Annex 3

Guidelines on procedures and data requirements for changes to approved biotherapeutic products

Guidelines published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these WHO Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA.

Abbreviations

ALIFAR	Asociación Latinoamericana de Industrias Farmacéuticas
BSE	bovine spongiform encephalopathy
DNA	deoxyribonucleic acid
GCP	good clinical practice
GLP	good laboratory practice(s)
GMP	good manufacturing practice(s)
HPLC	high-performance liquid chromatography
HSA	Health Sciences Authority
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IGBA	International Generic and Biosimilar Medicines Association
IQ	installation qualification
MCB	master cell bank
NRA	national regulatory authority
OQ	operational qualification
PAS	prior approval supplement
PDA	Parenteral Drug Association
PK/PD	pharmacokinetic/pharmacodynamic
PPTA	Plasma Protein Therapeutics Association
PQ	performance qualification
SBP	similar biotherapeutic product
TSE	transmissible spongiform encephalopathy
WCB	working cell bank

1. Introduction

Biotherapeutic products are an increasingly important component of global health care. Several WHO guidelines on the evaluation of biotherapeutic products have been produced (*1–3*) that provide a set of principles on the regulatory evaluation of such products. During international consultations on the development of these guidelines, and their subsequent implementation, it became clear that there was a need for WHO guidance on making post-approval changes to biotherapeutic products in order to help address the complexity and other challenges associated with the global life-cycle management of such products. In May 2014, the Sixty-seventh World Health Assembly adopted two relevant resolutions: one on promoting access to biotherapeutic products and ensuring their quality, safety and efficacy (*4*) and the other on regulatory systems strengthening (*5*). In support of these resolutions, WHO was requested to provide guidance on how to deal with increasingly complex biotherapeutic products, including similar biotherapeutic products (SBPs). In addition, the 16th International Conference of Drug Regulatory Authorities recommended that WHO assist Member States in ensuring regulatory oversight throughout the life-cycle of biotherapeutic products (*6*).

This document is intended to provide guidance to national regulatory authorities (NRAs) and manufacturers on regulating changes to already licensed biotherapeutic products in order to assure their continued quality, safety and efficacy, as well as continuity in supply and access. The term "biotherapeutic products" as used in this document collectively includes the originator products and SBPs (also called "biosimilars").

Changes are essential for the continual improvement of the manufacturing process and for maintaining state-of-the-art control of biotherapeutic products, and often need to be implemented after the product has been approved (that is, when it has been licensed or when marketing authorization has been received). Changes may be made for a variety of reasons, including: (a) to maintain routine production (for example, replenishment of reference standards, or change of raw materials); (b) to improve product quality, or the efficiency and consistency of manufacture (for example, changes in the manufacturing process, equipment or facility, or adding a new manufacturing site); (c) to make safety or efficacy changes (for example, adding a new indication, changing the dosage regimen, or adding information on co-administration with other medicines); (d) to update product labelling information (for example, improvement of the management of risk by addition of a warning statement for a particular target population, or limiting the target population); or (e) to address administrative changes (for example, change in the proper/nonproprietary or trade name of a biotherapeutic product).

NRAs and marketing authorization holders should recognize that:

- any change to a biotherapeutic product has a potential impact on the quality, safety and/or efficacy of that product;
- any change to the information associated with the product (that is, product labelling information) may have an impact on its safe and effective use.

The regulation of changes to approved biotherapeutic products is key to ensuring that products of consistent quality, safety and efficacy are marketed after they receive authorization or licensure. Many NRAs of Member States have requested guidance on the data needed to support changes to approved biotherapeutic products in order to ensure comparability of the pre-change and post-change products with respect to quality, safety and efficacy. Although it is difficult to provide a set of guidelines that apply to all national situations, an attempt has been made to cover a range of possible changes in manufacture, quality control, safety, efficacy and product labelling information.

This document is intended to serve as a guide for establishing national requirements for the regulation of post-approval changes to biotherapeutic products. 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. If an NRA so desires, these WHO Guidelines may be adopted as definitive national requirements. It is possible that modifications to this document may be justified due to risk–benefit and legal considerations specific to each NRA. In such cases, it is recommended that any modifications should not depart from the principles outlined in this document. NRAs are encouraged to apply the concepts of reliance or work-sharing or to use collaborative approaches when reviewing post-approval changes, as indicated in section 8 below.

2. Purpose and scope

These WHO Guidelines provide guidance for NRAs and marketing authorization holders on the regulation of changes to the original marketing authorization dossier or product licence for an approved biotherapeutic product in terms of: (a) the procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable NRAs to evaluate the potential impact of the change on the quality, safety and efficacy of the product. Additionally, the purpose of these WHO Guidelines is to assist NRAs in establishing regulatory procedures for post-approval changes to such products.

The guidance applies in principle to all biologically active protein products used in the treatment of human diseases (for example, plasma-fractionated products) and those intentionally modified by, for example, fusion

proteins, PEGylation, conjugation with a cytotoxic drug or modification of rDNA sequences. The guidance also applies to protein products used for in vivo diagnosis (for example, monoclonal antibody products used for imaging).

While these WHO Guidelines apply to products that have received a licence or a marketing authorization, the principles described herein may also apply to quality changes that occur during development of a product and where comparability needs to be demonstrated. However, the amount and type of data submitted for such products will be limited and will vary according to the nature of each product and its stage of development. In addition, the legal status of investigational products varies from country to country and should therefore be discussed with the NRA.

Prophylactic vaccines against infectious diseases, and gene and cell therapy products, are not covered by these WHO Guidelines. Detailed and specific guidance for prophylactic vaccines are available in a separate WHO Guidelines document (*7*). However, the principles set out in this document may apply to low molecular weight heparins. Other WHO guidelines with relevance to this area include those covering good manufacturing practices (GMP) for biological and pharmaceutical products (*8*, *9*).

3. Terminology

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

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

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

Change: refers to a change that includes, but is not limited to, the product composition, manufacturing process, quality controls, analytical methods, equipment, facilities or product labelling information made to an approved marketing authorization or licence by the marketing authorization holder. Also referred to as "variations" or "post-notice of compliance changes" in other documents (*10–14*).

Comparability exercise: the activities – including study design, conducting of studies and evaluation of data – that are designed to investigate whether a pre-change product and a post-change product are highly similar (*1*).

Comparability protocol: a well-defined plan for future implementation of quality change(s) (for example, manufacturing-related changes, change of analytical method or site transfer). Also referred to as "post-approval change management protocol" in other documents (*15*). A comparability protocol establishes the tests to be performed and acceptable limits to be achieved to demonstrate the comparability of pre-change and post-change products following specific quality change(s).

Container closure system: refers to the following components:

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

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

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

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

Dosage form: the physical form in which a pharmaceutical product is presented by the manufacturer (form of presentation) and the form in which it is administered (form of administration). Also referred to as "pharmaceutical form" in other documents.

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

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

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

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

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

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

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

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

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

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

Marketing authorization holder: any person or legal entity that has received a marketing authorization or licence to manufacture and/or distribute

a medicine. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or licence.

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

Primary packaging site: site involved in the activity of putting a drug in its primary container which is, or may be, in direct contact with the dosage form.

Process validation: documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

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

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

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

Quality change: a change in the manufacturing process, product composition, quality control testing, equipment or facility. Also referred to as "chemistry manufacturing and control (CMC) change" in other documents.

Raw materials: a general term used to denote the culture media components, reagents or solvents intended for use in the production of starting material, drug substance, intermediates or drug products.

Real-time release testing: testing that provides the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls (*16*, *17*).

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

Safety and efficacy change: a change that has an impact on the clinical use of the biotherapeutic product in relation to safety, efficacy, dosage and

administration, and that requires data from clinical or post-marketing studies, and in some instances clinically relevant nonclinical studies, to support the change.

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

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

Similar biotherapeutic product (SBP): a biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product, and which was developed and approved on the basis of the principles outlined in relevant WHO guidelines (*2*, *3*).

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

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

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

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

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

4. General considerations

Changes to approved biotherapeutic products or SBPs are categorized on the basis of a risk analysis which takes into consideration the complexity of the production process and product, the patient population and the proposed changes. When a change affects the manufacturing or the control strategy, the assessment should include evaluation of the impact of the change on quality (that is, identity, strength, purity and potency) as it may relate to the safety and/or efficacy of the product. When a change affects the clinical use of a product or of product labelling information, this assessment should include evaluation of the effect of the change on the safety and efficacy of the product.

Prior to implementing a change with a potential impact on quality, the marketing authorization holder should demonstrate through appropriate studies (analytical testing, functional assays and, if needed, clinical and/or nonclinical studies) that the pre-change and post-change products are comparable in terms of quality, safety and efficacy.

For each change, the marketing authorization holder should decide if the information in the original marketing authorization or product licence needs to be supplemented (that is, requires an official submission of a supplement to the NRA) based on the recommendations provided in these WHO Guidelines. Supplements requiring approval by the NRA prior to the implementation of a change – that is, for changes that potentially have a major or moderate impact – are referred to as prior approval supplements (PASs) and must be submitted in advance to the NRA. For supplements that do not require approval prior to implementation – that is, for changes that potentially have a minor impact on product quality – the NRA should be notified following implementation of the change.

For each change, the supplement should contain information developed by the marketing authorization holder to allow the NRA to assess the effects of the change. All changes, regardless of their impact on quality, safety and efficacy, should be recorded and retained by the manufacturer or marketing authorization holder in accordance with the applicable regulatory requirements for document retention (*8*, *9*).

For manufacturing changes not specifically described in these WHO Guidelines, the marketing authorization holder is encouraged to use scientific judgement, leverage competent regulatory authority guidance or to contact the NRA to determine the potential impact of the change on quality, safety and efficacy in order to discuss the appropriate reporting category.

Assessment of the extent to which a quality change (also referred to as a manufacturing change) affects the quality attributes of the product is generally

accomplished by comparing manufacturing steps and test results from in-process, release, and characterization testing of the pre-change product (for example, using historical data) with those of the post-change product. It can then be determined if the test results are comparable – that is, if the drug substance, intermediate or drug product made after the change is comparable to, and/or meets the predefined acceptance criteria of, the drug substance or drug product made before the change. Where minor differences in quality are identified, these may be considered acceptable provided that they are shown not to have an adverse impact on the quality, safety or efficacy of the product (see sections 5.1 and 5.2). In some cases, additional supporting data may be required, as noted in Appendices 2, 3 and 4 below.

A marketing authorization holder or manufacturer making a change to an approved biotherapeutic product should also conform to other applicable laws and regulations, including good manufacturing practices (GMP), good laboratory practices (GLP) and good clinical practices (GCPs). Marketing authorization holders and drug substance/product manufacturers should also comply with relevant GMP validation and record-keeping requirements and should ensure that relevant records are readily available for examination by authorized NRA personnel during inspections. For example, changes in equipment used in the manufacturing process generally require installation qualifications (IQs), operational qualifications (OQs) and performance qualifications (PQs). This information does not need to be included in a PAS for equipment changes but is part of GMP requirements and should be available during inspections. Inspections (on-site or paper-based) may occur routinely or may be required during submission review of a PAS for a major manufacturing change such as a move to a new facility.

Certain major changes, such as changes to the molecule (for example, changing amino acid sequence or conjugating to PEG moieties) will lead to a new molecular entity and are not considered as post-approval changes. For these changes, submission of a product licence application for a new marketing authorization may be required. In some countries, a change in the quantity of drug substance per dose of biotherapeutic product also requires a product licence application for a new marketing authorization.

The implementation of new regulations for post-approval changes should take product supply into consideration. Any negative impact on access to approved products should be minimized. Therefore, NRAs are strongly encouraged to establish requirements that are commensurate with their own regulatory capacity, experience and resources. NRAs of countries procuring products are encouraged to consider establishing procedures for the expedited approval of changes based on previous expert review and approval of the same changes by the NRAs of the countries where these products are licensed, or based on the decision of a recognized regional regulatory authority. If a change has been

approved by another competent NRA, the NRA receiving the submission may choose to recognize this approval decision or may make an independent decision based on its own assessment. Foreign approval documentation may accompany the required information and may be used as supporting evidence for the post-approval change, as outlined in this document. The responsibility for the final regulatory decision on the approval of the change still lies with the receiving NRA (see section 8 and Appendix 1).

