South African Health Products
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BIOLOGICAL MEDICINES AMENDMENT GUIDELINES

This guideline document is intended to provide recommendations to applicants wishing to submit amendments for registered biological medicines. It represents the South African Health Products Regulatory Authority's (SAHPRA) 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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GLOSSARY

ABBREVIATION	MEANING
BSE	Bovine Spongiform Encephalopathy
CP	Comparability Protocol
CTD	Common Technical Document (ICH)
DNA	Deoxyribonucleic Acid
eCTD	Electronic Common Technical Document
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCR	Holder of the Certificate of Registration
ICH	International Council for Harmonization
HPLC	High-Performance Liquid Chromatography
MCB	Master Cell Bank
NRA	National Regulatory Authority
PAA	Prior Approval Amendment
PI	Professional Information
PIL	Patient Information Leaflet
QC	Quality Control
SAHPRA	South African Health Products Regulatory Authority
SOP	Standard Operating Procedures
TSE	Transmissible Spongiform Encephalopathy
WCB	Working Cell Bank
WHO	World Health Organisation

DEFINITIONS

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

TERM	MEANING
Adjuvant	A substance or combination of substances used in conjunction with a biological medicine to achieve (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	An application for a change in the original registration application, submitted to SAHPRA per applicable guidelines.
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 amodified form intended to furnish the specified activity or effect. Also referred to 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), for e.g., rHu-anti-haemophilic 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 decisions from the 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, active and non-active ingredients, manufacturing process, quality controls, equipment, containers, shelf life, storage conditions, facilities or product labelling information by the marketing authorisation holder. This is also referred to as a 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)	The 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, a 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	This system refers to the following components: • A 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.)* • A 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	This is 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 are 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 to as a 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)	An HCR refers to a person or legal entity 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 registration.
Intermediate	A material produced during steps in the manufacturing of a medicine that must undergo further processing before it becomes a final product.
Manufacturer	This refers to a person manufacturing a medicine and includes a manufacturing pharmacy.
Master cell bank (MCB)	An MCB is an aliquot of a single pool of cells, which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions.
Prior approval amendment (PAA)	A PAA is an amendment requiring approval from the SAHPRA prior to implementation of the amendment. Also referred to as change application dossier in other documents.

Product Labelling Information	Printed materials that accompany a prescription medicine and refer to all labelling items as per the Medicines and Related Substances Act, 101 of 1965, General Regulations # 10, #11 and # 12): • Professional Information (PI), including prescribing information, that provides product information on indication, dosage and administration, safety and efficacy results, contraindications, warnings, and a description of the product for health care providers • Inner label or container label • Outer label or carton • Patient Information Leaflet (PIL)
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.
Vaccine	Preparations containing antigens capable of inducing a specific and active immunity in humans against an infectious 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.
Working Cell Bank (WCB)	The WCB is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the master cell bank under defined culture conditions.

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 amendment application for SAHPRA approval or notifying 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 which ensures 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. However, in this guideline, an attempt has been made to cover a range of possible changes to 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 variation addendum for Human and Veterinary Medicines [2.08], European Union (EU) variation classification guidelines and the World Health Organisation (WHO) Guideline for procedures and data requirements for changes to approved vaccine (TRS 993 Annex-4 2015).

2. SCOPE

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

a) procedures and criteria for the appropriate categorisation 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 guideline document mainly covers quality-related changes for biological medicines. However, there are a few administrative changes relating to Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF) which are covered by these guidelines. For other administrative changes, safety changes, efficacy changes and product labelling changes (PI/PIL), the applicant must use the latest SAHPRA variation addendum published on the SAHPRA website (https://www.sahpra.org.za/). Section 6 of this guideline document outlines the exceptions that applies to biological medicines for safety, efficacy and/or product labelling information changes.

3. LEGAL PROVISION

Medicines and Related Substances Act, 101 of 1965, as amended and the relevant Regulations.

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. 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's Inspectorate Unit. [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 SAHPRA's 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 to.

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 are included 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, Appendix 3 for the final product and Appendix 4 for Plasma Master File.

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 categorized into major changes (Type II amendments), moderate changes (Type IB amendments,) and minor changes (Type IA amendments)

All changes are identified as:

- Type II amendments
- Type IB amendments
- Type IA amendments
- Type IAIN amendments

The implementation of all Type II and Type IB amendments requires reporting to SAHPRA in order to amend the information in the original registration application. The Type II amendments must be reviewed and approved by SAHPRA prior to implementation. Minor amendments of Type IAIN require immediate notification to SAHPRA. Type IA amendments may be implemented by HCR without prior approval from SAHPRA. However, a notification of this implementation should be provided to SAHPRA within 12 months of implementation. Following the receipt of notification for Type IA and Type IAIN amendments, SAHPRA will review the notification and provide feedback to the HCR within 30 days. **Further information on each amendment is provided below:**

- Appendices 2 and 3 provide an extensive list of Type II, Type IB, and Type IA changes, including the information required to support each change.
- Appendix 2 includes changes to the active biological substance or intermediates and Appendix 3 includes changes to the final product. If a quality change has a potential impact on the quality, safety and therapeutic efficacy of the medicine and is considered to be a Type II, Type IB, or Type IA amendment, but is not included in Appendix 2, 3 or 4, then the amendment should be submitted as "Z" code [see section 7.3].

SAHPRA will establish a mechanism that allows for the update of this guideline when new regulatory category classifications are needed.

5.1 Type II amendments

Type II amendments 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 Type II amendment and receive an approval notification from SAHPRA before implementation of the change by the manufacturer. For a change under this category, the amendment application 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 biological substance and Appendix 3 for the final product.

Additional information 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, Type II amendments 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 Type IB amendments

Type IB amendments 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 a Type IB amendment application to SAHPRA. SAHPRA will check within seven (7) working days whether the proposed change can be considered a Type IB amendment, and whether the classification of the amendment is correct and complete ('validation') before issuing the acknowledgement of receipt. Thus, within 60 working days following the acknowledgement of receipt of a valid Type IB amendment application, SAHPRA will notify the HCR of the outcome of the evaluation procedure. However, if SAHPRA does not send the HCR the outcome of its evaluation within 60 working days following the acknowledgement of receipt for the Type IB amendment, then the Type IB amendment will be deemed acceptable.

5.3 Type IA amendments

Type IA amendments 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. Type IA amendments are implementable by the HCR. However, SAHPRA should be notified of the changes within 12 months of implementation. Following receipt of such notification, SAHPRA will review the notification for Type IA amendments within 30 working days and provide evaluation outcome to the HCR.

The justification and supporting documentation for Type IA amendment should be submitted with the notification and should also be made available by HCR upon request from SAHPRA. When Type IA affects the lot release specifications (e.g., narrowing of a specification, or compliance with pharmacopoeial changes) and affects the quality control testing as summarised in the lot release protocol, the HCR should inform the institution responsible for reviewing the release of lots. Type IA amendments that are related to Type IB or Type II changes should be included in the application for Type IB or Type II amendments.

5.4 Type IAIN amendments

Type IAIN amendments are minor amendments of Type IA that require immediate notification to SAHPRA. Following receipt of notification, SAHPRA will review the notification for Type IAIN amendment within 30 working days and provide the evaluation outcome to the HCR.

