance (safety surveillance) data. Product Labelling Information Changes require approval prior to implementation of the change. The following list contains some examples of Product Labelling Information Changes that are associated with changes that impact clinical use:

1. Addition, strengthening, or clarification of text relating to contraindications, warnings, precautions, and adverse reactions of the product Labelling information. These changes may include the provision of recommended risk-management actions (e.g. required testing prior to vaccination, specific monitoring, ensuring patient awareness of certain risks), or the identification of a specific sub-population as being at greater risk such as those with a concomitant condition, those taking concomitant medicine, or a specific age group.
2. Addition of an adverse reaction due to information reported to the HCR or SAHPRA.

3. The instructions for use including dosage, administration and preparation for administration revised to optimise the safe use of the medicine.

4.An existing indication has been withdrawn in its entirety or altered for risk management purposes including reduction in scope, but without expanding, explicitly or implicitly, the claims of the medicine.

5. An existing route of administration, dosage form and/or strength has been deleted due to safety reasons.

6. A new medicines or drug interaction has been added, or an existing drug interaction has been better characterised, that alters the conditions of use in terms of risk management (e.g. a precautionary statement is added as the result of the new data).

Administrative Product Labelling Information Changes

Administrative Product Labelling Information Changes are changes to the Labelling items which do not require supportive data or approval by SAHPRA prior to implementation; however, a copy of the most recent revised product Labelling information items should be submitted to SAHPRA as general correspondence to the MA or product licence.

The following are examples of Administrative Product Labelling Information Changes:

1. Minor changes to the layout of the product Labelling information items or revision of typographical errors without changing the content of the label.
2. Update of the HCR contact information (e.g. customer service number, website addresses) or distributor's name.
3. Update of the existing information for referenced literature without adding or removing references.
4. Product Labelling Information Changes made to comply with an official compendium (e.g. change of the common name).
5. Minor changes to the text to add clarity as it relates to maintaining consistency with common label phrase standards (e.g. change from "not recommended for children" to "not for use in children").

APPENDIX 5:

FORMAT OF THE AMENDMENT SCHEDULE / COVERING LETTER

The following template for the covering letter should be followed for pre- or post-registration CTD amendments. Items not applicable to the submission may be omitted providing the omission is confirmed/identified.

Company letterhead
Date
The CEO of SAHPRA
Department of Health
Private bag
X828 Pretoria
0001

CODE (Refer General Information guideline section 13)

Attention:

Dear Madam/Sir

Product Proprietary Name					
Application Number					
Registered Biological medicine		Old medicine		Reply to BMC Response	

1 Attached herewith:

Original medicine registration certificate*	
If already submitted: Application……. Dated……. Reference No……..	
Administrative amendment fee, if relevant	
Registration certificate amendment fee, if relevant	

* Certified copy of original may be submitted on submission of amendment, with amended certificate only being issued on approval of amendment and submission of original certificate.

2 This amendment involves: (Description of change (*including justification*), conditions fulfilled, supporting data and categories, e.g.

Description of change	Conditions to be fulfilled	Supporting data	Category
Deletion of a test	*None*	*1,6*	*Minor*
Addition of a new step (eg. Filtration)	*3*	*1-4, 7*	*Moderate*
Generation of new master seed lot	*1*	*1-2,5, 7-9*	*Moderate*

and the following supporting documentation is provided:

(Items not applicable to the submission may be omitted providing the omission is confirmed/identified)

3 List of changes/amendments to the CTD

The Module 1.2.1 f) **Amendment history** reflects the particulars of the previous pharmaceutical amendments (if applicable). *Include this history here for amendments previously in the MRF1 format.* Other amended Modules are as follows:

***Note**:* Landscape format is recommended for this table. **A column headed "Effect of amendment" is only applicable to Module 3.2.P.1 and should NOT be included for the whole table.**

Modules	Comparison between Modules		Reason for amendment	Reviewer's comment
	Existing	Amended		
*Example 1 is **not acceptable** – it will take longer to evaluate as the changes have not been identified for easy reference.* *The format of example 2 is recommended as evaluation is facilitated by the identification of the specific items.*				
Example 1 10 (b)	Stability report: XXX	Stability report YYY replaces report XXX	Includes stability data on 2 batches stored for 36 months	
Example 2 10 (b)	**Pages 10.0, 10.1, 10.3.1 Stability data on two production batches stored for 24 months at 25 ºC/60 % RH and for 3 months at 40 ºC/75 % RH submitted.**	**Pages 10.0, 10.2.1, 10.2.2, 10.3.1, 10.3.2 Stability data on the same two production batches stored for 36 months at 25 ºC/60 % RH included.**	Extension of the shelf-life to 36 months applied for.	
	No index in 10 (b), attached data only referred to.	**Detailed index included in 10 (b)**	Administrative update to facilitate review.	
10 (c)	**Shelf-life of 24 months approved.**	**A discussion of the results is included and a 36 months' shelf-life is inferred.**	Extension of the shelf-life to 36 months applied for.	

Note Stability specification limits should be reflected in the stability report.
Out-of-specification results should be addressed.

I declare that

- **the amendments are in line with the relevant current guidelines and/or a motivation for any deviation has been submitted**
- **no amendments, other than those stated in the list of changes/amendments, have been made.**

_____
Signature of HCR/applicant or delegate

Name	Title	Qualification	Designation	e-mail	Tel number