To ensure product supply and encourage adequate reporting of changes by manufacturers, NRAs should consider establishing procedures for the concurrent (that is, parallel) review of changes to the product. The manufacturing of biotherapeutic products requires, for example, the replenishment of biological starting materials such as WCBs and secondary/working reference standards which are considered as routine changes. Consequently, these changes often need to be reviewed concurrently with other manufacturing or safety and efficacy changes. Conversely, clinical safety and efficacy changes, such as the addition of a new indication or new age group for the use of a biotherapeutic product, require considerable supporting data including clinical studies; thus, review time should not impact the review of unrelated manufacturing changes or the immediate implementation of urgent changes to product labelling information. However, multiple related changes, or those supported by the same information, may be submitted in the same supplement (see "Multiple changes" in section 8).

In these WHO Guidelines, descriptions of the reporting categories for quality changes are provided in section 6, and the reporting categories for information changes on safety, efficacy and product labelling are provided in section 7. Proposed regulatory procedures for the reporting of changes to NRAs are described in section 8. Examples of suggested review timelines for changes in the various categories are given in Appendix 1. A comprehensive list of quality changes and the type of information that should be included in a supplement application are provided in Appendix 2 (for the drug substance and intermediates) and in Appendix 3 (for the drug product). Examples of changes that affect clinical use of a product and product labelling information (on safety, efficacy, dosage, administration and product components) are provided in Appendix 4.

5. Special considerations

5.1 Comparability exercise

The need for – and extent of – a comparability exercise depends upon the potential impact of the change(s) on the quality, safety and efficacy of the product. Comparability exercises can range from analytical testing alone (for example, where process changes have no impact on any quality attribute) to a comprehensive exercise requiring nonclinical and clinical bridging studies. For example, a change in the culture conditions or in the purification process may

cause the alteration of the glycosylation profile of the product, including site-directed glycosylation. Alteration of glycosylation profiles may cause a change in the pharmacokinetic/pharmacodynamic (PK/PD) profile of the product (see also section 5.2 on "Bridging studies"). If comparability can be demonstrated through analytical studies alone, nonclinical or clinical studies with the post-change product are not necessary. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and/or differences are observed between some critical quality attributes of the pre-change and post-change product, it may be necessary to include a combination of quality, nonclinical and/or clinical studies in the comparability exercise (*1*, *11*).

5.2 Bridging studies

Nonclinical and clinical bridging studies are studies in which a parameter of interest (such as a manufacturing process or formulation) is directly compared with a changed version of that parameter with respect to the effect of the change on the product's clinical performance. If the physicochemical properties, biological activity, purity and/or level of impurities of the pre-change and post-change product are comparable, the safety and efficacy of the biotherapeutic product can be inferred. However, nonclinical and/or clinical bridging studies may be required when analytical data alone either do not establish comparability or are insufficient to do so. The comparison of efficacy responses and safety outcomes (for example, PK/PD profile, or rates of common adverse events and serious adverse events) is often the primary objective. For ethical reasons, it is desirable to apply the 3R principles (Replacement, Reduction, Refinement) to the use of animals where scientifically appropriate. The following are examples of changes that are likely to require nonclinical and/or clinical bridging studies: (a) generation of a new MCB derived from a different host cell line; (b) a new dosage form; (c) a new formulation (for example, a new excipient); (d) a new presentation (for example, addition of pre-filled pens to vials); (e) a new route of administration; and (f) a new dosing schedule. For these and comparable changes, any proposed use of alternative approaches to a bridging study must be justified and discussed with the NRA.

5.3 Similar biotherapeutic products

Following approval, an SBP is considered to be independent from the reference product and has its own life-cycle (*3*). The manufacturer is not required to re-establish similarity to the reference product when comparability exercises are conducted.

A major change in clinical use for an SBP that relies on the previously demonstrated similarity provided in the original approval of the SBP may be considered by the NRA on a case-by-case basis. For example, a new indication

given to the reference product after approval of an SBP should not automatically be given to the SBP. However, when new safety information on the reference product is added after the original approval of the SBP, the labelling information changes of the SBP should follow the changes made for the reference product unless it can be demonstrated that the new information on the reference product is not relevant to the SBP.

6. Reporting categories for quality changes

On the basis of the potential effect of the quality change (for example, manufacturing change) on the quality attributes (that is, identity, strength, purity and potency) of the biotherapeutic product, and on the potential impacts of this on the safety or efficacy of the product, a change should be categorized as:

- a major quality change
- a moderate quality change
- a minor quality change, or
- a quality change with no impact.

The implementation of changes in the major or moderate categories must be reported to the NRA in order to supplement the information in the original marketing authorization or product licence. Major and moderate quality changes should be reviewed and approved by the NRA prior to implementation of the change (that is, prior to distribution of the post-change product).

Quality changes that are expected to have minimal potential to have an impact, or to have no impact on the quality, safety or efficacy of the biotherapeutic product, do not require submission of a PAS. The changes included in these categories may be implemented by the marketing authorization holder without prior review and approval by the NRA. However, quality changes with minimal potential to have an impact should be notified to the NRA within established timelines following implementation.

For each approved product, the marketing authorization holder or manufacturer should maintain a comprehensive chronological list of all quality changes, including minor quality changes. Additionally, this list should include a description of the quality changes, including the manufacturing site(s) or area(s) involved, the date each change was made, and references to relevant validations and standard operating procedures. All data supporting minor quality changes, as listed in Appendices 2 and 3 below, should be available on request to the NRA or during inspections in accordance with local regulations.

Further information on each category of change is given below in sections 6.1–6.4, with Appendices 2 and 3 providing a comprehensive list of major, moderate and minor quality changes, and the information required to

support each change. The quality changes listed in Appendices 2 and 3 should be reported or recorded in the appropriate categories, as recommended in this section and in the appendices. If a quality change may potentially have an impact on the quality, safety and efficacy of the biotherapeutic product, but is not included in Appendix 2 or 3, the NRA may be consulted for the correct classification. When procedures and timelines for such consultations are not in place, manufacturers should determine the classification of the change on the basis of a change-specific risk assessment using the principles and examples provided in these WHO Guidelines. The NRA should consider establishing a mechanism that allows for its guidelines to be updated to address technological changes requiring regulatory category classifications.

6.1 Major quality changes

Major quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have significant potential to have an impact on the quality, safety or efficacy of the biotherapeutic product or SBP. The marketing authorization holder should submit a PAS and receive a notification of approval from the NRA before implementing the change. NRAs should consider establishing a mechanism that allows for clear review timelines and a consistent means of ensuring that those timelines are met (see section 8 and Appendix 1).

For a change in this category, the PAS should specify the products concerned and should include a detailed description of the proposed change. Additional supporting information is needed for the drug substance (as noted in Appendix 2) and for the drug product (as noted in Appendix 3) and could include: (a) information on the methods used and studies performed to evaluate the effect of the change on the product's quality attributes; (b) the data derived from those studies; (c) relevant validation protocols and results; and (d) updated product labelling information. In some cases, major quality changes may also require nonclinical and/or clinical data. Relevant considerations on the data required can be found in the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (*1*).

6.2 Moderate quality changes

Moderate quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a moderate potential to have an impact on the quality, safety or efficacy of the biotherapeutic product or SBP. The marketing authorization holder should submit a PAS and receive a notification of approval from the NRA before implementing the change. The

requirements for the PAS for moderate quality changes are the same as those for major quality changes (see section 6.1); however, the amount of supporting data required will generally be less than that required for major changes and the review timeline should be shorter.

6.3 Minor quality changes

Minor quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a minimal potential to have an impact on the quality, safety or efficacy of the biotherapeutic product or SBP. Changes in this category may be implemented by the marketing authorization holder without prior review by the NRA. However, the NRA should be notified of the changes within a specified timeline (see Appendix 1). The justification and supporting documentation for minor quality changes are not needed for such notification but should be made available by the marketing authorization holder upon request from the NRA.

When a minor quality change affects the lot release specifications (for example, narrowing of a specification, or compliance with pharmacopoeial changes) and affects the quality control testing as summarized in the lot release protocol, the marketing authorization holder should inform the institution responsible for reviewing the release of lots (see introductory sections in Appendices 2 and 3).

Minor quality changes that are related to a major or moderate change should be described in the supplement for the major or moderate quality change (see section 8.2 for additional details).

6.4 Quality changes with no impact

Quality changes that have no impact on product quality, safety or efficacy may be implemented by the marketing authorization holder without prior review by the NRA. Information on such changes must be retained as part of the manufacturer's GMP records or marketing authorization holder's product records, as applicable. These changes must comply with the applicable GMP requirements and must be available for review during GMP inspections. Examples of such changes include, but are not limited to:

- non-critical changes to the licensed application, including spelling corrections and editorial clarifications made to documents (such as validation summaries and/or reports, analytical procedures, standard operating procedures or production documentation summaries) that have no impact on the quality, safety and efficacy of the product;
- replacement of equipment with identical equipment;

- change in specifications for a compendial raw material, a compendial excipient or a compendial container closure component to comply with an updated pharmacopoeial standard/monograph;
- transfer of quality control testing activities to a different facility within a GMP-compliant site;
- with the exception of a potency assay or a bioassay, transfer of the quality control testing activities for a pharmacopoeial assay to a different facility within the same company;
- change in the in-process controls performed at non-critical manufacturing steps;
- addition of a new GMP-compliant storage warehouse for raw materials, master and working cell banks, and drug substance;
- installation of non-process-related equipment or rooms to improve the facility, such as warehousing refrigerators or freezers;
- addition of time point(s) into the post-approval stability protocol;
- deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life.

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

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

- safety and efficacy change;
- product labelling information change;
- urgent product labelling information change; or
- administrative product labelling information change (in cases where prior approval before implementation is needed).

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

Further information on each category is provided below in sections 7.1–7.4. In addition, examples of efficacy, safety and product labelling

information changes considered to be appropriate for each category are provided in Appendix 4.

7.1 Safety and efficacy changes

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

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

- addition or expansion of a safety claim or efficacy claim, including expansion of the population that is exposed;
- change in the strength or route of administration;[1]
- change in the recommended dose and/or dosing schedule;
- co-administration with other biotherapeutic products or medicines;
- deletion or reduction of existing risk-management measures (for example, contraindications, adverse events, warnings or cautionary text/statements in the product labelling information).

The type and scope of the required nonclinical and/or clinical safety and efficacy data are determined case by case on the basis of risk–benefit considerations related to the impact of the changes, the biotherapeutic product attributes and the disease that the biotherapeutic product is designed to prevent. Other considerations include:

- the nature of the disease treated (that is, morbidity and mortality, acute or chronic disease, current availability of disease therapy, and size and nature of patient population);
- safety considerations (for example, adverse drug reactions observed, adverse events in specific patient populations, management of adverse reactions and change in rates of adverse reactions);
- the availability of animal models.

[1] Some NRAs consider that changes in the route of administration or strength may require a new marketing authorization.

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

For nonclinical and clinical studies, the recommendations given in the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (*1*) should apply. Guidance on approaches to the nonclinical and clinical comparability exercise can also be found in WHO guidelines on the evaluation of SBPs (*2*, *3*).

For a change under this category, the marketing authorization holder should submit a supplement to the NRA that includes the following where applicable:

- a detailed description of – and rationale for – the proposed change;
- a summary of the methods used and studies performed to evaluate the effect of the change on the safety or efficacy of the biotherapeutic product;
- amended product labelling information;
- information on clinical studies (protocol, statistical analysis plan and clinical study report);
- information on clinical assay methods (standard operating procedures) and validations; and
- the pharmacovigilance plan.

7.2 Product labelling information changes

Product labelling information changes are changes to the labelling items that have the potential to improve the management of risk to the population for which use of the biotherapeutic product is currently approved through:

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

Product labelling information changes require the filing of a PAS and a notification of approval from the NRA prior to distribution of the product. Supplements for product labelling information changes related to the clinical use of a product often require data from pharmacovigilance reports (that is, periodic safety update reports). Changes supported by large clinical or nonclinical studies are usually not considered as product labelling information changes but as safety and efficacy changes.

For a change under this category, the marketing authorization holder should submit to the NRA a PAS that includes the following where applicable:

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

7.3 Urgent product labelling information changes

Urgent product labelling information changes are changes to the labelling items that need to be implemented in an expedited manner in order to mitigate a potential risk to the population in which the biotherapeutic product is currently approved for use. Marketing authorization holders should consult with the NRA and agree on the required supporting documentation and time frames for the labelling changes or the need for a Dear Health-Care Professional Letter (that is, a formal letter from a manufacturer to health-care professionals) to convey the information prior to the submission of the supplement(s).