6. AMENDMENT TYPE FOR SAFETY, EFFICACY AND/OR PRODUCT LABELLING INFORMATION CHANGES

6.1. For safety, efficacy and/or product labelling information changes, SAHPRA variations addendum for human and veterinary medicines specifically Section 4.1 (Clinical and Pharmacovigilance), 5.1 (General) and 5.2 (Clinical and Pharmacovigilance) is also applicable for biological medicines. **Thus,** all relevant C.I codes will apply to biological medicines as they do for small molecules. However, the following exceptions with respect to codes and Type IB amendments timelines will apply for Biological Medicines:

6.1.1 Exception 1 > Clinical codes: All clinical codes must be preceded by the alphabet (Q). This will ensure that the amendment application is routed correctly to the Biological Medicines Unit.

6.2 All biological clinical variations should be submitted separately from qualityvariations.

7. PROCEDURES

The establishment of procedures and criteria for adequate oversight of changes to the registered medicine is the responsibility of SAHPRA. As such, SAHPRA has established this guideline regarding the submission procedures and timelines to be considered by HCRs when preparing to submit an amendment for a change.

Because Type II amendments or Efficacy and Safety amendments require extensive documentation and data, the review times will be longer than for Type IB, Type IA amendments or Product Labelling Information amendments. Furthermore, SAHPRA may establish different timelines for reviews of Type II amendments not requiring clinical data, compared to Safety and Efficacy amendments 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 also consult with SAHPRA on the adequacy of clinical data required to support a Safety, Efficacy or Product Labelling Information Change.

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:

- Type II amendment, or
- Type IB amendment, or
- Type IA
- Type IAIN

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

7.1 Procedures for Amendments

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

a) A cover letter (Module 1.0) that includes:
   i the type of submission (e.g., Type II amendment, Type IB, Type IA)
   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 (Module 1.2.1) signed and dated

c) GMP documentation information (Module 1.7), 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 (Module 1.5.2.1)

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 e-submission (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.

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 letter by which the change cannot be implemented, and the 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 products 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 Type II amendments or Type IB amendments 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., Type IA amendments and Administrative Product Labelling Information Changes) may be filed together with other submissions whether or not they are related and/or supported by 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 Type IA amendments

Type IA amendments are implementable by the HCR. However, SAHPRA should be notified of the changes within 12 months of implementation. The relevant supporting documents for Type IA amendments are outlined in Appendices 2-4. Type IA amendments that have previously been implemented and are related and/or consequential to a Type IB or II amendment should be described in the relevant parts of the documentation when applying for the Type IB or II amendments. If SAHPRA determines (during an inspection or a review of related changes) that the information for the change fails to demonstrate the continued safety or efficacy of the product manufactured using the changes, SAHPRA may work to resolve the problem 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 manufactured using the changes or to remove the product from distribution pending resolution of the issues related to the changes.

7.3 "Z" Codes

Applicants can submit "z" code variations for unforeseen changes not accounted for in this guideline. The "z" code should be classified according to latest SAHPRA BAU variations communication.

8. SPECIAL CONSIDERATIONS

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 Type II amendments 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 Type II amendment to support annual changes in the influenza strain composition.

To allow for timely distribution of vaccines, SAHPRA will review 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 formulation year) should also be provided.

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.

8.2.1 Introduction

There are several influenza vaccines registered and marketed in South Africa. 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 (PI) and the Patient Information Leaflet (PIL).

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 PI and the PIL. 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 February of the year of the intended Influenza season will allow for a 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.

8.2.3 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).

8.4 Approach for the submission of the applications for COVID-19 strains update

8.4.1. COVID-19 vaccine strain updates for Registered vaccines may be submitted as Type II amendments.

8.4.2 Regulatory data requirements for approved vaccines to support a strain change variation are as follows:

a. The updated vaccine should closely match circulating SARS-CoV-2 strains in South Africa and should be monovalent.

b. Clinical trial data with the specific adapted vaccine would not be required prior to approval of the recommended updated composition, provided predictable clinical reactogenicity and immunogenicity with different compositions have been previously demonstrated (use of prior knowledge on a specific vaccine).

c. Immune responses in animals or humans with the approved antigen composition to indicate levels of cross-reactivity against emerging variants of concern.

d. Clinical trial data on one or two strain changes would be adequate to demonstrate predictability of performance of the specific product technology, provided no major changes to the manufacturing process or vaccine construct are introduced.

e. Characterisation and validation of any updates to the manufacturing process, including the introduction of additional/alternative types of technology, to be provided as part of the CMC/quality package.

f. The use of prior knowledge on a specific product is acceptable for the approval of strain changes for currently authorised or approved COVID-19 vaccines. Spike antigen change procedures should take into consideration all available information and data from studies, and at the present time can be based on quality and non-clinical data.

g. Post-registration commitments may need to be agreed, e.g., to gather data on vaccine effectiveness against severe outcomes as well as symptomatic disease. Immunogenicity data from clinical trials are to be considered to support future antigen change decisions.

9. REFERENCES

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17. WHO Guidelines on procedure and data requirements for changes to approved biotherapeutic products, proposed guidelinesWHO/BS/2017.2311)
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26. Biosimilar Medicines: Quality, Non-Clinical and Clinical Requirements Guideline, 2.30 Biosimilars Aug14 V3

10. 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 will be longer than for moderate changes. The suggested review timelines are shown in Table 1 below. 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 approval or as a request for supplementary documentation. In the 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, SAHPRA may communicate with the HCR during the initial assessment period without stopping the clock to be able to finalise the assessment within the proposed timeline.

Table 1. Reporting categories for Amendments and suggested review timelines

QUALITY		
Amendment type	**Procedure**	**Suggested review timelines**
Type II	Prior Approval Amendment	≤ 120 working days
Type IB	Implementable after 60 working days	60 working days
Type IA	Require notification to SAHPRA [a]	As per article 8 of EU variation regulation (30-day review time from date of notification)
Type IAIN	Immediate notification	As per article 8 of EU variation regulation (30-day review time from date of notification)

[a] *Type IA amendments that are related to Type IB or Type II amendments should be included in the Prior Approval Amendment application (e.g., a minor change, such as the narrowing of a specification, should be included in the application for Type IB or Type II amendments which includes updated quality control release information).*

11. APPENDIX 2: POST-APPROVAL CHANGES TO THE ACTIVE BIOLOGICAL SUBSTANCE

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information for an active biological substance. 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 Type II, Type IB or Type IA amendment 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 Type IB Change are not fulfilled, the change is considered a Type II 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 is not provided, is different or is not considered applicable, adequate scientific justification should be provided; and (c) the *Amendment Type* (e.g. Type II, Type IB, or Type IA amendment).

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.

B. QUALITY CHANGES (Q) B.I ACTIVE BIOLOGICAL INGREDIENT

[In this guideline, this section/code is expanded to also cover changes to raw materials/reagents of biological origin and reference standards/materials]

(Q) B.I.a Manufacture

Description of Change:	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.1.a.1 Change in the manufacturer of a starting material/ reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier			
(Q) B.I.a.1.e. Change to an active biological ingredient manufacturing facility or change in the manufacturing facility of starting materials/active bulk/reagents/any intermediates of the active biological ingredient used in the manufacturing process of active biological ingredient	None	1-4,6-8	II
	1-4	2, 4-8	II
(Q) B.I.a.1.j Changes to quality control testing arrangement for a biological active ingredient: replacement or addition of site a site where batch control/testing including a biological/immunological/immune chemical method takes place		1 & 11	II
(Q) B.I.a.1.k. New storage site of master cell bank and/or working cell bank		9, 10	IB

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.

