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



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# Contents

# 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*), providing a set of principles on the regulatory evaluation of such products. During international consultations on the development of the WHO guidelines, and also during their implementation, it became clear that there was a need to develop WHO guidelines for changes of approved biotherapeutic products in order to resolve complexity and current challenges of global life-cycle management. 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 which WHO was requested to provide guidance, especially on dealing 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*). The present 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 the document collectively includes the originator products and SBPs (also called "biosimilars").

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

NRAs and MA holders should recognize that:

- any change to a biotherapeutic product has a potential impact on quality, safety and/or efficacy of that product; and
- any change to the information associated with the product (i.e. 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. WHO provides support to its Member States through the provision of written standards and guidelines *(1–3, 7–9)*. Many NRAs of Member States have requested further guidance on the data needed to support changes to approved biotherapeutic products in order to ensure comparability of the pre-change and post-change product 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 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 alter the principles outlined in these guidelines. NRAs are encouraged to apply the concepts of reliance, of work-sharing or to use collaborative approaches when reviewing post-approval changes, as indicated in section 8 of this document.

## 2. Scope

This document provides 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 guidelines apply, in principle, to all biologically active protein products which are used in the treatment of human diseases (e.g. plasma-fractionated products) and those intentionally modified by, for example, fusion proteins, PEGylation, conjugation with a cytotoxic drug, or modification of rDNA sequences. These guidelines also apply to protein products used for in vivo diagnosis (e.g. monoclonal antibody products used for imaging).

While these 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 the 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, gene and cell therapy products are not covered by these guidelines. Detailed and specific guidelines for prophylactic vaccines are available in separate guidelines *(9)*. However, the principles set out in this document may apply to low molecular weight heparins.

# 3. Terminology

The definitions given below apply to the terms used in this document. They may have different meaning 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 diseases. For the purpose of this guideline, 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 instance, fusion proteins, PEGylation, conjugation with a cytotoxic drug, or modification of rDNA sequences. It also includes protein products used for in vivo diagnosis (e.g. 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, conduct 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) (e.g. manufacturing-related changes, change of analytical method, 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 comparability of pre-change and post-change product 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 (e.g. vial, 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 (e.g. carton, tray).
- A functional secondary container closure system is a packaging material that is not in direct contact with the product 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 (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality *(16)*.

**Dosage form:** In these guidelines, "dosage form" refers to 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" *(9)*.

**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 these guidelines and other documents *(9)*.

**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 "licence application" in 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 *(9)*.

**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 involves 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; and
- outer label or carton.

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

**Quality change:** In the context of this document, quality change refers to a change in the manufacturing process, product composition, quality control testing, equipment or facility. 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:** In the context of this document, safety and efficacy changes refer to changes that have an impact on the clinical use of the biotherapeutic product in relation to safety, efficacy, dosage and administration, and that require data from clinical or post-marketing studies, and in some instances clinically-relevant nonclinical studies, to support the change.

**Secondary packaging facility:** Site involves in packaging activities using packaging component that is not, and will not be, in direct contact with the dosage form (e.g. putting the primary container in the outer container, 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 that was developed and approved on the basis of the principles outlined in WHO guidelines on evaluation of SBPs *(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 (e.g. plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (e.g. cell substrates, host/vector production cells, eggs, viral strains, etc.).

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

**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 (i.e. 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 (i.e. identity, strength, purity, 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 (i.e. requires an official submission of a supplement to the NRA) based on the recommendations provided in these guidelines. Supplements requiring approval prior to implementation of a change – i.e. changes that potentially have a major or moderate impact – are referred to as prior approval supplements (PASs) and require submission of a PAS to the NRA. Supplements that do not require approval prior to implementation – i.e. changes that potentially have a minor impact on product quality – should be notified to the NRA following implementation.

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 the 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 *(7, 8)*.