7.4 Administrative product labelling information changes

Administrative product labelling information changes are changes that are not expected to affect the safe and efficacious use of the biotherapeutic product. In some cases these changes may require reporting to the NRA and receipt of approval prior to implementation, while in other cases reporting may not be required.

- Examples of product labelling information changes that require approval by the NRA prior to implementation are changes in the proper/nonproprietary name or trade name of the biotherapeutic product. Changes in this category are considered important for reasons of liability and monitoring.
- Examples of product labelling information changes that do not require approval by the NRA prior to implementation are administrative changes such as those related to labelling (for example, minor changes in format without any negative effect on

readability). These changes should be reported to the NRA as part of a subsequent PAS for safety and efficacy changes or product labelling information changes when updated product labelling information is included.

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

8. Procedures

The establishment of procedures and criteria for the adequate oversight of changes to approved biotherapeutic products is the responsibility of the regulator. Therefore, NRAs should establish written instructions regarding submission procedures and timelines (with action dates) for consultation by marketing authorization holders as they prepare to submit a supplement for a change. These instructions should cover: (a) the identification of emergency use; (b) expanded access; and (c) expedited and/or priority review, timelines and procedures for life-saving medications to address an unmet need. As supplements for a major quality change or an efficacy and safety change require extensive documentation and data, the review times should be longer than those for supplements for moderate quality changes or product labelling information changes. Furthermore, NRAs may establish different timelines for the review of major quality changes that do not require clinical data as compared with safety and efficacy changes that do require clinical data. Appendix 1 provides examples of different regulatory categories and their suggested review timelines.

If a change is not included in Appendices 2, 3 or 4, marketing authorization holders are encouraged to use scientific judgement, leverage competent regulatory authority guidance or to contact the NRA to determine the appropriate category of a supplement prior to submission of the information in support of a change. Similarly, marketing authorization holders should consult NRAs for major changes that require the inclusion of a GMP certificate and which may trigger a pre-submission inspection, or that may require clinical and/or nonclinical data to support a change in safety and efficacy or in product labelling information. Marketing authorization holders are encouraged to contact the NRA regarding plans for future changes and proposed filing dates for changes to existing products in order to assist NRAs in planning the allocation of review resources. NRAs should establish procedures with appropriate timelines for the conducting and recording of communications between themselves and marketing authorization holders.

To assist in the acceptance of submissions for review, the covering letter or the Module 1 documentation of the Common Technical Document

accompanying a supplement for a quality change should clearly specify the selected category by labelling the submission as either a major quality change or a moderate quality change.

The covering letter accompanying a supplement for a safety, efficacy or product labelling information change should specify that the change is being reported in the selected category by labelling the submission as:

- a safety and efficacy change;
- a product labelling information change;
- an urgent product labelling information change; or
- an administrative product labelling information change (in cases where prior approval is needed before implementation).

Major quality change supplements that contain both quality data and revised product labelling information but no clinical and/or nonclinical data should be labelled "Major quality change and Product labelling information change" and the covering letter should specify that the submission includes both quality changes and revised product labelling information items.

Major quality change supplements that contain quality, safety and efficacy data (from clinical studies and/or clinically relevant nonclinical studies) and revised product labelling information, should be labelled "Major quality change and Safety and efficacy change" and the covering letter should specify that the submission includes quality changes, results from clinical and/or nonclinical studies, and revised product labelling information items.

Each supplement should include a list of all the changes contained in the submission. The list should describe each change in sufficient detail to allow the NRA to determine quickly whether the appropriate reporting category has been used. If the submission has been inappropriately classified, the marketing authorization holder should be notified. Minor quality changes that are related/consequential to moderate or major quality changes should be described in the PAS. In addition, any minor changes that have been implemented should be annotated in the affected documents (for example, Common Technical Document sections) and reported in any future filing to the NRA. For example, a minor change such as narrowing of a specification should be included in a supplement for a moderate or major change which includes updated quality control release information.

The regulation of post-approval changes is part of the entire regulatory framework which includes marketing authorization, GMP inspection and post-marketing surveillance. These activities are often performed by different units of the NRA. It is essential that these different units – especially the marketing authorization (or regulatory affairs) and GMP inspection units – interact and

exchange information effectively, and that the roles and responsibilities of each unit are clearly defined, particularly when they operate as separate entities. When multiple units are involved in the evaluation of a supplement, a formal decision-making process should be in place to discuss, for example, whether a change may require a GMP inspection or may be reviewed during the next routine inspection. Procedures should also be established so that the outcomes of inspections are verified or taken into account prior to the approval of supplements. Good coordination and communication between different units of the NRA are pivotal in ensuring continuity of supply and access to products of assured quality, safety and efficacy. Some regulatory authorities may be willing to cooperate more closely and to share information on GMP inspections under a mutual agreement (for example, the Pharmaceutical Inspection Cooperation Scheme – PIC/S).

Expedited review procedures

NRAs of product-procuring countries that decide to recognize or rely on the decisions of other NRAs should establish alternative regulatory procedures for the expedited approval of changes based on previous expert review and approval by the NRA of the country where the biotherapeutic products are licensed (see Appendix 1). Accordingly, the product-procuring NRAs should also create a list of the NRA approvals they will recognize. On the basis of regulatory and regional considerations, procedures for recognition of the decisions of other NRAs on the approval of changes could include the following pathways:

- The NRA recognizes the decision of other regulatory authorities and does not perform a review of supporting data, but is notified of the change. The submission consists of a covering letter from the marketing authorization holder informing the procuring NRA about the change and including as an attachment a copy of the approval letter from the NRA of the licensing country stating the relevant changes.
- The NRA performs an assessment of the decision of the NRA of the licensing country to determine whether recognition of that NRA's decision is appropriate. The submission consists of:
  - the covering letter from the marketing authorization holder informing the procuring NRA of the change;
  - a copy of the approval letter issued by the NRA of the licensing country;
  - assessment reports and relevant correspondence from the NRA of the licensing country (if made available by the NRA);
  - a detailed description of the change; and

  - supporting data submitted as necessary if assessment reports are not available.
- The NRA performs a partial review and evaluation of a complete package of supporting data, as originally submitted in the product-licensing country.

Similarly, recognition of inspection activities conducted by the authorities that license the product may be considered as part of the expedited review process and may be included in the regulatory pathways listed above.

Additionally, for previously approved changes addressing urgent safety issues in the product labelling information, procedures should be in place to allow for the expedited implementation of such changes (see section 8.3 and Appendix 1).

In special or urgent circumstances, a marketing authorization holder may ask the NRA to expedite the review of a supplement for public health reasons (for example, a product shortage or safety update) or if a delay in making the change would impose extraordinary hardship on the marketing authorization holder or manufacturer.

Multiple changes

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

Multiple major or moderate quality changes for the same product may be filed in a single submission provided that the changes are related and/or supported by the same information. Minor quality changes that were implemented previously and that are related and/or consequential to a moderate or major quality change should be described in the PAS for the moderate or major quality change. If the proposed changes are related, the marketing authorization holder should indicate the association between them. The marketing authorization holder should also clearly specify which supporting data support which change. Such changes could affect both the drug substance and the drug product. If too many changes are filed within the same submission, or if major issues are identified with a change and extensive time would be required to review them, the NRA may ask the marketing authorization holder to divide the changes into separate submissions and to resubmit the file. 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 the case of numerous changes of the same category, the NRA may reclassify

the submission to the next higher level on the basis of the potential impact of the totality of the changes on the quality, safety and efficacy of the biotherapeutic product or SBP. This reclassification should be communicated to the marketing authorization holder at the start of the assessment.

8.1 Procedures for prior approval supplements

The procedures in this section apply to all changes requiring approval prior to implementation: namely, major and moderate quality changes, safety and efficacy changes, product labelling information changes, urgent product labelling information changes and selected administrative product labelling information changes.

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

- a covering letter that includes:
  - the type of submission (for example, major quality change, moderate quality change or safety and efficacy change),
  - a list of the change(s) and a rationale for the change(s) with sufficient detail (including a justification for the selected reporting category) to allow for processing and reviewer assignments by NRAs,
  - an indication of the general type of supporting data, and
  - cross-referenced information (including product name, marketing authorization holder's name, submission type and date of submission/approval);
- completed documents or forms based on NRA requirements, such as a medicine submission application form, signed and dated;
- the anticipated date for implementation of the change (recognizing that in some cases the implementation of the change may be delayed after approval to allow for depletion of the previously approved biotherapeutic or to allow for global staggered approval depending on supply/demand);
- GMP information (for example, inspection history and/or evidence of GMP compliance rating by experienced NRAs), as applicable;
- when relevant, a side-by-side comparison showing the differences between the approved manufacturing process (including quality control tests) and the proposed one(s) (see section 5);
- when relevant, clinical and/or nonclinical study reports, pharmacovigilance reports, and annotated and clean drafts of product labelling information (see section 7).

In addition to the above general information, the specific information required to support the various quality changes is outlined in Appendices 2 and 3. It should be noted that the general information is not repeated under each of the various changes outlined in the appendices. All data recommended to support a change should be provided with the submission, in addition to the general information as appropriate. If recommended supporting data are not submitted, a detailed rationale should be provided to explain why.

If the same change is applicable to multiple products, a separate submission is generally required for each product – though the data may be cross-referenced. NRAs may in some cases allow a common change to be bundled into one submission for multiple products. When cross-references are made to information that has been submitted previously, details of the cross-referenced information should be provided in the covering letter.

Submissions filed in electronic or paper format should be based on the requirements of the NRA. The data submitted should be well organized and should be provided in the format defined by the NRA.

After the NRA completes the review of the supporting data in a supplement, the following outcomes are possible:

- If the NRA determines that the information submitted in a supplement supports the quality, safety and efficacy of the product manufactured with the change, the NRA will issue a written notification of approval stating that the change can be implemented and the product manufactured with the change can be distributed.
- If the NRA determines that the information submitted in a supplement fails to support the quality, safety or efficacy of the product manufactured with the change, the NRA will issue a written request notification for additional documentation, information and clarification to be submitted by the marketing authorization holder. If the identified deficiencies are minor, they may be addressed without stopping the review process. If the deficiencies are major or are not resolved during the allotted review period following rounds of questions and requests for more information, the NRA may decide to issue a written notification of noncompliance, as a result of which the review process is stopped, the change may not be implemented and the product manufactured with the change may not be distributed. In the case of a notification of noncompliance being issued, the following outcomes are possible:
  - If the marketing authorization holder's response document to the notification of noncompliance is adequate and all identified deficiencies are resolved in a satisfactory manner, the NRA will

issue a written notification of approval stating that the change can be implemented and the product manufactured with the change can be distributed.

– If the information in the marketing authorization holder's response document to the notification of noncompliance is not adequate and not all identified deficiencies are resolved in a satisfactory manner, the NRA will issue a written notification of rejection stating that the change cannot be implemented and the product manufactured with the change cannot be distributed.

The NRA should establish procedures and timelines for the review of marketing authorization holders' responses to the notification of noncompliance in cases where the review has been stopped. Documentation subsequent to the original supplement submission (in response to information requests or notifications of noncompliance) should be submitted and filed as amendments to the original supplement, and all communications with sponsors should be properly recorded.

Appeal procedures should be established for resolving disagreements and disputes between the NRA and the marketing authorization holder. Such procedures should allow the marketing authorization holder to request a re-evaluation of the submitted application in case the application is initially rejected by the NRA.

NRAs may consider the use of a "comparability protocol" when a marketing authorization holder submits 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 future implementation of a quality change. This will include the tests to be done and acceptable limits to be achieved when assessing the effect of specific changes on the quality, safety or efficacy of a biotherapeutic product or SBP. For some changes, the routine quality tests performed to release the drug substance or drug product are not considered sufficient for assessing the impact of the change, and additional in-process tests and characterization tests may be needed. Comparability protocols are often used for the routine replenishment of WCBs and reference standards used in quality control tests when the remaining aliquots of reference standards expire or diminish.