Supporting documents

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 three (3) batches and/or leveraging data from scientifically justified representative batches or batches not necessarily 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 three (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 are acceptable. The data should cover a minimum of three (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 three (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.
9. Amendment to the relevant section of the dossier.
10. The amendment schedule should clearly outline the "present" and "proposed" storage site.
11. Information demonstrating technology transfer qualification.

Q) B.I.a.1N Change in supplier of raw materials/reagents of biological origin (e.g., production eggs, foetal calf serum, human serum albumin)	None	1, 2, 3	IB
	1	1, 2	IA

Condition:

1. The change is for compendial raw materials/reagents of biological origin (excluding human plasma-derived materials).

Supporting Data

1. 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).
2. 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.
3. Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk).

Description of Change **(Q (B.I.a.2 Changes in the manufacturing process of the active biological Ingredient.**	**Conditions to be Fulfilled**	**Supporting Data**	**Amendment Type**
(Q) B.I.a.2.i Change to the active biological ingredient fermentation, viral propagation or cellular propagation process (upstream manufacturing process)			
a. a critical change (e.g., incorporation of disposable bioreactor technology)	None	1-7, 9, 11	II
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	IB
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	IB

(Q) B.I.a.2.ii Change to the active biological ingredient purification process involving (downstream manufacturing process)			
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	II
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	IB
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	IA
(Q) B.I.a.2.iii Change in source of raw materials/reagents of biological origin	None	4, 7, 12-13	IB
	8	4, 7	IA
(Q) B.I.a.2.iv Introduction of reprocessing steps	14	8, 10-11, 14	IB

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

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 sub cultivations, information on the characterisation and testing of the post-production cell bank for recombinant product/s, or of the active biological ingredient for non-recombinant product/s.
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 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 three (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 three (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 are acceptable. The data should cover a minimum of three (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 three (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 are acceptable. The data should cover a minimum of three (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	Amendment Type
(Q) B.I.a.2.v. Changes to the cell banks			
a. generation of a new Master Cell Bank (MCB)	1	1-2,5,7-9	IB
b. generation of a new Working Cell Bank (WCB)	None	1-2	IB
	2-4	1-2	IA[IN]
c. extension of shelf life of the MCB or WCB	5	1-2	IB
(Q) B.I.a.2.vi 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	II
b. generation of a new WSL	2-3	5-9, 11	IB
	2-4	5-6, 11	IAIN
(Q) B.I.a.2.vii Change in cell bank/seed lot testing site	6	10	IA
(Q) B.I.a.2.viii Change in cell bank/seed lot qualification protocol	None	3-4	IB
	7	4	IA

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 license. 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. the 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 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.
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 three (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 three (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 are acceptable. The data should cover a minimum of three (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 three (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	Amendment Type
(Q) B.I.a.2.ix 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	1-5	IB
	3-4	125	IA
b. introduction of new equipment with the same operating principles but different product contact material used in a critical step new product-contact equipment to be used during viral inactivation)	None	1, 3- 5	IB
	3-4	1,4,5	IA
c. introduction of new equipment with different operating principles but the same product contact material	None	1-3, 5	IB
	4	1,2,5	IA
d. replacement of product-contact equipment with equivalent equipment	none	3	IA
e. change of product-contact equipment from dedicated to shared	1,2	1, 6	IA
f. relocation of equipment to another room in the same facility/suite/premises	2,4,5	None	IA

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 (2) full production batches should be made available upon request and reported by the MAH if outside specification (with the 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.

(Q) B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active biological substance	**Conditions to be fulfilled**	**Supporting Documents**	**Amendment Type**
c) the change requires assessment of the comparability of a biological/immunological active substance	None	1, 2, 5, 6, 7,8	II
e) the scale for a biological/immunological active substance is increased/decreased without process change (e.g., duplication of line)	None	1,2,3,4	IB

Supporting Data

1. Amendment of the relevant section(s) of the dossier (presented in the CTD format).
2. The batch numbers of the tested batches having the proposed batch size.
3. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with the proposed action).
4. Copy of approved specifications of the active substance (and of the intermediate, if applicable).
5. A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g., use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance.
6. Comparability of the pre- and post-change active biological ingredient with respect to physico- chemical characterisation, biological activity, and impurity profile. Occasionally, bridging nonclinical 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 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 three (3) batches may be acceptable where justified and agreed upon by SAHPRA.
8. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating parameters with at least three (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 are acceptable. The data should cover a minimum of three (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 three (3) batches and/or use of forced degradation conditions for stability testing may be acceptable where justified and agreed upon by SAHPRA.

(Q) B.I.a.4 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, 3, 7	IA
b. addition of new in-process test and limits	4, 5, 10, 11	2, 4, 5, 7,8, 10	IA
c. deletion of a non-significant in-process test	4, 5, 6	2, 7, 9	IAIN
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	II
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,	II
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	2, 4, 5, 6, 7, 8, 10	IB
g. change in in-process controls testing facility	3-5, 7, 8	11	IA

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 substance.
2. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed active biological substance
3. Updated active biological substance 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 substance. Batch data on the next two (2) 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 batches of the pre- and post- change active biological substance. Matrixing, bracketing, the use of smaller scale batches, and/or the use of less than three (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.

(Q) B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza	**Conditions to be fulfilled**	**Supporting data**	**Amendment Type**
a) replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	See section 8.2 of the guideline above	See section 8.2 of the guideline above	II

(Q) B.I.a.6 Covid-19 vaccines strains update: Changes to the Covid-19 vaccines strains	Conditions to be fulfilled	Supporting data	Amendment Type
a) replacement or changes to the COVID-19 vaccines strain(s) in a seasonal, pre- pandemic or a pandemic situations	See section 8.4 of this guideline above	See section 8.4 of this guideline above	II

(Q) B.I.b Control of the Active biological substance

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.I.b.1 Change in the specification parameters and/or limits of an active biological substance, starting material/intermediate/reagent used in the manufacturing process of the active biological substance, involving:			
a. tightening of an acceptance criterion for medicinal products subject to official control authority batch release	1, 8, 9	1	IAIN
b. tightening of specification limits	1,8,9	1	IA
c. addition of new specification parameters to the specification with its corresponding test method	1-3	1-3,9	IA
d. deletion of non-significant specification parameter	None	1,9	IAIN
e. deletion of a specification parameter which may have a significant effect on the overall quality of the active biological ingredient and/or finished			II
f. widening of an acceptance criterion or change outside the approved specification limits range for the active biological substance	None	1,5, 8	II
g. 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	1,5,8	II

(Q) B.I.b.1.ii 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	IB
(Q) B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance			
a. minor changes to an approved analytical procedure	4-7	1,4-5	IA
b. deletion of an analytical procedure for the active biological ingredient or starting material/reagent/intermediate, if an alternative test procedure is already authorised	10	9	IB
c. other changes to a test procedure including replacement or deletion of analytical procedure for a reagent, which does not have a significant effect on the overall quality of the active biological substance	None	1-3,4-5	IA
d. substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance	None	1-5	II
e. other changes to a test procedure (including replacement or addition) for the active biological ingredient or a starting material/intermediate	None	1-5	IB
g. a change from an in-house analytical procedure to a recognized compendial/pharmacopeial analytical procedure	4,7	1-3	IA

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 is within recognised 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. 10. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IAIN notification.