For manufacturing changes not specifically described in these 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 the quality change (also referred to as manufacturing change) affects the quality attributes (i.e. identity, strength, purity, potency) of the product is generally accomplished by comparing manufacturing steps and test results from in-process, release, and characterization testing of pre-change (e.g. historical data) and post-change processes and determining if the test results are comparable – i.e. drug substance, intermediate or drug product made after the change should be shown to be comparable to, and/or to meet the predefined acceptance criteria of, the drug substance or drug product made before the change. In the case that minor differences in quality are identified, these differences may be considered acceptable provided that they are shown not to have an adverse impact on the

quality, safety, and efficacy of the product (see also sections 5.1 and 5.2). In some cases, additional supporting data may be required, as noted in Appendices 2, 3 and 4.

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 (GMPs), good laboratory practices (GLPs) and good clinical practices (GCPs). Marketing authorization holders and drug substance/ product manufacturers should 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 (e.g. changing amino acid sequence or conjugating to PEG moieties, etc.) 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 requires a product licence application for a new marketing authorization.

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 (i.e. parallel) review of changes to the product. The manufacturing of biotherapeutic products requires, for example, the replenishment of biological starting materials such as working cell banks 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. On the other hand, clinical safety and efficacy changes, such as the addition of a new indication or new age group for 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 under "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 recommendations on the 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 (safety, efficacy, dosage, administration, product components) are provided in Appendix 4.

# 5. Special considerations

## 5.1 Comparability exercise

The need for and the extent of a comparability exercise depend on the potential impact of the change(s) on the quality, safety and efficacy of the product. Comparability exercises can range from analytical testing alone (e.g. where process changes have no impact on any quality attribute) to a comprehensive exercise requiring nonclinical and clinical bridging studies. For instance, 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 assurance of comparability can be shown 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 bridging studies and clinical bridging trials 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, 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 or are insufficient to establish comparability. The comparison of efficacy responses and safety outcomes (e.g. PK/PD, rates of common and serious adverse events) is often the primary objective. For ethical reasons, it is desirable to apply the 3R principles (reduction, replacement, 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 (e.g. a new excipient); (d) a new presentation (e.g. addition of pre-filled pens to vials); (e) a new route of administration and (f) a new dosing schedule. 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 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 be automatically given to the SBP. However, when new safety information is added in the reference product after the original approval of the SBP, labelling information changes of the SBP should follow the changes made in 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 (e.g. manufacturing change) on the quality attributes (i.e. identity, strength, purity, potency) of the biotherapeutic product and on their potential impact 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.

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 (i.e. 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, should be available on request from the NRA or during inspections in accordance with local regulations.

Further information on each category is given below. Appendices 2 and 3 provide a comprehensive list of major, moderate and minor quality changes and the information that is 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 guidelines. The NRA should consider establishing a mechanism that allows for its guidelines to be updated to address technological changes requiring new 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 to ensure 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 information on the following: the methods used and studies performed to evaluate the effect of the change on the product's quality attributes; the data derived from those studies; relevant validation protocols and results; and updated product labelling information. In some cases, major quality changes may also require nonclinical and/or clinical data. Relevant considerations can be found in WHO's *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 content of the moderate quality changes are the same as those for the major quality changes (see section 6.1); however, the amount of supporting data required will generally be less than for major changes and the review time 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. The changes included in this category may be implemented by the marketing authorization holder without prior review by the NRA, but 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 with the 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 (e.g. 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 quality, safety and efficacy of product may be implemented by the marketing authorization holder without prior review by the NRA. These 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 corrections to spelling mistakes, and editorial changes made to documents (such as validation summaries and/or reports, analytical procedures, standard operating procedures or production documentation summaries for added clarity) that have no impact on the quality, safety and efficacy of the product;
- replacement of equipment with an 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-approved 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 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 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 in 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 (i.e. carton), and inner label (i.e. 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 (see Appendix 4 for examples of efficacy, safety and product labelling information changes that are considered to be appropriate for each category).

## 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 and that require data from clinical studies and, in some instances, from clinically-relevant nonclinical studies to support the change. Safety and efficacy changes 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, such as:

- 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; or
- deletion or reduction of existing risk management measures (e.g. 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 (i.e. morbidity and mortality, acute or chronic disease, current availability of disease therapy, and size and nature of patient population);

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

- safety considerations (e.g. 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.

Marketing authorization holders are encouraged to consult with the NRAs 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. NRAs should be consulted on the data required to support such changes.