The purpose of a comparability protocol is to provide transparency in the data requirements for changes and increase the predictability of the effects of changes. This allows for the more expedient distribution of a product by

permitting the marketing authorization holder to submit a protocol for a change which, if approved, may justify a reduced reporting category for the change when the comparability data are obtained and the change is implemented. It is for the NRA to decide whether or not to include the review and approval of comparability protocols in its approach to regulating changes to approved biotherapeutic products or SBPs; however, the concept of using comparability protocols is encouraged. For NRAs currently taking this approach, a comparability protocol can be provided in the original submission. Otherwise, a new comparability protocol, or a change to an existing one, requires submission of a supplement and approval prior to implementation because it may result in a lower reporting category for the changes covered in the comparability protocol once the actual comparability data are submitted. The change in reporting category for a change covered by a comparability protocol and the supporting data to be generated should be established by the NRA at the time the comparability protocol is approved. For a minor quality change that results from the execution of a comparability protocol, the change should be notified to the NRA immediately after implementation. For some marketing authorization holders with multiple related products and facilities, an expanded change protocol can be proposed. The scope of an expanded change protocol may cover multiple related products or manufacturing changes (for example, facility changes) (*15*).

Production documents

Production documents (that is, executed batch records) are not generally required to support changes to the marketing authorization dossier or product licence. However, such documents may be requested during review and should be made available to the NRA on request. These documents should be retained in accordance with GMP and should be available in their local official language during inspections. If English translations are required, NRAs are encouraged to establish a mechanism to make this requirement known to marketing authorization holders accordingly.

8.2 Procedures for minor quality changes and quality changes with no impact

Implementation of minor quality changes does not require prior approval from the NRA but should be notified to the NRA. Each NRA is responsible for determining the timelines for reporting the notification (for example, annually). Supporting data should not be provided with the notification unless it may help in justifying the reporting category. However, as recommended in Appendices 2 and 3 below, the minor quality changes should be recorded or compiled with related supporting data generated by the manufacturer in a document or file

dedicated to minor changes. The documents or files for all minor quality changes should be available to the NRA on request or during inspection.

NRAs may audit minor quality changes by requesting and reviewing the supporting data, as deemed appropriate during an inspection or review of related changes. If the classification of a change or the supporting data are not considered to be acceptable then the marketing authorization holder may be requested to file a supplement for a major or moderate quality change.

Minor quality changes that have previously been implemented and are related and/or consequential to a major or moderate quality change should be described in the relevant parts of the documentation when submitting a PAS for the major or moderate change. As for all minor quality changes, the supporting data for these changes do not need to be included in the supplement but should be retained by the manufacturer.

Changes that have no impact on the quality, safety and efficacy of the product are not reported, but if the NRA 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, the NRA may work to resolve the problem with the marketing authorization holder. If the NRA 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 marketing authorization holder 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.

8.3 Procedures for urgent product labelling information changes

For urgent changes to product labelling information which address safety updates and have the potential to have an impact on public health (for example, addition of a contraindication or a warning), NRAs should establish a specific mechanism to allow for the immediate or expedited approval and implementation of such changes on a case-by-case basis after previous agreement between the NRAs and marketing authorization holders.

Since product labelling safety updates invariably need to be implemented and are generally approved, NRAs in procuring countries should establish a mechanism by which urgent product labelling changes that have been approved in the country where the biotherapeutic products in question are produced and/or licensed may be implemented immediately upon receipt of the supplement from marketing authorization holders or manufacturers. Such accelerated procedures would contribute to the dissemination of the most current information to health-care providers and would help to mitigate discrepancies between the labels used in the various countries and posted on websites.

8.4 Procedures for administrative product labelling information changes

Depending on the scope of the change, administrative product labelling information changes may require approval prior to implementation. For example, changes in the proper/nonproprietary name or trade name of the biotherapeutic product require approval before implementation, while minor formatting changes do not (see section 7.4 for further details).

For an administrative product labelling information change that requires approval prior to implementation the marketing authorization holder should submit a supplement containing background information on the change and annotated and clean drafts of the product labelling information.

Administrative product labelling information changes that do not need prior approval and that have been implemented since the last approved product labelling information should be included when submitting a subsequent PAS for safety and efficacy changes or for product labelling information changes. In these cases, the product labelling information should be annotated when filing the next PAS to indicate the new changes and those administrative changes that have been implemented since the last approval.

9. Authors and acknowledgements

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Further changes were subsequently made to document WHO/BS/2017.2311 by the WHO Expert Committee on Biological Standardization.

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Appendix 1

Reporting categories and suggested review timelines

It is recommended that NRAs establish review timelines to allow marketing authorization holders or applicants to plan the implementation of changes. The review timelines are established taking into consideration the country or regional situation, the capability of the NRA, the impact of the change and the amount of data required to support the change. Consequently, the review time frames for major changes should be longer than those for moderate changes. The suggested review times in the table below are shown as examples; they are based on the experience of several NRAs and apply to situations where the NRA performs a full review or assessment of the supplement. The review time would start when the supplement has been accepted for review and found to be complete, and would end at the time when the initial assessment is shared with the marketing authorization holder by the issuance of either a notification of approval or a notification of noncompliance with a list of comments and deficiencies. In case of the latter, the marketing authorization holder may seek approval for the change by submitting an amendment to the supplement with responses to all the comments in the notification of noncompliance. The NRA should also establish timelines for the secondary review cycle following the receipt of responses from the marketing authorization holder. If minor deficiencies are identified during the initial review cycle, the NRA may communicate these to the marketing authorization holder without stopping the review clock in order to try to finalize the assessment within the established timeline (see section 8.1).

Expedited implementation procedures should be in place for dealing with product labelling information changes which address urgent safety issues (see section 8.3).

Reporting categories for post-approval changes and suggested review timelines

Quality changes		
Reporting category	**Procedure**	**Suggested review timeline**
Major quality changes	PAS	3–6 months
Moderate quality changes	PAS	1–3 months
Minor quality changes	Require notification to the NRA[a, b]	N/A
Quality changes with no impact	Do not require notification to the NRA	N/A

Table *continued*

Safety, efficacy and product labelling information changes		
Reporting category	**Procedure**	**Suggested review timeline**
Safety and efficacy changes	PAS	10 months
Product labelling information changes	PAS	5 months
Urgent product labelling information changes[c]	PAS for urgent safety restrictions	Immediate implementation on receipt of supplement by the NRA
Administrative product labelling information changes	PAS	30 days
	Do not require approval prior to implementation[d]	N/A

N/A: not applicable.

[a] Each NRA is responsible for determining the timeline for reporting the notification (for example, annually). However, NRAs should establish a mechanism to ensure that notifications are received no later than one year post-implementation. In a case where a minor quality change results from the use of a comparability protocol, the change should be notified to the NRA immediately after implementation.

[b] Minor quality changes impacting the registered details may be bundled with moderate or major quality changes, if needed.

[c] Urgent product labelling information changes are applicable only to label changes which address urgent safety updates or have the potential to have an impact on public health, with immediate implementation allowed after prior agreement between NRAs and marketing authorization holders.

[d] Administrative product labelling information changes that do not require approval prior to implementation and that have been implemented since the last approved product labelling information change should be reported by including all changes in subsequent PAS for safety and efficacy changes or product labelling information changes when updated product labelling information is included.

NRAs that procure biotherapeutic products from countries other than their own are encouraged to establish alternative accelerated timelines for changes that have previously been approved by the other NRAs. Accordingly, those NRAs should create a list of the NRA approvals they will recognize. On the basis of the regulatory pathway options provided in section 8, the following examples of accelerated timelines could be established:

- The NRA recognizes the decision of other regulatory authorities and does not perform a review of supporting data but is informed of the change. Using this approach, NRAs could allow changes to be implemented immediately after receipt of the change notification.

- The NRA performs an assessment of the decision of the NRA of the licensing country to determine if recognition of the latter NRA's decision is appropriate. Using this approach, NRAs could establish abbreviated review timelines – such as 2 months for major quality changes, 4 months for safety and efficacy changes, and immediate implementation on receipt of the change notification for moderate quality changes and product labelling information changes.
- The NRA performs a partial review and evaluation of a complete supporting data package, as originally submitted to the licensing country. Using this approach, timelines would be expected to be shorter than the timelines described in the above table.

Appendix 2

Changes to the drug substance

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information for the drug substance. The information summarized in the table below provides guidance on:

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

Marketing authorization holders should use scientific judgement, leverage competent regulatory authority guidance or contact the NRA if a change is not included in the table and has the potential to impact on product quality. Marketing authorization holders should also contact the NRA when a change is considered at the next higher reporting category because any of the conditions outlined are not fulfilled and where the supporting data are not described. NRAs should establish procedures, with appropriate timelines, on the conducting and recording of communications between themselves and marketing authorization holders.

Supporting data should be provided according to the submission format accepted by the NRA – see for example (*1*, *2*).

Additional information on data requirements to support quality changes can be found in WHO good manufacturing practices for biological products (*3*), WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (*4*) and in relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines (*5*, *6*).

Quality changes to comply with updated compendia and/or pharmacopoeias

NRAs should make a list of the recognized compendia and/or pharmacopoeias. Manufacturers are expected to comply with the current versions of compendia/pharmacopoeias, as referenced in the approved marketing authorization. Changes linked to a change in the compendial/pharmacopoeial methods or specifications for a drug substance do not need to be submitted for review if reference is made to the current edition of the compendium or pharmacopoeia, but the changes should be notified to the NRA with information on them available for inspection.

In some cases, changes introduced to comply with recognized compendia/pharmacopoeias may require approval by the NRA prior to implementation regardless of the timing of the change in relation to the date when the compendium/pharmacopoeia was updated. For example, supplement submission and approval by the NRA may be required for some changes to quality control tests performed for product release (for example, to potency tests), for changes that have an impact on any product labelling information items, and for changes that may affect the quality, safety or efficacy of the product.

Quality changes affecting lot release

While WHO recognizes that independent lot release by NRAs or national control laboratories is required for vaccines, in some countries this lot release system also applies to other types of products such as plasma-fractionated products. Where post-approval changes to the drug substance affect the lot release protocol (for example, changes to test procedures, reference standards or laboratory sites) or sample testing requirements for lot release, the marketing authorization holder should inform the institution responsible for reviewing the release of product lots. These procedures apply to changes that have been authorized by the NRA in the case of major and moderate quality changes and to changes that have been implemented in the case of minor quality changes. For example, the qualification of a new lot of reference standard against the approved reference standard may be considered a minor quality change if the qualification of a new standard is performed in accordance with an approved protocol and specification. Nevertheless, these changes must be reported to the NRA or national control laboratory as appropriate.

Manufacture

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

Conditions

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

Supporting data

1. Evidence of GMP compliance of the facility.
2. Name, address and responsibilities (for example, fermentation, purification) of the proposed facility.
3. Summary of the process validation studies and results.

Table *continued*

4. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may be required if quality data alone are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality comparability findings, the nature and level of the knowledge of the product, existing relevant nonclinical and clinical data, and aspects of their use.
5. Justification for the classification of any manufacturing process and/or control changes as moderate or minor.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified and agreed by the NRA.
7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, use of smaller-scale batches and/or use of fewer than three batches of drug substance for stability testing may be acceptable where justified (*6*).
8. Updated post-approval stability protocol.
9. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If no revisions, the manufacturer should state that no changes were made to the change-over procedures.
10. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.

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

Conditions

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

Supporting data

1. Qualification of the cell bank according to guidelines considered acceptable by the NRA.
2. Information on the characterization and testing of the MCB/WCB, and cells from the end-of-production passage or post-production passage.
3. Justification of the change to the cell bank qualification protocol.
4. Updated cell bank qualification protocol.

Table *continued*

5. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality-comparability findings, the nature and level of knowledge of the product, existing relevant nonclinical and clinical data, and aspects of its use.
6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the drug substance derived from the new cell bank. Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified (*6*).
8. Updated post-approval stability protocol.
9. Evidence that the new company/facility is GMP-compliant.
10. Supporting nonclinical and clinical data or a request for a waiver of in vivo studies with justification.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
6. Change to the fermentation or cell culture process:			
a. A critical change (a change with high potential to have an impact on the quality of the drug substance or drug product; for example, incorporation of disposable bioreactor technology)	None	1–7, 9, 11	Major
b. A change with moderate potential to have an impact on the quality of the drug substance or drug product (for example, extension of the in vitro cell age beyond validated parameters)	1, 3	1–6, 8, 10	Moderate
c. A noncritical change with minimal potential to have an impact on the quality of the drug substance or drug product, such as: • a change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, intermediate storage conditions, sensitivity of detection of adventitious agents or production scale; • duplication of a fermentation train; or • addition of similar/comparable bioreactors	1–5, 7–10	1, 2, 4, 8	Minor

Table *continued*

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

[1] HPLC = high-performance liquid chromatography.