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 demonstrate 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/evidence that consistency of quality and of the production process is maintained. 9. Amendment of the relevant section(s) of the dossier (e.g., description of the analytical methodology, a summary of validation data.

(Q) B.I.b.N.1. Reference Standards or Materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
a. qualification of a new reference standard against a new primary international standard	None	1-2	IB
b. change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1-2	IB
c. 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	IA
d. change to reference standard qualification protocol	None	3-4	IB
e. extension of reference standard shelf life	2	5	IB

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, 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 to support the extension of reference standard shelf life.

(Q) B.I.c Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.I.c.1. change in the immediate packaging/ primary container closure system(s) for the storage and shipment of the active biological ingredient (Qualitative and/or quantitative composition)	None	1-2,4, 5	II
	1	1,3, 5	IA

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 three (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 are acceptable. The data should cover a minimum of three (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 three (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	Amendment Type
(Q) B.I.c.2 Change in the specifications parameters and/or limits of the immediate packaging / primary container closure system for the active biological substance, involving:			
a. tightening of specification limits	8	1	IA

b. addition of new specification parameters	3	1-3	IA
c. deletion of non-significant specification parameter	1-2	1-2	IA_{IN}
d. addition or replacement of a specification parameter as a result of safety issues		1-2	II
e. widening of an acceptance criterion	None	1-2	IB
(Q) B.I.c.3 Change in the test procedure for the immediate packaging of the active biological ingredient			
a. minor changes to an analytical procedure	4-7	1-3	IA
b. replacement of an analytical procedure	6-7	1-3	IA
c. deletion of analytical procedure if an alternative test procedure is already authorised	1-2	1-2	IA

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 or analytical procedure 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 or analytical procedure for a primary container closure system.
3. Description of the analytical procedure and, if applicable, validation data.

(Q) B.I.d Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.I.d.1 Change in the shelf life/hold-time for the active biological ingredient or for a stored intermediate of the active biological ingredient, involving:			
(Q) B.I.d.1.a.1. reduction	None	1-5	IB
	6	2-4	IA
(Q) B.I.d.1.a.3 extension	None	1- 5	II
	1-5	1-2,5	IB

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 manufacturing 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	Amendment Type
(Q) B.I.d.1.b Change in the storage conditions for the active biological substance, involving:			
1. addition or change of storage conditions for the active biological ingredient (e.g. relaxation or tightening of temperature criterion	None	1-4	IB
	1-2	1-3	IA
2. change in storage conditions of biological active ingredient, when the stability studies have not been performed in accordance with the currently approved stability protocol	1	1-4	II

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 labelled 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).

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.I.d.1.c Change in the approved stability protocol / post-approval stability protocol of the active biological substance , 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	IB
	1	1-2,4- 6	IA
b. addition of time point(s) into the post-approval stability protocol	None	4-6	IA
c. addition of test(s) into the post-approval stability protocol	2	1,2, 4, 6	IA
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf life	None	4-6	IA
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf life	3	4- 6	IA

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.

12 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 Type II, Type IB, or Type IA 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 Type IB amendment are not fulfilled, the change is considered a Type II amendment

(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., Type II, Type IB and Type IA 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 (6) months of the implementation of the updated compendial/pharmacopoeial requirements.

Q) B. II. FINISHED PRODUCT

(Q) B.II.a Description and Composition of the Final Product [In this guideline, this section/code is expanded to also cover changes to adjuvant and diluent]

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 guidance.*

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.a.3 Change in the description or composition (excipients) 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 authorisation. HCRs are encouraged to contact SAHPRA for further guidance.*	None	1-10	II
b. change in fill volume (same concentration, different volume)	None	1,3,5,7,10	II
	1-2	1,3,5,7	IB
	1-3	5,7	IA
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	II

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 ingredients 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 three (3) commercial scale final product batches produced with the proposed changes under real-time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme are acceptable. The data should cover a minimum of three (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.

(Q) B.II.a.N1 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	Amendment Type
Change to diluent, involving:			
a. change in manufacturing process	none	1-5	II
	1, 3	1-4	IB
b. replacement or addition to the source of a diluent	None	1-5	II
	1-3	1-3	IB
c. change in facility used to manufacture a diluent (same company)	1-2	3, 5	IA
d. addition of a diluent filling line	1-2,4	1-3,5	IA
e. deletion of a diluent	None	None	IA

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.

(Q) B.II.a.N2 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	Amendment Type
(Q) B.II.a.N2.1 Change involving an approved chemical/synthetic adjuvant:			
a. change in supplier of a chemical/synthetic adjuvant	None	4-6,10	IB
	1-2	5	IA
b. change in manufacture of a chemical/synthetic adjuvant	None	4-6,10	IB
c. change in specifications of a chemical/synthetic adjuvant (including the tests and/or the analytical procedures)	None	6-10	IB
	1,3	7-9	IA

(Q) B.II.a.N2.2 Change involving a biological adjuvant

a. change in supplier of a biological adjuvant	None	1-7,10-11,12	II
b. change in manufacture of a biological adjuvant	None	1-7,10-11	II
	4	1-5,7	IB
c. change in specifications of a biological adjuvant (including the tests and/or the analytical procedures)	None	6-10	IB
	1,3	7-9	IA

Conditions

1. Any change in specifications of the adjuvant is within the approved ranges (i.e. tightening of acceptance criteria).
2. The adjuvant is an aluminium 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 three (3) commercial scale final product batches produced with the proposed changes under real-time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme are 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 (3) 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.

(Q) B.II.b Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.b.1 Replacement or addition of manufacturing site for part or all of the manufacturing process of the finished product			
a. secondary packaging site	2-3	1-3	IAIN
b. primary packaging site	None	1-7	II
	1-5	1-3, 5-8	IB
c. site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing process		1-7	II
d. site which requires an initial or product specific inspection		1-7	II
e. site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging for non-sterile medicinal product		1-7	IB
f. N/A			
g. conversion of a drug product manufacturing facility from single product to multiproduct facility	none	9-10	IB
h. deletion of a final product manufacturing facility or packaging facility	None	1	IB

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 (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 are acceptable. The data should cover a minimum of three (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 (3) 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 changeover 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	Amendment Type
(Q) B.II.b.2. Change to importer, batch release arrangements and quality control (QC) testing of the final product, 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.*			
(Q) B.II.b.2.b replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method	None	1-2	II
(Q) B.II.b.2.c. replacement or addition of a manufacturer responsible for importation and/or batch release	None	1-2	II
(Q) B.II.b.2.c.3 Including batch control/testing for a biological/immunological product and any of the test methods performed at that site is a biological/immunological/immunological chemical method		1-2	II
(Q) B.II.b.2.d 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	IB
(Q) B.II.b.2.e transfer of QC testing activities for a pharmacopoeial assay to a new company	1	1-2	IB
Conditions			
1. The transferred QC test is not a potency assay or a bioassay.			
Supporting Data			
1. Information demonstrating technology transfer qualification(s). 2. Evidence that the new company/facility is GMP compliant.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.b.3 Change in the manufacturing process of the final product including an intermediate used in the manufacture of the finished product			
(Q) B.II.b.3.b substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	None	1-7	II
(Q) B.II.b.3.c the product is a biologic/immunologic medicinal product and the change requires an assessment of comparability	I	1-7	II
(Q) B.II.b.3.g addition of a new step (e.g. filtration)	3	1-4, 7	IB
(Q) B.II.3.h addition or replacement of equipment (e.g. formulation tank, filter housing, filling line and head, and lyophilizer) within the existing filling areas	None	1-3, 6, 8	II
	5	3	IB
(Q) B.II.b.3.i. addition or replacement of equipment (e.g., lyophilizer) in a new area (e.g., adjacent room)	None	1-3	IB
(Q) B.II.b.4 Change in batch size including batch size ranges (upscaling and downscaling) of the final product			
a. scale-up of the manufacturing process at the formulation/filling stage	1-4	1,3 -4, 7, 8	IB
b. addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	1-4	1-4, 6, 8	IA