For nonclinical and clinical studies, the recommendations given in WHO's *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's guidelines on evaluation of similar biotherapeutic products (*2, 3*).

For a change under this category, the marketing authorization holder should submit a supplement to the NRA that may include the following:

- a detailed description and rationale of 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;
- clinical studies (protocol, statistical analysis plan and clinical study report);
- 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 by:

- the identification or characterization of any adverse event resulting in the addition or strengthening of risk-management measures for an adverse event which was identified 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 prior to distribution of the product. Supplements for product labelling information changes related to clinical use of a product often require data from pharmacovigilance reports (i.e. 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 may include the following:

- 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 (i.e. a formal letter by a manufacturer to health care professionals to convey the information) prior to the submission of such supplements.

## 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. For instance:

- Examples of product labelling information changes that require approval by the NRA prior to implementation are changes in the proper/ non-proprietary name or trade name of the biotherapeutic product. The 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 (e.g. 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 the NRA regarding reporting category of labelling changes of approved products.

# 8. Procedures

Establishment of procedures and criteria for adequate oversight of changes is the responsibility of the regulators. Therefore, NRAs should establish written instructions regarding the submission procedures and timelines with action dates (including identification of emergency use, expanded access, expedited and/or priority review, timelines, and procedures for life-saving medications to address an unmet need) for consultation by marketing authorization holders as they prepare to submit a supplement for a change. 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 reviews of major quality changes that do not require clinical data as compared with safety and efficacy changes that do require clinical data. Appendix 1 gives examples of regulatory categories and review timelines.

If the 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 should generally be encouraged to contact the NRA regarding plans for future changes and proposed filing dates for changes to existing products in order to assist NRAs to plan the allocation of review resources. NRAs should establish procedures on the conduct and the recording of communications between themselves and marketing authorization holders with appropriate timelines.

To assist in the acceptance of submissions for review, the covering letter or the Module 1 documentation of Common Technical Document accompanying a supplement for a quality change should specify that the change is being reported in the selected category by labelling the submission as 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 (e.g. Common Technical Document sections) and reported in any future filing to the NRA. For instance, 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.

Regulation of post-approval changes is part of the entire regulatory framework which includes marketing authorization, GMP inspection and post-marketing surveillance (PMS). 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 instance, 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 is 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 the mutual agreement (e.g. the Pharmaceutical Inspection Cooperation Scheme, or 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. Therefore, 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 about 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 8.4 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 (e.g. 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 instance, 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 are supported by the same information. Minor quality changes that were implemented previously and that are

related/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: 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 (e.g. major quality change, moderate quality change, safety and efficacy change),
  - a list of the change(s) and a rationale for the change(s) with sufficient detail 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), if applicable;
- 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 after approval of a change, in some cases the implementation of the change may be delayed to allow depletion of the previously approved biotherapeutic or to allow for global staggered approval depending on supply/ demand);
- GMP information (e.g. inspection history, evidence of GMP compliance rating by experienced NRAs), as applicable;
- a rationale for the change and a justification for the selected reporting category;

- when relevant, a side-by-side comparison showing the differences between the approved manufacturing process (including quality control tests) compared to the proposed ones (see section 5);
- when relevant, clinical and/or nonclinical study reports, pharmacovigilance reports, and annotated and clean drafts of product labelling information (see section 6).

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 although the data may be cross-referenced. NRAs may also 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 indicated 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 in a supplement supports the quality, safety or efficacy of the product manufactured with the change, the NRA will issue a written approval notification 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 demonstrate 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 period allotted for the review through rounds of questions and requests for more information, the NRA may decide to issue a written notification of noncompliance by means 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 noncompliance notification being issued, the following outcomes are possible:

- If the marketing authorization holder's response document to the noncompliance notification 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 noncompliance notification 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 is stopped. Documentation subsequent to the original supplement submission (in response to information requests or noncompliance notifications) should be submitted and filed as amendments to the original supplement, and 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 finally rejected by the NRA.

NRAs may consider the following approach 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, including the tests to be done and acceptable limits to be achieved to assess 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 of data requirements for changes and predictability of changes. This allows for a 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 (e.g. facilities changes) *(15)*.