Table *continued*

Conditions

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

Supporting data

1. Justification for the classification of the change(s) as critical, moderate or noncritical in terms of its impact on the quality of the drug substance.
2. Flow diagram (including process and in-process controls) of the proposed manufacturing process(es) and a brief narrative description of the proposed manufacturing process(es).
3. If the change results in an increase in the number of population doublings or subcultivations, information on the characterization and testing of the post-production cell bank for recombinant product or of the drug substance for non-recombinant product.
4. For drug substance obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, use and previous acceptance of the material) (*7*).
5. Process validation results.

Table *continued*

6. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality–comparability findings, the nature and level of knowledge of the product, existing relevant nonclinical and clinical data, and aspects of its use.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and should be reported by the marketing authorization holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and.
9. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months and one batch of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug substance for stability testing may be acceptable where justified (*6*).

Table *continued*

10. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes with at least one commercial-scale drug substance batch produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug substance under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified.
11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the drug product manufactured using the post-change drug substance into the stability programme.
12. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) (*7*).
13. Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times, resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the drug substance.
14. Demonstration that the new or revised holding step has no negative impact on the quality of the drug substance (data from one commercial-scale or scientifically justified representative drug substance batch should be provided).

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

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
b, Introduction of new equipment with the same operating principles but different product contact material	None	1, 3–5	Moderate
	3, 4	1, 4, 5	Minor
c. Introduction of new equipment with different operating principles but the same product contact material	None	1–3, 5	Moderate
	4	1, 2, 5	Minor
d. Replacement of product-contact equipment with equivalent equipment	None	3	Minor
e. Change of product-contact equipment from dedicated to shared	1, 2	1, 6	Minor
f. Relocation of major equipment to another room in the same facility/suite/ premises	2, 4, 5	None	Minor

Conditions

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

Supporting data

1. Information on the in-process control testing.
2. Process validation study reports.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the drug substance produced with the approved and proposed product contact equipment/material. Batch data on the next two full-production batches should be made available on request and reported by the marketing authorization holder if outside specification (with proposed action).

Table *continued*

4. Information on leachables and extractables.
5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
6. Information describing the change-over procedures for the shared product-contact equipment.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
12. Change in specification for the materials, involving the following:			
a. Narrowing of the approved specification limits for starting materials/ intermediates	1–4	1–3, 5	Minor
b. Widening of the approved specification limits for starting materials/ intermediates	None	1–3, 5, 7	Moderate
	3–7	3–6	Minor
13. Change in supplier of raw materials of biological origin (for example, fetal calf serum, insulin, trypsin)	None	4, 6, 9, 10	Moderate
	8	4, 6	Minor
14. Change in source of raw materials of biological origin (for example, bovine trypsin to porcine trypsin)	None	4, 7, 9, 10	Moderate
	8	4, 7	Minor

Conditions

1. The change in specification for the materials is within the approved limits.
2. The grade of the materials is the same or is of higher quality, where appropriate.
3. There is no change in the drug substance specification outside the approved limits.
4. There is no change in the impurity profile of the drug substance outside the approved limits.
5. The change has no significant effect on the overall quality of the drug substance and/or drug product and there are no changes to the cell banks.
6. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.

Table *continued*

7. The test does not concern a critical attribute (for example, content, impurity, any critical physical characteristics or microbial purity). 8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).	
Supporting data	
1. Revised information on the quality and controls of the materials (for example, raw materials, starting materials, solvents, reagents and catalysts) used in the manufacture of the post-change drug substance. 2. Updated drug substance specification, if changed. 3. Copies or summaries of analytical procedures if new analytical procedures are used. 4. For drug substance obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/ transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, use and previous acceptance of the material) (*7*). 5. Comparative table or description, where applicable, of pre-change and post-change in-process tests/limits. 6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and reported by the marketing authorization holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified. 7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified. 8. Justification/risk assessment showing that the attribute is non-significant. 9. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) (*7*). 10. Information demonstrating suitability of the auxiliary materials/reagents of both sources through the comparability of the drug substance.	

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
15. Change to in-process tests and/or acceptance criteria applied during manufacture of the drug substance, involving the following:			
a. Narrowing of approved in-process limits	1, 3, 6, 7	1, 4	Minor
b. Addition of new in-process test and limits	2, 3, 6	1–5, 8	Minor
c. Deletion of a non-significant in-process test	1–4, 6	1, 4, 7	Minor
d. Widening of the approved in-process limits	None	1–4, 6, 8	Moderate
	1–4	1, 4, 5, 8	Minor
e. Deletion of an in-process test which may have a significant effect on the overall quality of the drug substance	None	1, 4, 6, 8	Moderate
f. Addition or replacement of an in-process test as a result of a safety or quality issue	None	1–4, 6, 8	Moderate
16. Change in the in-process controls testing site *Note: Transfer of in-process control testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and is reviewed during inspections.*	1–3, 5, 6	9	Minor

Conditions

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

Table *continued*

Supporting data

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

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

Table *continued*

Conditions

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

Supporting data

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

Control of the drug substance

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

Conditions

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

Supporting data

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

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

Conditions

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

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
21. Changes in the control strategy of the drug substance, involving the following:			
a. Change from end-product testing to upstream controls for some test(s) (for example, real-time release testing, process analytical technology)	None	1–3, 5	Major
b. Addition of a new critical quality attribute in the control strategy	None	1–5	Moderate
c. Deletion of a critical quality attribute from the control strategy	None	1, 5	Moderate
Conditions None			
Supporting data 1. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance. 2. Updated copy of the proposed drug substance specifications. 3. Copies or summaries of analytical procedures if new analytical procedures are used. 4. Copies or summaries of validation reports if new analytical procedures are used to monitor the new CQA at release. 5. Justification and supporting data for each proposed change to the control strategy.			

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

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
e. Change from an in-house analytical procedure to a recognized compendial/ pharmacopoeial analytical procedure	None	1–5	Moderate
	2, 6	1–3	Minor
f. Widening of an approved acceptance criterion	None	1, 5, 6	Moderate
g. Narrowing of an approved acceptance criterion	1, 4, 7	1	Minor

Conditions

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

Supporting data

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

Reference standards or materials

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

Conditions

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

Table *continued*

Supporting data

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

Drug substance container closure system

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

Conditions

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (including results of transportation or compatibility studies, if appropriate).

Supporting data

1. Updated dossier sections describing information on the proposed container closure system (for example, description, composition, materials of construction of primary packaging components, specifications).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing) and compliance with pharmacopoeial standards, if applicable.
3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (for example, results of transportation or compatibility studies, and extractable/leachable studies).

Table *continued*

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

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

Conditions

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

Supporting data

1. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
2. Information on the proposed container closure system (for example, description, materials of construction of primary packaging components, specifications).

Table *continued*

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

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

Conditions

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

Table *continued*

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

Supporting data

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

Stability

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

Conditions

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

Supporting data

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

Table *continued*

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
33. Change in the post-approval stability protocol of the drug substance, involving the following:			
a. Substantial change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure or change in storage temperature	None	1–5	Moderate
	1	1, 2, 4, 5	Minor
b. Addition of test(s) into the post-approval stability protocol	2	1, 2, 4, 5	Minor
c. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 5	Minor

Conditions

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

Table *continued*

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
34. Change in the storage conditions for the drug substance, involving the following:			
a. Addition or change to storage conditions for the drug substance (for example, widening or narrowing of a temperature criterion)	None	1–4	Moderate
	1, 2	1–3	Minor
b. Addition of a cautionary statement	None	1, 3, 4	Moderate
	1	1, 3, 4	Minor
c. Deletion of a cautionary statement	None	1, 3, 5	Minor

Conditions

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

Supporting data

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

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Appendix 3

Changes to the drug product

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information of the drug product. The information summarized in the drug product table provides guidance on:

- the **conditions to be fulfilled** in order for a given change to be classified as major, moderate or minor (if any of the conditions outlined for a given change are not fulfilled, the change is automatically considered to be at the next higher reporting category – for example, if any of the conditions recommended for a moderate quality change are not fulfilled, the change is considered to be a major quality change);
- the **supporting data** for a given change, either to be submitted to the NRA and/or maintained by the marketing authorization holder (if any of the supporting data outlined for a given change are not provided, are different or are not considered applicable, adequate scientific justification should be provided); and
- the **reporting category** (major, moderate or minor quality change).

Marketing authorization holders should use scientific judgement, leverage competent regulatory authority guidance or contact the NRA if a change is not included in the table and has the potential to impact on product quality. Marketing authorization holders should also contact the NRA when a change is considered at the next higher reporting category because any of the conditions outlined are not fulfilled and where the supporting data are not described. NRAs should establish procedures, with appropriate timelines, on the conducting and recording of communications between themselves and marketing authorization holders.

Supporting data should be provided according to the submission format accepted by the NRA – see for example (*1*, *2*).

Additional information on data requirements to support quality changes can be found in WHO good manufacturing practices for biological products (*3*), WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (4) and in relevant ICH guidelines (*5*, *6*).

Quality changes to comply with updated compendia and/or pharmacopoeias

NRAs should make a list of the recognized compendia and/or pharmacopoeias. Manufacturers are expected to comply with the current version of compendia/pharmacopoeias as referenced in the approved marketing authorization. Changes in the compendial/pharmacopoeial methods or specifications for a drug product do not need to be submitted for review if reference is made to the current edition of the compendium or pharmacopoeia, but the changes should be notified to the NRA, with information on them available for inspection.

In some cases, changes made to comply with recognized compendia/pharmacopoeias may require approval by the NRA prior to implementation regardless of the timing of the change in relation to the date when the compendium/pharmacopoeia was updated. For example, supplement submission and approval by the NRA may be required for some changes to quality control tests performed for product release (for example, to potency tests), for changes that have an impact on any product labelling information item, and for changes that may affect the quality, safety or efficacy of the product.

Quality changes affecting lot release

While WHO recognizes that independent lot release by NRAs or national control laboratories is required for vaccines, in some countries this lot release system also applies to other types of products, such as plasma-fractionated products. Where post-approval changes to the final product affect the lot release protocol (for example, changes to test procedures, reference standards or laboratory sites) or sample testing requirements for lot release, the marketing authorization holder should inform the institution responsible for reviewing the release of product lots. These procedures apply to changes that have been authorized by the NRA in the case of major and moderate quality changes and to changes that have been implemented in the case of minor quality changes. For example, the qualification of a new lot of reference standard against the approved reference standard may be considered a minor quality change if the qualification of a new standard is performed in accordance with an approved protocol and specification. Nevertheless, these changes must be reported to the NRA or national control laboratory as appropriate.

Description and composition of the drug product

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

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

Conditions

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

Table *continued*

Supporting data

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

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
36. Change to the diluent, involving the following:			
a. Change in manufacturing process	None	1–5	Moderate
	1, 3	1–4	Minor
b. Replacement of or addition to the source of a diluent	None	1–6	Moderate
	1–3	1–3	Minor
c. Change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5	Minor
d. Addition of a diluent filling line	1, 2, 4	1, 3, 5	Minor
e. Deletion of a diluent	None	None	Minor

Conditions

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

Supporting data

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

Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
37. Change in the approved design space, involving the following:			
a. Establishment of a new design space	None	1	Major
b. Expansion of the approved design space	None	1	Major
c. Reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space)	1	1	Minor
Conditions			
1. The reduction in design space is not necessitated by recurring problems that have arisen during manufacture.			
Supporting data			
1. Pharmaceutical development data to support the establishment or changes to the design space.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
38. Change involving a drug product manufacturer/ manufacturing facility, involving the following:			
a. Replacement or addition of a manufacturing facility for the drug product (including formulation/filling and primary packaging)	None	1–7	Major
	1–5	1–3, 5–8	Moderate
b. Conversion of a drug product manufacturing facility from single-product to multi-product facility	None	9, 10	Moderate
c. Replacement or addition of a secondary packaging facility, including secondary functional packaging (that is, assembly) facility	2, 3	1–3	Minor

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
d. Deletion of a drug product manufacturing facility or packaging site	6, 7	None	Minor

Conditions

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

Supporting data

1. Name, address and responsibilities (for example, formulation, filling, primary/secondary packaging) of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP-compliant.
3. Confirmation that the description of the manufacturing process of the drug product has not changed (other than the change in facility), or submission of supporting data on the revised description of the manufacturing process if the process has changed.
4. Comparative description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
5. Summary of the process validation studies and results.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.