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 utilized.)
3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the final product.
5. For product contactequipment, the change is considered 'like for like' (i.e. in terms 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 three (3) commercial scale final product batches produced with the proposed changes under real-time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme are acceptable. The data should cover a minimum of three (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	Amendment Type
(Q) B.II.b.5 Change to in-process tests and/or limits applied during the manufacturing process of the finished product:			
a. tightening of in-process limits	2,3,7	1,4	IA
b. addition of new in-process test and limits	2,3,6,	1-5, 8	IA
c. deletion of a non-significant in-process test	2- 4	1,4,7	IAIN
d. 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	II
e. widening of the approved in-process limits	None	1-4,6,8	II
	1-3	1,4,5,8	IB
f. Addition or replacement of an in-process test as a result of a safety or quality issue	None	1-4, 6, 8	IB
g. 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	IA

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 specifications 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 (2) 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 (3) 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.

(Q) B.II.c Control of Excipients

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.c.1. Change in the specifications parameters and/or limits of an excipient, involving: ***Note:*** *Excludes adjuvants, refer to adjuvant specific changes.*			
a. tightening of specification limits	3-4, 6, 7	1	IA
b. addition of a new specification parameter to the specification with its corresponding test methods	4	1-3	IA
c. deletion of a non-significant specification parameter	5, 8	1,2	IAIN
d. change outside the approved specification limit range/widening of specification	None	1,3	II
e. deletion of specification parameter which may have a significant effect on the overall quality of the finished product	None	1,4	II
(Q) B.II.c.2 Change in the test procedure for an excipient			
a. minor changes to an approved analytical procedure	None	1-2	IA
b. deletion of analytical procedure	5, 8	1,4	IA
c. substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent	None	1,4	II
d. replacement of an analytical procedure	1-3	1-2	IB
e. a change from an in-house analytical procedure to a recognised compendial analytical procedure	None	1-2	IA

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 is 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).
4. Justification for deletion or replacement of a test.

Description of Change (Q) B.II.c.3 Change in source of an excipients or reagent with TSE risk:	Conditions to be Fulfilled	Supporting Data	Amendment Type
a) Change from TSE risk material (e.g., animal) to vegetable or synthetic origin			
1. for excipients or reagents not used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal	None	1,3,5,6	IA

2. for excipients or reagents used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product	None	1,3,5,6	IB
(**Q**) **B.II.c.3.b.** change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by TSE certificate of suitability	None	2-7	II

(**Q**) **B.II.c.3.b.N1** Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5	2-7	IB
(Q) B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	**Conditions to be fulfilled**	**Supporting document**	**Amendment type**
(**Q**) **B.II.c.4 a**. minor change in synthesis or recovery of a non- pharmacopoeial excipient or a novel excipient	7-8	5	IA
(Q) B.II.c.4 b. the specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished product		2-7	II
(Q) B.II.c.4.c. the excipient is a biological of immunological substance. ***Note:*** *excludes biological adjuvants, refer to adjuvant specific changes.*	None	2-7	II
	1,2	2-7	IA
	2	2-3,5-7	IB

(Q) B.II.c.4.d change in supplier for a plasma-derived excipient (e.g., human serum albumin)	None	4-8	II
	3-4	5,6,9	IB
(Q) B.II.c.4.e 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	IB
	1,5	3	IA
(Q) B.II.c.4.f change in excipient testing site	1	10	IA

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.
7. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with ICH/VICH limits), or in physico-chemical properties.
8. Adjuvants are excluded.

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 terms 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 are acceptable. The data should cover a minimum of three (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 (3) 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 works under acceptable quality standards.

(Q) B.II Control of Final Product			
Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Amendment Type**
(Q) B.II.d.1 Change in the specifications used to release the final product, involving:			
(Q) B.II.d.1.a. tightening of an acceptance criterion	1,3,6,7	1	IA
(**Q) B.II.d.1.b.** tightening of specifications limits for medicinal products subject to official control authority batch release	1,3,6,7	1	IAIN
(Q) B.II.d.1.c. addition of a new specification parameter to the specification with its corresponding test method	1-2, 7	1-3, 5	IA
(Q) B.II.d.1.d. deletion of non-significant specification parameter (e.g deletion of an obsolete parameter such as odour, taste or identification test for a colouring or flavouring material	5,7	1, 6	IA
(Q) B.II.d.1.e. change outside the approved specifications limits or widening of specification limits	None	1,5 7	II
(Q) B.II.d.1.f. deletion of a specification parameter which may have a significant effect on the overall quality of finished product	None	1,6 7	II
(Q)B.II.d.2 Change in the analytical procedure for the final product, involving:			
a. minor changes to an approved analytical procedure	none	1-5	IB
	1 ,3-5	2, 4 5	IA
b. deletion of a test analytical procedure	None	1,6.7	II
c. substantial change to, or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent		1-5	II

d. other changes to an analytical procedure, including replacement or addition of an analytical procedure	None	1-5	IB
	4,8	1,4,5	IA
e. Update of the analytical procedure to comply with updated monograph or change from an in-house analytical procedure to a recognised compendia analytical procedure	none	1-5	IB
	1,5	1,5,7	IB

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 is within recognised 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.

(Q) B.II.d.N1. Reference Standards or Materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
a. qualification of a new reference standard against a new primary international standard	None	1-2	IB
b. change the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1-2	IA
c. 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	IA
d. change to reference standard qualification protocol	None	3-4	IB
e. extension of reference standard shelf life	2	5	IB

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(s) 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 or retest data to support the extension of reference standard shelf life.

(Q) B.II.e Container Closure System

(Q) B.II.e.1. Change in immediate packaging of the finished product	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.e.1.a.3. modification of a primary container closure system (e.g., new coating, adhesive, stopper, type of glass and etc.) ***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*	None	1-6	II
	1-3	3	IA
(Q) B.II.e.1.b Change in type of container or addition of a new container	**Conditions to be Fulfilled**	**Supporting Data**	**Amendment Type**
(Q) B.II.e.1.b.2 Sterile medicinal products and biological /Immunological medicinal product	None	1-6	II
(Q) B.II.e.1.b.N2. addition of a secondary functional container closure system (e.g., pre- filled auto injector)	None	1-3,6	IB
(Q) B.II.e.1.b.N2.1 (Q) 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	IB
(Q) B.II.e.1.b.3. deletion of a container closure system	None	1	IB

Conditions

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

Supporting Data
1. Revised product labelling information, as appropriate. 2. For sterile products, process validation 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 three (3) commercial scale final product batches produced with the proposed changes under real-time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme are acceptable. The data should cover a minimum of three (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 (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	Amendment Type
(Q) B.II.e.2. Change in the specifications' parameters and/or limits of the immediate packaging or a primary container closure component or functional secondary container closure component of the final product:			
a. tightening of specification limits	8	1	IA
b. addition of new specification parameter	3	1-2	IA
c. deletion of non-significant specification parameter	1-2	1-2	IA
d. addition or replacement of a specification parameter as a result of a safety or quality issue	None	1-2	IB
e. widening of specification limits	None	1-2	IB
(Q) B.II.e.3. Change in analytical procedure for the immediate packaging / primary container closure component or functional secondary container closure component of the final product, involving:			
a. minor changes to an analytical procedure	4-7	1-3	IA
b. other changes to analytical procedure, including replacement or addition of an analytical procedure	6-7	1-3	IA
c. deletion of analytical procedure if an alternative analytical procedure is already authorised	9	1	IA

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 or analytical procedure 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.