**Production documents**

Production documents (i.e. 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 (e.g. annually). Supporting data should not be provided with the notification unless it may help justifying the reporting category. However, the minor quality changes should be recorded or compiled with related supporting data generated by the manufacturer, as recommended in Appendices 2 and 3, 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, 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/ 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 will try 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, the NRA 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 (e.g. addition of a contraindication or a warning), NRAs should establish a specific mechanism to allow for 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 should establish a mechanism by which urgent product labelling changes that have been approved in the country where biotherapeutic products are produced and/or licensed may be implemented immediately upon receipt of the supplement by the NRAs of the countries procuring the biotherapeutic products. Such accelerated procedures would contribute to the dissemination of the most current information to health-care providers and would also help 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/ non-proprietary 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.

# Authors and acknowledgements

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# Appendix 1

## Reporting categories and suggested review timelines

It is recommended that national regulatory agencies (NRAs) establish review timelines to allow marketing authorization holders or applicants to plan the implementation of changes. The review times 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 an approval notification or a noncompliance notification 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 categories | Procedures | Suggested review timelines[1] |
|---|---|---|
| **Major quality changes** | Prior approval supplement (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 |

[1] The review timelines are established by taking into consideration the country or regional situation and the capability of the NRA.

**Safety, efficacy and product labelling information changes**

| Reporting categories | Procedures | Suggested review timelines[1] |
|---|---|---|
| **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 (e.g. 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 about the change. Using this approach, NRAs could allow changes to be implemented immediately after receipt of the change notification.

[1] The review timelines are established by taking into consideration the country or regional situation and the capability of the NRA.

- 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 two months for major quality changes, four 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 could range from those shown in the table or could be abbreviated as described above.

# 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 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 – e.g. 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*** (e.g. 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 if it may have potential to have an 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 the supporting data are not described. NRAs should establish procedures, with appropriate timelines, on the conduct and the recording of communications between themselves and marketing authorization holders.

Supporting data should be provided according to the submission format accepted by the NRA (e.g. *(1, 2)*).

For additional information on data requirements to support quality changes, WHO's guidelines on GMP requirements and on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology *(3, 4)* should be considered, as should relevant International Conference on Harmonisation (ICH) guidelines *(5, 6)*.

### Quality changes to comply with updated compendia and/or pharmacopoeias

NRAs should make a list of the recognized compendia/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 agency and 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 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 (e.g. potency), for changes that have an impact on any items of the product labelling information, and changes that may potentially 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 applies to other types of products such as plasma-fractionated products. Where post-approval changes to the drug substance affect the lot release protocol (e.g. 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 instance, 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:**<br>*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).<br>2. Any changes to the manufacturing process and/or controls are considered either moderate or minor (e.g. 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 (e.g. recurrent out-of-specification events, environmental monitoring failures, etc.). |
| **Supporting data** | |
| 1. | Evidence of GMP compliance of the facility. |
| 2. | Name, address and responsibilities (e.g. fermentation, purification) of the proposed facility. |
| 3. | Summary of the process validation studies and results. |
| 4. | Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may be required if quality data alone are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality comparability findings, the nature and level of the knowledge of the product, existing relevant nonclinical and clinical data, and aspects of their use. |
| 5. | Justification for the classification of any manufacturing process and/or control changes as moderate or minor. |
| 6. | Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified and agreed by the 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 (e.g. it can be proven that the relevant effect, if present, can be 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:**<br>*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 a master cell bank (MCB) into a new culture medium | None | 1, 2, 5, 6–8, 10 | Major |
| b. Generation of a new MCB | 1 | 1, 2, 5, 6–8 | 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 (i.e. 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.
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 (e.g. 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** | **Supporting** | **Reporting** |
|---|---|---|---|

| | be fulfilled | data | 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, e.g. 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 (e.g. 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:<br>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;<br>duplication of a fermentation train; or<br>addition of similar/comparable bioreactors | 1–5, 7–10 | 1, 2, 4, 8 | Minor |
| **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, e.g. 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 (e.g. 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 (e.g. 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 |
| **Conditions** | | | |

[1] HPLC = high-performance liquid chromatography.