Table *continued*

7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (*6*).
8. Rationale for considering the proposed formulation/filling facility as equivalent.
9. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If there are no revisions, the manufacturer should state that no changes were made to the change-over procedures.
10. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.

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

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
d. Addition of a new step (for example, filtration)	3	1–6	Moderate
e. Product-contact equipment change from dedicated to shared (for example, formulation tank, filter housing, filling line and head, lyophilizer)	6, 7	2, 9	Minor

Conditions

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

Supporting data

1. Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed drug product.
2. Information on the in-process control testing, as applicable.
3. Process validation results (for example, media fills), as appropriate.
4. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.

Table *continued*

5. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (6).
6. Information on leachables and extractables, as applicable.
7. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
8. The rationale for regarding the equipment as similar/comparable, as applicable.
9. Information describing the change-over procedures for the shared product-contact equipment.

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

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
f. Addition or replacement of an in-process test as a result of a safety or quality issue	None	1–4, 6, 8	Moderate
41. Change in in-process controls testing site *Note: Transfer of in-process control testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections.*	1–3, 5, 6	9	Minor

Conditions

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

Supporting data

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

Table *continued*

6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product (certificates of analysis should be provided). Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable.
7. Justification/risk assessment showing that the attribute is non-significant.
8. Justification for the new in-process test and limits.
9. Evidence that the new company/facility is GMP-compliant.

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

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or improves precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient.

Table *continued*

4. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements).
5. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
6. The analytical procedure remains the same, or changes in the test procedure are minor.
7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, change in total impurity limits).
8. An alternative test analytical procedure is already authorized for the specification attribute/test and this procedure has not been added through a minor change submission.

Supporting data

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

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

Conditions

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

Table *continued*

Supporting data

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

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

Table *continued*

49. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient)	None 1, 5, 6	2, 3, 5–7 3	Moderate Minor
50. Change in excipient testing site *Note: Transfer of testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change and is reviewed during inspections.*	1	10	Minor

Conditions

1. There is no change to the specification of the excipient or drug product outside the approved limits.
2. The change does not concern a human plasma-derived excipient.
3. The human plasma-derived excipient from the new supplier is an approved medicinal product and no manufacturing changes were made by the supplier of the new excipient since its last approval in the country/jurisdiction of the NRA.
4. The excipient does not influence the structure/conformation of the active ingredient.
5. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material (7).
6. Any new excipient does not require the assessment of viral safety data.

Supporting data

1. Declaration from the manufacturer of the excipient that the excipient is entirely of vegetable or synthetic origin.
2. Details of the source of the excipient (for example, animal species, country of origin) and the steps undertaken during processing to minimize the risk of TSE exposure (*7*).
3. Information demonstrating comparability in terms of physicochemical properties, and the impurity profile of the proposed excipient compared to the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed excipient.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three commercial-scale batches of the proposed excipient.

Table *continued*

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

Control of the drug product

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

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
b. Transfer of the quality control testing activities for a pharmacopoeial assay to a new company not approved in the current marketing authorization or licence	None	1, 2	Moderate
	1	1, 2	Minor

Conditions

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

Supporting data

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

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

Table *continued*

Conditions

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

Supporting data

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

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

Conditions

None

Supporting data

1. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed product.

Table *continued*

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

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

Conditions

1. There is no change to the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability.
2. The additional test is not intended to monitor new impurity species.
3. The method of analysis is the same (for example, a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
4. The modified analytical procedure maintains or improves the performance parameters of the method.
5. The change does not concern potency-testing.

Table *continued*

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

Supporting data

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

Reference standards

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
56. Replacement of a primary reference standard	None	1, 2	Moderate
57. Change of the reference standards from a pharmacopoeial or international standard to in-house (no relationship with international standard)	None	1, 2	Moderate

Table *continued*

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

Conditions

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

Supporting data

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

Drug product container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
62. Modification of a primary container closure system (for example, new coating, adhesive, stopper, type of glass) *Note: The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation (see **change 35d**).*	None	1–7	Moderate
	4	3, 7	Minor
	1–3	3	Minor
63. Change from a reusable container to a disposable container with no changes in product contact material (for example, change from reusable pen to disposable pen)	None	1, 3, 6	Moderate
64. Deletion of a container closure system *Note: The NRA should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate.*	None	1	Minor

Conditions

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

Table *continued*

Supporting data

1. Revised product labelling information, as appropriate.
2. For sterilized products, process validation results, unless otherwise justified.
3. Update dossier containing information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary packaging components).
4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and biological reactivity tests.
5. Summary of release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
6. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced (unless otherwise justified) with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (for example, it can be proven that the relevant effect, if present, can already be observed within 3 months). Comparative pre-change test results do not need to be generated concurrently; relevant historical results for batches on the stability programme are acceptable. Additionally, the manufacturer should commit to undertake real-time stability studies to confirm the full shelf-life/hold-time of the drug product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than three batches of drug product for stability testing may be acceptable where justified (*6*).
7. Information demonstrating the suitability of the proposed container/closure system with respect to its relevant properties (for example, results from last media fills; results of interaction studies demonstrating preservation of protein integrity and maintenance of sterility for sterile products; maintenance of sterility in multidose containers; user testing).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
65. Change in the supplier for a primary container closure component, involving the following:			
a. Replacement or addition of a supplier *Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data, such as is shown for **change 62** on modification of a primary container closure system.*	1, 2	1, 2	Minor
b. Deletion of a supplier	None	None	Minor

Conditions

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

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
66. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving the following:			
a. Deletion of a test	1, 2	1, 2	Minor
b. Addition of a test	3	1, 2	Minor
c. Replacement of an analytical procedure	6, 7	1–3	Minor
d. Minor changes to an analytical procedure	4–7	1–3	Minor

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
e. Widening of an acceptance criterion	None	1, 2	Moderate
f. Narrowing of an acceptance criterion	8	1	Minor

Conditions

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

Supporting data

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

Stability

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

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
b. Reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1–5	Moderate
Conditions None			
Supporting data 1. Updated product labelling information, as appropriate. 2. Proposed storage conditions and shelf-life, as appropriate. 3. Updated post-approval stability protocol. 4. Justification of the change to the post-approval stability protocol or stability commitment. 5. Results of stability testing under real-time/real-temperature conditions covering the proposed shelf-life generated on at least three commercial-scale batches unless otherwise justified.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
68. Change in the post-approval stability protocol of the drug product, involving the following:			
a. Substantial change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure, or change in storage temperature	None	1–5	Moderate
b. Addition of test(s) into the post-approval stability protocol	1	1, 2, 4, 5	Minor
c. Deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 5	Minor
d. Replacement of sterility testing by the container/ closure system integrity testing	None 3	1, 2, 4, 5 4, 5	Moderate Minor

Table *continued*

Conditions

1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities.
2. Deletion of time point(s) is done according to relevant guidelines (for example, (*6*)).
3. The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application related to the drug product.

Supporting data

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

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

Table *continued*

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

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Annex 4

Technical Specifications Series (TSS) for WHO Prequalification – Diagnostic Assessment

Human immunodeficiency virus (HIV) rapid diagnostic tests for professional use and/or self-testing

TSS–1

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The draft technical specifications document was then posted on the WHO Prequalification website for public consultation on 15 September 2016. Various stakeholders, including manufacturers submitting to WHO prequalification of in vitro diagnostic medical devices (IVDs), IVD manufacturing industry associations, various national and international regulatory bodies, and IVD standards organizations, were informed of the consultation in order to solicit feedback. A two-month response period was provided.

Second-round public comments were then received from the following: Dr P Akolkar, Center for Biologics Evaluation and Research, United States Food and Drug Administration, MD, USA; Ms S Best, National Serology Reference Laboratory, Victoria, Australia; Dr J Duncan, London, the United Kingdom; Epicentre and Médecins sans Frontières International Office, Paris, France; Dr C Kosack, Dr A Page and Ms E Tran, Geneva, Switzerland; Dr R Galli, bioLytical™ Laboratories Inc., Vancouver, Canada; Ms D Lepine, Medical Devices Bureau, Health Canada, Ottawa, Canada; Dr M Nübling, WHO, Geneva, Switzerland; OraSure Technologies Inc., PA, the USA; Dr H Scheiblauer, Paul-Ehrlich-Institut, Langen, Germany; UNITAID/PSI HIV Self-Testing Africa (STAR) project

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Following incorporation of the second-round public comments, a revised draft was published on the WHO Biologicals website for a final round of public consultation between 18 June and 18 September 2017. The comments received were incorporated to produce the document WHO/BS/2017.2305. The document was adopted by the WHO Expert Committee on Biological Standardization as a WHO written standard on 20 October 2017.

Abbreviations

Ag	antigen
CE	Conformité Européenne (European Conformity)
CRF	circulating recombinant form
HIV	human immunodeficiency virus
IVD	in vitro diagnostic medical device
RDT	rapid diagnostic test

A Introduction

The purpose of this document is to provide technical guidance to in vitro diagnostic medical device (IVD) manufacturers that intend to seek WHO prequalification of rapid diagnostic tests (RDTs) for the detection of human immunodeficiency virus (HIV).

The minimum performance requirements for WHO prequalification are summarized in this document, and apply equally to RDTs intended solely for HIV detection and to those tests where HIV detection is one component of a multi-detection assay (for example, an HIV/syphilis dual-detection RDT). This document applies to RDTs intended to be used as an aid to diagnosis of HIV infection. The current version of this document does not address IVDs that discriminate between the detection of HIV-1 and HIV-2 infection, IVDs intended as confirmatory tests, or the requirements for accompanying quality control materials.

For the purpose of this document, the use of certain verbal forms is as follows:

- "shall" indicates that the manufacturer is required to comply with the technical specifications;

- "should" indicates that the manufacturer is recommended to comply with the technical specifications but it is not a requirement; and
- "may" indicates that the technical specifications are a suggestion but not a requirement.

A documented justification and rationale shall be provided by the manufacturer when the WHO prequalification submission does not comply with the required technical specifications outlined in this document.

Minimum performance requirements for WHO prequalification are summarized in this document– and where possible, WHO performance requirements are aligned with published guidance, standards and/or regulatory documents. Although references to source documents are provided, it should be noted that WHO prequalification in some cases has additional requirements.

For WHO prequalification purposes, manufacturers shall provide evidence in support of the clinical performance of an IVD to demonstrate that reasonable steps have been taken to ensure that a properly manufactured IVD, when correctly operated by the intended user, will detect the target analyte and fulfil its indications for use.

The WHO prequalification requirements summarized in this document do not extend to the demonstration of clinical utility – that is, the effectiveness and/or benefits of an IVD, relative to and/or in combination with other measures, as a tool to inform clinical intervention in a given population or health-care setting. To demonstrate clinical utility, a separate set of studies is required. Clinical utility studies usually inform programmatic strategy and are thus the responsibility of programme managers, ministries of health and other related bodies in individual WHO Member States. Such studies do not fall under the scope of WHO prequalification.

B How to apply these specifications

For WHO prequalification purposes, an IVD intended for professional use only (by a laboratory professional, health-care worker or trained lay provider) shall be supported by studies outlined in Parts 1 and 2 of this document.

An IVD intended both for professional use and for self-testing shall be supported by the studies outlined in Parts 1 and 2 of this document. In addition, the claim for self-testing shall be supported by studies that qualify the usability of the IVD among a broad range of self-testing users, as outlined in Part 3.

An IVD intended for self-testing only shall be supported by studies outlined in Parts 1, 2 and 3.

For an IVD with an intended use that has been amended to include self-testing, and for which performance in professional use is already established,

and Parts 1 and 2 of this document have already been satisfied, the additional claim for self-testing shall be supported by studies outlined in Part 3.

These requirements are summarized below in Table 1.

Table 1
Summary of requirements for submission for WHO prequalification based on the intended use of the IVD

Intended use	Parts of the TSS to be fulfilled
Professional use	Parts 1 and 2
Self-testing	Parts 1, 2 and 3
Prequalified professional-use IVD with additional claim for self-testing	Part 3, with the provision that any adaptations made do not impact the established safety and performance

C Other guidance documents

This document should be read in conjunction with other relevant WHO guidance documentation, including:

- Technical Guidance Series for WHO Prequalification – Diagnostic Assessment
- Sample Product Dossiers for WHO Prequalification – Diagnostic Assessment
- Instructions for Compilation of a Product Dossier (WHO document PQDx_018).