(Q) B.II.e.4. Change in shape or dimensions of the container or closure (immediate packaging)	Conditions to be fulfilled	Supporting Data	Amendment Type
a. non-sterile medicinal products		1,3,4,5	IA
b. the change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product	None	1-6	II
c. sterile medicinal products		1,2,3,4,5	IB

Conditions:

1. No change in the qualitative or quantitative composition of the container.
2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and at least three (3) months (six months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if it is outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

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 three (3) commercial scale final product batches produced with the proposed changes under real-time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on stability programme are acceptable. The data should cover a minimum of three (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 (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.

(Q) B.II.e.5 Change in pack size of the finished product	Conditions to be fulfilled	Supporting Data	Amendment Type
(Q) B.II.e.5.a. Change in the number of units (e.g. ampoules, etc.) in a pack:			
1. change within a range of the currently approved pack sizes	1,2	1,3	IAIN
2. change outside the range of the currently approved pack sizes		1,2,3	IB
(Q) B.II.e.5.b. deletion of pack size(s)	3	1,2	IA
(Q) B.II.e.5.c Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	None	1,2,3	II
Conditions: 1. The new pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics. 2. The primary packaging material remains the same. 3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.			
Supporting Data: 1. Amendment to the relevant section of the dossier 2. Justification for the new fill weight /fill volume. 3. Stability data or declaration that stability studies will be conducted in accordance with the relevant stability guideline. 4. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics.			

(Q) B.II.e.6. Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)	Conditions to be fulfilled	Supporting documents	Amendment Type
a. change that affects the product information	1	1	IAIN
b. change that does not affect the product information	1	1	IA
Conditions: 1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
Supporting documents: 1. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.			

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.e.7 Change in the supplier of packaging components or devices (when mentioned in the dossier)			
a. deletion of a supplier	None	None	IA
b. replacement or addition of a supplier	None	1-3	IB
	1-2	2	IA
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 (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 (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.

Q) B.II.f Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.f.1 . Change in the shelf life or storage conditions for the final product, involving:			
a. reduction (includes reduction as 1.) packaged for sale, 2.) after opening and 3.) after dilution or reconstitution)	None	1-5	IB
	6	2-4	IAIN
b. extension (includes extension of shelf life of the final product as 1.) packaged for sale, 2.) after opening and 3.) after dilution or reconstitution)	None	1-5	IB
	1-5	1-2,5	IB
c. change in storage conditions of the biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	None	1-5	II

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 manufacturing 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	Amendment Type
(Q) B.II.f.1.d . Change in the labelled storage conditions for the final product or the diluted or reconstituted medicine, involving:			
1. 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	IB
	1-2	1-4	IA
2. addition of a cautionary statement (e.g., do not freeze)	1	1-2,4-5	IA
3. deletion of a cautionary statement (e.g. do not freeze)	None	1-2,4,6	IB

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 labelled 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 otherwisejustified.

Description of Change	Conditions to be Fulfilled	Supporting Data	Amendment Type
(Q) B.II.f.1.e. Change to an approved stability protocol of the final product, involving: [NB this code has been expanded to include 6 sub-codes as listed below]			
1. major change to the approved stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature	None	1-6	IB
2. addition of time point(s) into the post-approval stability protocol	None	4-5	IA
3. addition of test(s) into the post-approval stability protocol	1	4-5	IA
4. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf life	None	4-5	IA
5. deletion of time point(s) from the post-approval stability protocol within the approved shelf life	2	4-5	IA
6. replacement of the sterility testing by the container/closure system integrity testing	None	1-2,4-5	IB
	3	4-5	IA
Conditions			
1. The addition of test(s) is not due to stability concerns or to the identification of newimpurities. 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	Amendment type
(Q) B.II.h.1. Update to the 'Adventitious Agents Safety Evaluation' information (section 3.2.A.2)			
a) Studies related to manufacturing steps investigated for the first time for one or more	None		II
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier:			
1) with modification of risk assessment	None		II
2) without modification of risk assessment	None	1,2,3	IB

Supporting Data
1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents. 2. Justification that the studies do not modify the risk assessment. 3. Amendment of product information (where applicable).

(Q) B.III CEP/TSE/MONOGRAPHS

(Q) B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:	Conditions to be Fulfilled	Supporting Data	Amendment Type
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. new certificate from an already approved manufacturer	1, 2, 3, 4, 5, 8, 11	1, 2, 3, 4, 5	IAIN
2. updated certificate from an already approved manufacturer	1, 2, 3, 4, 8	1, 2, 3, 4, 5	IA
3. new certificate from a new manufacturer (replacement or addition)	1, 2, 3, 4, 5, 8, 11	1, 2, 3, 4, 5	IAIN
4. deletion of certificates (in case multiple certificates exist per material)	10	3	IA
5. new certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free	None	1, 2, 3, 4, 5, 6	IB
b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/ reagent/intermediate/or excipient			
1. new certificate for an active substance from a new or an already approved manufacturer	3, 5, 6, 11	1, 2, 3, 4, 5	IAIN
2. new certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	3, 6, 9	1, 2, 3, 4, 5	IA
3. updated certificate from an already approved manufacturer	7, 9	1, 2, 3, 4, 5	IA
4. deletion of certificates (in case multiple certificates exist per material)	10	3	IA

Conditions:

1. The finished product release and end of shelf life specifications remain the same.
2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g., particle size profiles, polymorphic form), if applicable.
3. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. For active substances only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5. The active substance/starting material/reagent/intermediate/excipient is not sterile.
6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE
7. For veterinary medicinal products: there has been no change in the source of material.
8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
9. If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should only be manufactured in compliance with the relevant country's requirements.
10. At least one manufacturer for the same substance remains in the dossier.
11. If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP, it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Supporting Data:

1. Copy of the current (updated) Ph. Eur. Certificate of Suitability.
2. In the case of an addition of a manufacturing site, the variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form.
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
   Where applicable, a document providing information of any materials falling within the scope of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, including those which are used in the manufacture of the active substance/excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the centralized Procedure, this information should be included in an updated TSE table A (and B, if relevant).

4. Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operates in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1. The manufacture of intermediates also requires a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.
5. Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2 Change to comply with Ph. Eur. or with a pharmacopoeia recognised by SAHPRA	Conditions to be Fulfilled	Supporting Data	Amendment Type
a) Change of specification(s) of a former non-EU Pharmacopoeial substance to fully comply with the Ph. Eur or any Pharmacopoeia recognised by SAHPRA			
1. active biological substance	1, 2, 3, 4, 5,	1, 2, 3, 4	IAIN
2. excipients/Active biological substance starting materials	1, 2, 4	1, 2, 3, 4	IA
b) Change to comply with an update of the relevant monograph of the Ph. Eur. or Pharmacopoeia recognised by SAHPRA	1, 2, 4, 5,	1, 2, 3, 4	IA
c) Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	1,4,5	1,2,3,4	IA

Conditions

1. The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.
2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g., particle size profiles, polymorphic form or, e.g. bioassays, aggregates).
3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened
4. Additional validation of a new or changed pharmacopoeial method is not required.
5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract.

Supporting data

1. Amendment of the relevant section(s) of the dossier (presented in the ZA-CTD format.
2. Comparative table of current and proposed specifications.
3. Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable.
4. Data to demonstrate the suitability of the monograph to control the substance, e.g., a comparison of the potential impurities with the transparency note of the monograph.

13. APPENDIX 4: (Q) D. PLASMA MASTER FILE (PMF) / VACCINE ANTIGEN MASTER FILE (VAMF)

(Q) D.1 change in the name and/or address of the VAMF certificate holder	**Conditions to be Fulfilled**	**Supporting Data**	**Amendment Type**
	1	1	IAIN
Conditions 1. The VAMF certificate holder must remain the same legal entity.			
Supporting Data 1. A formal document from a relevant official body in which the new name or new address is mentioned.			
(Q) D.2 change in the name and/or address of the PMF certificate holder	1	1	IAIN
Conditions 1. The PMF certificate holder must remain the same legal entity.			
Supporting Data: 1. A formal document from a relevant official body in which the new name or new address is mentioned.			
(Q) D.3 change or transfer of the current PMF certificate holder to a new PMF certificate holder, i.e. different legal entity		1-6	IAIN
Supporting Data 1. A document including the identification (name and address) of the current PMF Holder (transferor) and the identification (name and address) of the person to whom the transfer is to be granted (transferee) together with the proposed implementation date — signed by both companies. 2. Copy of the latest PMF Certificate page 'EMA Plasma Master File (PMF) Certificate of compliance with Community legislation'. 3. Proof of establishment of the new holder (Excerpt of the commercial register and the English translation of it) — signed by both companies. 4. Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee — signed by both companies. 5. Letter of Authorisation including contact details of the person responsible for communication between the competent authority and the PMF holder — signed by the transferee. 6. Letter of Undertaking to fulfil all open and remaining commitments (if any) -signed by the transferee.			

(Q) D.4 change in the name and/or address of a blood establishment including blood/plasma collection centers	1-2	1-3	IA
Conditions 1. The blood establishment must remain the same legal entity. 2. The change must be administrative (e.g. merger, takeover); change in the name of the blood establishment/ collection center provided the blood establishment must remain the same.			
Supporting Data 1. Signed declaration that the change does not involve a change of the quality system within the blood establishment. 2. Signed declaration that there is no change in the list of the collection centers. 3. Updated relevant sections and annexes of the PMF dossier.			
(Q) D.5 replacement or addition of a blood/plasma collection center within a blood establishment already included in the PMF		1-3	IB
Supporting Data 1. Epidemiological data for viral markers related to the blood/plasma collection center covering the last three (3) years. For newly-opened center(s) or in case no data is yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s). 2. Statement that the center is working under the same conditions as the other centers belonging to the blood establishment, as specified in the standard contract between blood establishment and PMF holder. 3. Updated relevant sections and annexes of the PMF dossier.			
(Q) D.6 Deletion or change of status (operational/nonoperational) of establishment(s)/centre(s) used for blood/ plasma collection or in the testing of donations and plasma	1-2	1	IA
Conditions 1. The reason for deletion or changes of status should not be related to a GMP issue. 2. The establishments(s)/center(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.			
Supporting data 1. Updated relevant sections and annexes of the PMF dossier.			
(Q) D.7 addition of a new blood establishment for the collection of blood/plasma not included in the PMF		2	II

(Q) D.8 replacement or addition of a blood center for testing of donations and/or plasma pools within an establishment already included in the PMF		1-2	IB
Supporting data 1. Statement that the testing is performed following the same SOPs and/or test methods as already accepted. 2. Updated relevant sections and annexes of the PMF dossier.			
(Q) D.9 addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF		2	II
(Q) D.10 replacement or addition of a new blood establishment or center(s) in which storage of plasma is carried out		1-2	IB
Supporting data: 1. Statement that the storage center is working following the same SOPs as the already accepted establishment. 2. Updated relevant sections and annexes of the PMF dossier.			
(Q) D.11 deletion of a blood establishment or center(s) in which storage of plasma is carried out	1	1	IA
Conditions 1. The reason for deletion should not be related to GMP issues.			
Supporting data 1. Updated relevant sections and annexes of the PMF dossier.			

(Q) D.12 replacement or addition of an organisation involved in the transport of plasma		1	IB
Supporting data 1. Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organisation, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.			
(Q) D.13 Deletion of an organisation involved in the transport of plasma	1	1	IA
Conditions 1. The reason for deletion should not be related to GMP issues.			
Supporting data 1. Updated relevant sections and annexes of the PMF dossier.			
(Q) D.14 addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	1	1-2	IA
Conditions 1. The new test kit is CE-marked.			
Supporting data 1. List of testing site(s) where the kit is used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the 'Guideline on the scientific data requirements for a PMF'.			
(Q) D.15 addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	**Conditions to be Fulfilled**	**Supporting Data**	**Amendment Type**
a) The new test kit has not previously been approved in the PMF for any blood center for testing of donations			II
b) The new test kit has been approved in the PMF for other blood center(s) for testing of donations		1-2	IA

Supporting data

1. List of testing center(s) where the kit is currently used and a list of testing center(s) where the kit will be used.
2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the 'Guideline on the scientific data requirements for a PMF'.

(Q) D.16 change of kit/method used to test pools (antibody or antigen or NAT test).			II
(Q) D.17 introduction or extension of inventory hold procedure.	1	1	IA

Condition

1. The inventory holding procedure is a more stringent procedure (e.g., release only after retesting of donors).

Supporting data

1. Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.

(**Q) D.18** Removal of inventory hold period or reduction in its length.		1	IB

Supporting data

1. Updated relevant sections of the PMF dossier

(Q) D.19 Replacement or addition of blood containers (e.g. bags, bottles)	**Conditions to be Fulfilled**	**Supporting Data**	**Amendment Type**
a) the new blood containers are CE-marked	1-2	1	IA
b) the new blood containers are not CE-marked			II

Conditions

1. The container is CE-marked.
2. The quality criteria of the blood in the container remain unchanged.

Supporting data

1. Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.