These documents are available at: http://www.who.int/diagnostics_laboratory/evaluations/en/

D Performance principles for WHO prequalification

D.1 Intended use

An IVD intended for WHO prequalification shall be accompanied by a sufficiently detailed intended use statement. This should allow for an understanding to be gained of at least the following:

- the function of the IVD (for example, to detect antibodies to HIV-1, HIV-2 and/or HIV p24 antigen (Ag), etc.) and whether it is qualitative, semi-quantitative or quantitative;

- the testing population for which the functions are intended (for example, detection of susceptible individuals) and the intended operational setting (for example, for use in near-patient testing); and
- clinical indication (for example, aid to diagnosis of HIV infection).

D.2 Diversity of specimen types, users and testing environments and impact on required studies

For WHO prequalification submission, clinical performance studies should be conducted using the specimen types that are most likely to be used in resource-limited WHO Member States (for example, capillary whole blood and oral fluid) and claimed in the instructions for use. If this is not possible, substantial data shall be presented to show the equivalence between specimen types used in performance studies.

Prequalified RDTs in low- and middle-income countries are likely to be used by laboratory professionals[1] and at point-of-care by health-care workers, trained lay providers[2] or by individuals who self-test. Depending on the intended use of an RDT, performance studies shall be designed to take into account not only the diversity of knowledge and skills across the population of RDT users, but also the likely operational settings in which testing will occur. For example, studies that comprise the testing of left-over/repository specimens by research and development staff at a manufacturer's facility shall not, on their own, be considered sufficient to meet many of the performance requirements summarized in this document.

D.3 Applicability of supporting evidence to an IVD under review

Performance studies shall be undertaken using the specific locked-down version of the IVD intended to be submitted for WHO prequalification. Where this is not possible, a justification shall be provided and additional supporting evidence may also be required. This may occur in the case of minor variations in design where no negative impact on performance has been demonstrated.

Specific information is provided in Parts 1 and 2 of this document for the numbers of lots required for particular studies. Each lot should comprise different batches of critical components. It is a manufacturer's responsibility to ensure (via risk analysis of their IVD) that the minimum number of lots chosen

[1] Medical technologists, medical laboratory technicians or similar, who have received a formal professional or paraprofessional certificate or tertiary education degree.

[2] Any person who performs functions related to health-care delivery and has been trained to deliver specific services but has received no formal professional or paraprofessional certification or tertiary education degree.

for estimating performance characteristics takes into account the variability in performance likely to arise from the diversity of key components and their formulation.

The true HIV status of a specimen shall be determined using a suitable reference method, for which justification shall be provided. Estimation (and reporting) of IVD performance shall include the rate of invalid test results. For certain analytical studies it may be acceptable to use contrived specimens (for example, normal human specimens that have been spiked with HIV antibodies). Although all reasonable attempts should be made to use natural specimens, justification should be provided where contrived specimens are used in the submitted studies. Clinical studies should be based on testing in natural specimens only.

For IVDs that include a claim for detection of multiple analytes, evidence of performance shall be provided for each claimed analyte. It should be noted that, depending on the design of an IVD, evidence generated in a similar, related product will usually not be considered sufficient by WHO to support performance claims in an IVD submitted for prequalification.

> *Example: an IVD designed to detect HIV antibodies only, and the same IVD designed for the dual detection of HIV and syphilis. It is unlikely that performance evidence presented for the HIV-only IVD would be acceptable for supporting performance claims for the dual-detection IVD.*

For an IVD with an intended use that has been expanded to include self-testing, changes are usually required to improve the usability of the IVD for this new testing population. Such changes may include the modification of:

- the instructions for use (for example, simplification of instructions to reflect new intended users);
- buffer vials;
- collection procedures;
- reading times, etc.

It is a manufacturer's responsibility to verify through testing (as summarized in Parts 1 and 2 of this document) that any changes made do not have an adverse impact on critical safety and performance characteristics of an IVD. Usability studies are undertaken to optimize the presentation of an IVD and the understanding of self-testing users. The minimum reporting requirements summarized in Part 3 of this document are not intended to be an exhaustive list or to indicate a particular order in which studies should be undertaken.

E Table of Requirements

Part 1	Establishing analytical performance characteristics
1.1	**Specimen type**
1.1.1	Demonstration of equivalence between specimen types
1.1.2	Demonstration of equivalence of claimed anticoagulants
1.2	**Specimen collection, storage and transport**
1.2.1	Specimen stability
1.3	**Precision of measurement**
1.3.1	Repeatability, reproducibility
1.4	**Performance panels**
1.4.1	Subtype panels
1.4.2	Mixed titre panels
1.5	**Validation of reading times**
1.5.1	Validation of reading times
1.6	**Analytical sensitivity**
1.6.1	Seroconversion
1.6.2	Limit of detection for HIV-1 p24 Ag, where appropriate
1.7	**Prozone/high-dose hook effect**
1.7.1	Prozone/high-dose hook effect
1.8	**Analytical specificity**
1.8.1	Potentially interfering substances
1.8.1.1	Endogenous
1.8.1.2	Exogenous
1.8.2	Cross-reactivity
1.9	**Metrological traceability of control material values**
1.9.1	Metrological traceability of control material values
1.10	**Stability**
1.10.1	Shelf-life (including transport stability)
1.10.2	In-use stability
1.11	**Flex studies**
1.11.1	Flex studies

Table *continued*

Part 2	**Establishing clinical performance characteristics (professional use and/or self-testing)**
2.1	**Diagnostic sensitivity and specificity**
2.1.1	Diagnostic sensitivity
2.1.2	Diagnostic specificity
Part 3	**Qualification of usability (self-testing)**
3.1	**Qualification of usability (self-testing)**
3.1.1	Labelling comprehension study
3.1.2	Results interpretation study
3.1.3	Observed untrained user study

Part 1 Establishing analytical performance characteristics

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.1 Specimen type			
1.1.1 Demonstration of equivalence between specimen types	For each claimed specimen type, testing in at least: • 25 HIV-positive specimens • 25 HIV-negative specimens.	1. The relationship between IVD performance in claimed specimen types and reference materials used for analytical studies shall be established. The design of subsequent studies shall then take that relationship into account. 2. If there is no equivalence between claimed specimen types then the impact that this will have on each subsequent performance claim shall be fully understood and described. Where a significant difference in performance exists between specimen types, equivalence may need to be investigated as part of a larger clinical study (see Part 2 below). *Example: an IVD intended for testing whole blood for which seroconversion sensitivity is estimated using panels of serum/plasma specimens.* • *The relationship between seroconversion sensitivity in serum/plasma to that of the same characteristic in whole blood shall be understood.* • *This might be achieved by comparing titres between end-point dilution series of matched specimen types (whole blood versus serum/plasma) from a set of positive patients.*	Technical Guidance Series for WHO Prequalification – Diagnostic Assessment (*1*) European Commission (*2*)
1.1.2 Demonstration of equivalence of claimed anticoagulants	At least 25 HIV-positive and 25 HIV-negative specimens for each claimed anticoagulant. The equivalence of specimen types shall be determined for all claimed analytes (for example, HIV-1 antibody, HIV-2 antibody, p24 Ag, as appropriate) (see Note 3).		

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
		3. In some cases it may be acceptable to use diluted or spiked specimens. This approach is acceptable in early development work, but all reasonable attempts should be made to use natural specimens. Justification should be provided if diluted or spiked specimens are used in the submitted studies. 4. Positive specimens (undiluted) shall be chosen so that the majority of them are near the IVD cut-off. 5. Paired specimens should be used (for example, if claiming equivalence of four anticoagulants then each subject should provide four samples – one in each anticoagulant).	
1.2 Specimen collection, storage and transport			
1.2.1 Specimen stability	Real-time studies taking into account: • storage conditions (duration at different temperatures, temperature limits, freeze/thaw cycles); • transport conditions, where applicable; • intended use (see Note 1); • specimen collection and/or transfer devices intended to be used with the IVD.	1. Evidence shall be provided which validates the maximum allowable time between specimen collection and its addition to the IVD in the setting where testing takes place.	Technical Guidance Series for WHO Prequalification – Diagnostic Assessment (*3*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.3 Precision of measurement			
1.3.1 Repeatability, reproducibility	Both repeatability (within-condition – see Note 1) and reproducibility (between-condition – see Note 1) shall be estimated using panels of at least: • 1 negative specimen; • 1 low-reactivity positive specimen (near assay cut-off); • 1 medium-reactivity positive specimen. Each panel member shall be tested: • in 5 replicates; • using 3 different lots; • over 5 days (not necessarily consecutive) with one run per day (alternating morning/afternoon); • at each of 3 different testing sites.	1. For example, within- or between-run, -lot, -day, -site, etc. 2. Precision shall be determined for each pathogen and/or analyte for which detection is claimed (for example, HIV-1 antibody, HIV-2 antibody, HIV-1 p24 Ag, as appropriate). 3. The testing panel should be composed of natural (that is, undiluted) specimens. Where this is not feasible, the stock specimens that are to be diluted should represent a range of stages of infection (antibody maturation) in order to take into account the limitations of mimicking low IVD reactivity with a high-avidity specimen. 4. IVDs which include whole blood as a specimen type shall include evidence of precision in (at a minimum) spiked whole blood specimens (negative whole blood spiked with highly reactive plasma/serum specimens to produce an appropriate range of reactivities in the IVD). 5. Where possible, the testing panel should be the same for all operators, lots and sites. 6. Lots shall comprise different batches of critical components.	CLSI EP05-A3 (*4*) ISO 13612:2002 (*5*) CLSI EP12-A2 (*6*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
	The effect of operator-to-operator variation on IVD performance should be included as part of the precision studies (see also Note 8). Testing should be done: • by personnel representative of intended users; • unassisted; • using **only** those materials provided with the IVD (for example, instructions for use, labels and other instructional materials).	7. Results shall be statistically analyzed to identify and isolate the sources and extent of any variance. In addition, the percentage of correctly identified, incorrectly identified and invalid results shall be tabulated for each specimen and be separately stratified according to site, lot, etc. This type of analysis is especially important for rapid tests that may not have any numerical values. 8. The effect of operator-to-operator variation on IVD performance may also be considered as a human factor when designing robustness (flex) studies (see section 1.11.1 below) and may be addressed as part of clinical studies in representative populations (see Part 2). 9. Users should be selected based on a pre-determined and contextually appropriate level of education, literacy and auxiliary skills that will challenge the usability of the IVD and reflect the diversity of intended users and operational settings.	
1.4 Performance panels			
1.4.1 Subtype panels	Testing of WHO International Reference Preparations and/or commercial HIV subtype panels shall include:	1. Testing should be performed using more than 1 lot of the final design (locked-down). 2. All confirmed subtype-positive specimens shall be detected by the IVD.	Health Products and Food Branch, Health Canada (*7*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
	• all HIV-1 subtypes (for example, A, B, C, D, G, etc.), HIV-2, HIV-1 group O, and common circulating recombinant forms (CRFs); • at least 10 each of the most common subtypes (Subtype C, Subtype A, Subtype B, CRF02_AG, CRF01_AE, CRF07_BC and Subtype G); • at least 3 less-common subtypes (other CRFs and unique recombinant forms.	3. All reasonable attempts shall be made to test rare subtypes. 4. For IVDs that include a claim for detection of HIV Ag, appropriate specimens for the same subtypes shall also be included in the testing panel. The use of panels of virus-like-particles (VLPs) or viral cultures may be considered acceptable – however their use in place of characterized specimens shall be justified.	
1.4.2 Mixed titre panels	Testing of a panel of specimens with a range of analyte concentrations (for example, antibody "mixed-titre" panel).		
1.5 Validation of reading times			
1.5.1 Validation of reading times	For IVDs for which a reading interval is specified (that is, time when result can first be read; time beyond which result should not be read), validation of critical time points shall be provided.	1. The ranges of humidity tested for shall be risk based, taking into consideration the likely operational settings. 2. The intended operating temperature, upon which reading time has been validated, shall be clearly stated in the instructions for use.	WHO Prequalification – Diagnostic Assessment (*8*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
	Performance studies shall be conducted at each of 3 temperatures (at the mid-point and two extremes of the claimed operating range); the effect of humidity on reading times shall also be investigated.	3. Some of these aspects could be evaluated within the flex studies (see section 1.11.1 below).	
1.6 Analytical sensitivity			
1.6.1 Seroconversion	A minimum of 25 commercial or well-characterized seroconversion panels shall be tested: • test at least 40 early seroconversion specimens (see Note 2); • all seroconversion specimens shall be reactive (see Note 3); • start with a negative bleed(s) and should have narrow bleeding intervals.	1. Specimens should have been collected at short intervals to cover the seroconversion period and should also cover the whole window period. 2. Early seroconversion: – p24 Ag and/or HIV RNA-positive; – not recognized by all Conformité Européenne (CE)-marked third-generation enzyme immunoassays; – indeterminate or negative by confirmatory assays. 3. Seroconversion: – p24 Ag and/or HIV RNA-positive; – recognized by all CE-marked third-generation enzyme immunoassays; – indeterminate or positive by confirmatory assays.	European Commission (*2*) Health Products and Food Branch, Health Canada (*7*) CLSI EP12-A2 (*6*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.6.2 Limit of detection for HIV-1 p24 Ag, where appropriate	Analytical sensitivity estimated as the concentration of HIV-1 p24 Ag at the assay cut-off. The determination shall comprise a minimum of 15–20 replicate tests of an 8-member dilution panel of a suitable biological reference material – for example, the First WHO International Reference Reagent for HIV-1 p24 antigen (NIBSC code 90/636).	4. Seroconversion sensitivity shall be reported to the user in the instructions for use. 5. Optimally, testing should be conducted using more than 1 lot of the final design (locked-down).	
1.7 Prozone/high-dose hook effect			
1.7.1 Prozone/high-dose hook effect	For each claimed analyte, the potential for a prozone/high-dose hook effect shall be determined: • using multiple highly reactive specimens (minimum of 20); • using at least 2 different concentrations (diluted by at least a factor of 10); • by the testing of several replicates by the same operator on the same day.	1. Specimens shall be chosen that have a high analyte concentration, as determined using an IVD method other than the IVD intended to be prequalified (for example, enzyme immunoassay). This second method shall be of a design not subject to prozoning. 2. An increase in signal upon dilution of a specimen implies a hook effect.	Health Products and Food Branch, Health Canada (*7*) Butch, AW (*9*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.8 Analytical specificity			
1.8.1 Potentially interfering substances	The potential for false results (false negatives and false positives) arising from interference from at least the substances/conditions listed below in sections 1.8.1.1 and 1.8.1.2 (see Note 1) shall be determined using: • a minimum of 100 specimens (either naturally occurring or spiked to a low reactivity); • each substance/condition represented, where possible, by at least 3–5 specimens from different individuals. Testing shall be undertaken using both HIV-negative and HIV-positive specimens (unspiked or spiked) with each potentially interfering substance at physiologically relevant dosages.	1. The risk assessment conducted for an IVD shall identify substances where the potential for interference can reasonably be expected for the analyte being detected (for example, HIV-1/2 antibodies and/or HIV-1 p24 Ag). 2. Where either the scientific literature and/or risk analysis identifies the potential for false results in co-infected individuals (for example, decreased sensitivity or specificity), further investigation shall be undertaken using both HIV-negative and HIV-positive specimens. 3. In addition to the substances listed here, IVDs that are used to test oral fluid shall take into account the effect of oral infections, such as Candida, as well as tobacco, mouthwash, concomitant medications, dental fixtures, toothpaste, food or drink (consumed immediately prior to testing), consumption of alcohol and teeth brushing. 4. Any observed interference shall be investigated and performance limitations of the IVD reported in the instructions for use. Results shall be reported with respect to each condition and not be reported as an aggregate of the total number of specimens tested in the study.	Health Products and Food Branch, Health Canada (*7*) European Commission (*2*) CLSI EP07-A2 (*10*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.8.1.1 Endogenous	• human antibodies to the expression system (for recombinants), for example, anti-*Escherichia coli* or human anti-mouse antibody (HAMA); • recipients of multiple blood transfusions, and pregnant (including multiparous) women; • haemoglobin, lipids, bilirubin and protein; • elevated immunoglobulin G and immunoglobulin M; • rheumatoid factor; • sickle-cell disease; • other autoimmune conditions including systemic lupus erythematosus (SLE) and anti-nuclear antibodies (ANA).		