(Q) **D.20** change in storage/transport	**Conditions to be Fulfilled**	**Supporting Data**	**Amendment Type**
a) storage and/or transport conditions	1	1	IA
b) maximum storage time for the plasma	1-2	1	IA
Conditions 1. The change should tighten the conditions and be in compliance with Ph. Eur. requirements for Human Plasma fractionation. 2. The maximum storage time is shorter than previously.			
Supporting data 1. Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).			
(Q) D.21 Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.		1	II
(Q) D.22 change in the plasma pool preparation (e.g., manufacturing method, pool size, storage of plasma pool samples)		1	IB
Supporting data 1. Updated relevant sections of the PMF dossier.			
(Q) D.23 changes in the steps that would be taken if it is found retrospectively that donation(s) should have been excluded from processing ('look-back' procedure)		1	II

14. APPENDIX 5: FORMAT OF COVER PAGE

The following templates must be included as part of the submission of a variation application to SAHPRA:

5.1 Letter of application – M1.0
5.2 Tabulated Schedule of Amendments – M1.5.2.1
5.3 Medicine Register Details – M1.5.2.2 5.4 Affidavit by the HCR / Applicant – M1.5.2.3

5.1 Letter of application

Instructions for applicants in gray (delete once read): Copy and paste the text in this document into your official company letterhead. Fill in all relevant information in the letter template, indicated by { }. Delete { } once information has been filled in.

THE CHIEF EXECUTIVE OFFICER
SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY BUILDING A
413 KIRKNESS STREET
LOFTUS PARK ARCARDIA
PRETORIA

Letter Date

{Working code e.g. eCTD- ANA/eSubmission ANA/, (All V
Codes}

Dear Madam,

APPLICATION FOR A VARIATION/AMENDMENT TO A REGISTERED PRODUCT

Registration Number(s)	
Product Proprietary name(s)	
API(s)	
Dosage strength (and Dosage form)	

Type of submission	<Type IA><Type IB><Type II><Response to recommendations> This refers to the overall submission, which is classified according to the most extensive procedure (e.g., if a Type IB and Type II are submitted together, the overall submission will be treated as a Type II, payment of each application type will apply.)
Sequence number	

Description of the submission

{Brief product description}

Format of the submission

We confirm that the CD/DVD burning session is closed and the submission is checked with an up-to- date and state-of-the-art anti-virus software: **{Name of the antivirus software and version of the checker}** and is virus-free.

Number of CDs/DVDs submitted: {number}
Application format: <eCTD><eSubmission>
If eCTD, state the name of the eCTD validation tool used to check compliance

If eSubmission, state briefly (2 lines max) why eSubmission was used instead of the SAHPRA preferred eCTD format

Summary of the variations / amendments applied for

Applicants are to list and describe all of the variations applied for, in order to aid SAHPRA with routing the application appropriately. The table is intended to be a relatively high-level summary, with more information on the exact nature of the variations provided in the amendment schedule.

Variations/changes included in this application			
Code	**Procedure**	**Code description**	**Summary**
E.g., (Q) C.I.2a	Type IB	Change(s) in the PI or PIL of a generic/biosimilar medicine following assessment of the same change for the reference product	Special warnings and precautions updated to reflect content of published local innovator PI [product name X, published 2018/05/21]

E.g., (Q) C.I.6a	Type II	Addition of a new therapeutic indication or modification of an approved one	Application for an additional indication for Myelofibrosis, supported by new clinical trial data. Indication has been approved by the EMA and FDA.

5.2 Tabulated schedule of amendments

The MRF1 PART 1Ac) / 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.

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. Furthermore, the table is applicable to both SAHPRA's ME&R and Clinical directorates. Only those variations / amendments listed in the table below may be reflected in the dossier.

The amended PARTs/Annexures/Modules are as follows:

Annexures / PARTs / Modules	**Comparison between Annexures / PARTs / 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	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), attacheddata 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 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.

Contact for validation errors:

Should there be validation errors, please contact:

Name and Surname}

{Designation}
{Email address}
{Contact number}

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 Yours faithfully,

{Name}
{Designation and contact

details} Signed:

5.3 Medicine Register Details

The following information should be included in Module 1.5.2.2.

Product to which this application refers

Proprietary name of medicine	**Registration/Reference number**	**Registered medicine (R) / Old Medicine (OM)**

Details (if there is no change to the "Current", indicate as such under "Proposed", do not state N/A)

	Current	Proposed
Proprietary Name		
HCR/Applicant		
Name of Address		
Contact person:		
Name		
Designation		
Telephone no.		
Manufacturer		
Name and Address		
SAHPRA License No.		
SMF Reference No.		
Packer		
Name and Address		
SAHPRA License No.		
SMF Reference No.		

FPRC		
Name and Address		
SAHPRA License No.		
SMF Reference No.		
FPRR		
Name and Address		
SAHPRA License No.		
SMF Reference No.		
Formulation	If the formulation is the same, confirmation to this effect will suffice.	

5.4 Affidavit by the HCR / Applicant

The following affidavit should be included in Module 1.5.2.3. The affidavit should be on company letterhead and include only those statements relevant to the application. In the case of a Transfer of the Certificate of Registration (To HCR), this must be done by the proposed HCR.

AFFIDAVIT BY THE HCR / APPLICANT

PRODUCT NAME: { } REGISTRATION NUMBER: { }

I, {insert full name and surname} Responsible Pharmacist [as defined in Section 22C (1)(b) of Act 101 of 1965] of {insert Company name} confirm that:

a) I am in possession of the master documentation pertaining to the above-mentioned medicine.

b) This master documentation is the same as that which was in existence when the medicine was initially registered or which has been updated in accordance with amendments of the medicine registration form (MRF1/CTD) in accordance with the provisions of the regulations under the Medicines and Related Substances Control Act, 1965 (Act 101of 1965).

c) The master documentation conforms with the Registration dossier;

d) The master documentation is properly authorized (i.e. signed and dated by at least the responsible pharmacist), *and* the quality assurance or production manager as applicable;

e) The master documentation has been supplied to the new manufacturer/packer or laboratory {state company and role} and that applicable control records have been compiled. I confirm further that I have signed these to indicate my approval that they contain all the requirements listed in the relevant master documents; namely

- formulation and method of manufacture and packaging in-process control procedures
- specifications pharmaceutical ingredients specifications for the final product specifications for the packaging material specifications for the label
- specifications for the package insert
- testing procedures for the pharmaceutical ingredients testing procedures for the final product
- testing procedures for the packaging materials.

f) I confirm that a technical agreement and/or signed contract(s) exist(s) with all third party manufacturer(s)/packer(s)/laboratory(ies) involved in manufacturing of this product.

g) For an alternative/additional manufacturer:

- I confirm that the manufacturing procedure (including equipment) is identical to the manufacturing procedure currently used or
- I confirm that the manufacturing procedure (including equipment) differs, but falls within the <Type IA><Type IAIN>< and><Type IB> amendment
- I confirm that the manufacturing procedure (or equipment) is different from the manufacturing procedure (or equipment) currently on file outside of the <Type IA><Type IAIN>< and><Type IB> amendments and that comparative data (efficacy), stability data or protocol (as applicable), and a validation protocol for the first three production batches, are submitted.

h) <I confirm that the PI will be updated to reflect the new HCR details and will submit the amended PI with the first update of the dossier after authorisation of this amendment. (for ToHCRs only)>

i) <I confirm that the Registration dossier will be fully updated to the current statutory format and current scientific standards within 12 months of transfer of the certificate of registration, or approval of additional, or change of manufacturer.>

OR

<I confirm that the Registration dossier will be fully updated to the current statutory format and current scientific standards by (stipulate date) in accordance with the programme as approved by the Inspectorate.>

Signed on {DD/MM/YYYY}:

15. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces [2.61_Biological_Medicines_Amendment_Guideline_V4]. It will be reviewed on this timeframe or as and when required