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.8.1.2 Exogenous	• relevant medicines, including: antiparasitic, antimalarial, antiretroviral and anti-tuberculosis medications; • common over-the-counter anti-inflammatory medications (aspirin, paracetamol and ibuprofen); • ethanol and caffeine.		
1.8.2 Cross-reactivity	The potential for false-positive results arising from cross-reactivity (see Note 1) shall be determined for a minimum of 100 specimens, including, where possible, at least 3–5 specimens representing each of the following: • non-HIV viral infections, including: hepatitis B, C infection and acute hepatitis A infection, cytomegalovirus, acute Epstein–Barr virus, varicella zoster virus, yellow fever virus post-immunization, measles, influenza A and B and tick-borne encephalitis;	1. The types of interferences tested for shall be risk based, taking into consideration the operational setting as well as the intended users for the analyte being detected (for example, HIV-1/2 antibodies and/or HIV-1 p24 Ag). 2. Any observed interference shall be investigated and performance limitations of the IVD reported in the instructions for use.	

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
	• other retroviruses, including human T-lymphotropic cell virus-1 and -2; • bacteria/parasites, including: malaria, visceral leishmaniasis, tuberculosis and human African trypanosomiasis; • influenza vaccine recipient; • vaccine-induced HIV seropositivity; • other unrelated conditions known to cause cross-reactivity in HIV IVDs.		
1.9 Metrological traceability of control material values			
1.9.1 Metrological traceability of control material values	The traceability of an assay-specific quality control specimen to a validated reference material shall be demonstrated – for example, the First WHO International Reference Panel for anti-human immunodeficiecy virus tests (NIBSC code 02/210) or the First WHO International Reference Reagent for HIV-1 p24 antigen (NIBSC code 90/636).	1. HIV RDT kits may not include external quality control specimens, but the IVD shall have a procedural control. The extent to which a control band corresponds to a valid test (identification of and traceability to a suitable reference) should be demonstrated. Comment 1: the nature of the procedural control (specimen addition or only reagent addition) shall be explained. Comment 2: an external control specimen is one that is run in conjunction with the IVD, but is physically separate from it – for example, an RDT cassette.	WHO Prequalification – Diagnostic Assessment (*8*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
		2. In some jurisdictions there is a requirement for the use of a "National Testing Panel" for lot release and IVD validation. Such a national requirement does not remove the need for evidence of traceability to a validated reference material as described here.	
1.10 Stability			
	Replicate testing shall be undertaken using a panel (for each claimed pathogen/analyte) consisting of at least: • 1 non-reactive specimen; • 2 low-reactivity specimens, near assay cut-off (see Note 2); • 1 medium-reactivity specimen. Wherever possible, specimens chosen for the testing panel shall reflect the main specimen types intended for use with the IVD (for example, capillary whole blood and/or oral fluid, as appropriate).	1. The testing panel shall include all claimed analytes and include whole blood specimens and/or oral fluid specimens, as appropriate, in accordance with intended use (for example to verify proper flow and absence of background interference, and to account for other variables). 2. Where detection of multiple genotypes and/or subtypes is claimed, equivalent performance (for example, sensitivity and specificity) shall have been demonstrated; otherwise evidence of stability in these genotypes/subtypes will need to be provided. 3. Ideally, the stability testing panel shall be composed of natural (that is, undiluted) specimens. Where this is not feasible, stock specimens to be diluted should represent a range of stages of infection (antibody maturation) so as to take into account the limitations of mimicking low IVD reactivity with a high-avidity specimen.	ISO 23640:2011 (*11*) CLSI EP25-A (*12*) Technical Guidance Series for WHO Prequalification – Diagnostic Assessment (*13*) ASTM D4169 - 14 (*14*)

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.10.1 Shelf-life (including transport stability)	Real-time, minimum of 3 lots of final design product and: • transport stressed (simulated) before real-time studies are undertaken; • IVD in final packaging subjected to drop-shock testing.	4. Lots shall comprise different batches of critical components. 5. Determination of shipping stability shall be performed using simulated extreme stress conditions, ensuring that application of those conditions is consistent and controlled. 6. Claims for stability shall be based on the second-last successful data point from the least-stable lot – with (where lots are different) a statistical analysis showing that the bulk of lots will be expected to meet the claimed life. For example, for testing conducted at 3, 6, 9, 12 and 15 months where stability was observed at 15 months, then the maximum stability claim shall be 12 months. 7. Accelerated studies do not replace the need for real-time studies. 8. In-use stability of labile components shall be determined using components in their final configuration.	
1.10.2 In-use stability	• minimum of 1 lot, using panel(s) compiled as above; • testing of all labile components (for example, buffers vials, sealed cartridges, etc. – see Note 8).		

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
1.11 Flex studies			
1.11.1 Flex studies	The influence of the following factors on expected positive and negative results shall be considered: • specimen and/or reagent volume; • buffer pH (measure of robustness – for example, as affected by evaporation of the buffer); • reading time (that is, the interval between when the first and last readings can be taken); • IVD sturdiness, including robustness of packaging and labelling lighting and humidity (see Note 3); • operating temperature.	1. Refer to WHO document PQDx_018 "Instructions for compilation of a product dossier" for other flex studies that may be relevant, taking into consideration the broad range of operational and environmental conditions consistent with intended use. 2. The factors listed opposite should be investigated in ways that not only reflect but also exceed likely operating conditions in low- and middle-income countries, so that the limitations of the device can be understood. For example, in addition to investigating deviations of temperature within those claimed in the instructions for use, temperature ranges should be investigated that exceed those of claimed operating conditions and which cause test failure (incorrect/ invalid results). 3. The impact of lighting can be two-fold – that is, the impact of lighting on packaging (for example, fading) and on the sufficiency of lighting to read the test lines.	WHO Prequalification – Diagnostic Assessment (*8*)

Part 2 Establishing clinical performance characteristics (professional use and/or self-testing)

Aspect	Testing requirements	Notes on testing requirements	Source documents
2.1 Diagnostic sensitivity and specificity			
	Diagnostic sensitivity and specificity shall be determined for each claimed specimen type. Testing should be conducted: • at different geographical settings (minimum of 2 regions); • by a variety of intended users; • using more than 1 lot.	1. Prequalified HIV RDTs are generally used by lay providers and health-care workers. For WHO prequalification purposes, these should be considered as the intended user rather than a trained laboratory professional. 2. Where an IVD is intended to detect multiple analytes without differentiating which analyte is detected, the testing panel shall comprise specimens that are reactive only for each individual analyte (that is, not dual HIV-1/HIV-2-positive, etc). 3. A separate specimen shall be collected prior to testing to establish the reference result. The testing algorithm used to determine the reference results shall include a state-of-the-art fourth-generation immunoassay, with all initially reactive specimens reflexed for full characterization of HIV status. 4. Problematic specimens – that is, those with unexpected results but which otherwise meet the selection criteria for a study – shall not be systematically excluded from analysis.	European Commission (*2*) Health Products and Food Branch, Health Canada (*7*)
2.1.1 Diagnostic sensitivity	Testing of: • at least 400 specimens confirmed to be HIV-1 antibody positive; • at least 100 specimens confirmed to be HIV-2 antibody positive (where HIV-2 detection is claimed; see Note 2); • at least 50 specimens confirmed to be HIV p24 Ag positive (where Ag detection is claimed; see Note 2).		

Table *continued*

Aspect	Testing requirements	Notes on testing requirements	Source documents
2.1.2 Diagnostic specificity	Testing of: • at least 1000 HIV antibody/ antigen negative specimens.	5. Consideration shall be given to the influence of antiretroviral medications present in a specimen on the serostatus of such specimens, and to how this might affect specimen selection. 6. Lots (locked-down design) shall comprise different batches of critical components. 7. Where possible, all tests that produce a discrepant result (between the assay under evaluation and the reference results) shall be repeated using the same lot, and then on all available lots and the variability noted. Performance characteristics shall be reported using initial results only. The results of further testing of specimens with discrepant results shall be reported separately as additional information on IVD performance. 8. All indeterminate results shall be included in the denominator data for analysis. 9. All invalid test results shall be recorded. 10. Estimates of diagnostic/clinical sensitivity and specificity shall be reported with 95% confidence intervals. 11. Results shall be expressed separately for each specimen type and for each specimen type per intended use (no aggregation of results).	