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 (i.e. the change in scale is linear).
11. The change in scale involves the use of the same bioreactor (i.e. 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 (e.g. ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g. name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, use and previous acceptance of the material) *(7)*.
5. Process validation results.
6. Comparability of the pre-change and post-change drug substance with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis, taking into consideration the quality–comparability findings, the nature and level of knowledge of the product, existing relevant nonclinical and clinical data, and aspects of its use.
7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified.
8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one commercial-scale batch of the pre-change and post-change drug substance. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Batch data on the next two full-production batches should be made available on request and should be reported by the marketing authorization holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and.
9. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug substance batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months and one batch of real-time data could be acceptable if properly justified (e.g. 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*).

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 (e.g. 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 (e.g. impact on viral clearance studies and BSE/TSE risk) *(7)*.
13. Data describing the root cause triggering the reprocessing, as well as validation data (e.g. 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, such as:**<br>*Note: New bioreactor technology (e.g. 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 |
| 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.<br>2. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.<br>3. The manufacturing process is not impacted by the change in product-contact equipment.<br>4. The change has no impact on product quality.<br>5. Re-qualification of the equipment follows the original qualification protocol. |
| **Supporting data** |
| 1. Information on the in-process control testing.<br>2. Process validation study reports.<br>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).<br>4. Information on leachables and extractables.<br>5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.<br>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 (e.g. 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 (e.g. 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.<br>2. The grade of the materials is the same or is of higher quality, where appropriate.<br>3. There is no change in the drug substance specification outside the approved limits.<br>4. There is no change in the impurity profile of the drug substance outside the approved limits.<br>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.<br>6. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.<br>7. The test does not concern a critical attribute (e.g. content, impurity, any critical physical characteristics or microbial purity).<br>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 (e.g. raw materials, starting materials, |

| | |
|---|---|
| | solvents, reagents, 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 (e.g. ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g. name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, 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 (e.g. 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**<br>*Note: Transfer of in-process control testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and is reviewed during inspections.* | 1–3, 5, 6 | 9 | Minor |
| **Conditions** | | | |

| |
|---|
| 1. No change in the drug substance specification outside the approved limits.<br>2. No change in the impurity profile of the drug substance outside the approved limits.<br>3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.<br>4. The test does not concern a critical attribute (e.g. content, impurity, any critical physical characteristics or microbial purity).<br>5. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.<br>6. No change in the approved in-process controls outside the approved limits.<br>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.<br>2. Updated drug substance specification, if changed.<br>3. Copies or summaries of analytical procedures if new analytical procedures are used.<br>4. Comparative table or description, where applicable, of pre-change and post-change in-process tests/limits.<br>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.<br>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.<br>7. Justification/risk assessment showing that the attribute is non-significant.<br>8. Justification for the new in-process test and limits.<br>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 |
| **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:**<br>*Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and 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.<br>2. No changes are made to the test method.<br>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.<br>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 (i.e. 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.<br>2. There is no change in drug substance specifications outside the approved ranges.<br>3. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph.<br>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.<br>2. Updated copy of the proposed drug substance specifications.<br>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.<br>4. Copies or summaries of validation reports if new analytical procedures are used.<br>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) (e.g. 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.<br>2. Updated copy of the proposed drug substance specifications.<br>3. Copies or summaries of analytical procedures if new analytical procedures are used.<br>4. Copies or summaries of validation reports if new analytical procedures are used to monitor the new CQA at release.<br>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 |
| 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 (e.g. new unqualified impurity, change in total impurity limits).<br>2. There is no change in the limits/acceptance criteria outside the approved limits for the approved assays used at release/ stability.<br>3. The addition of the test is not intended to monitor new impurity species.<br>4. The method of analysis is the same and is based on the same analytical technique or principle (e.g. change in column length or temperature, but not a different type of column or method) and no new impurities are detected.<br>5. The modified analytical procedure maintains or improves performance parameters of the method.<br>6. The change does not concern potency-testing.<br>7. Acceptance criteria for residual solvent are within recognized or approved acceptance limits (e.g. within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).<br>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.<br>2. Copies or summaries of analytical procedures if new analytical procedures are used.<br>3. Validation/qualification results if new analytical procedures are used.<br>4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.<br>5. Justification for the proposed drug substance specification (e.g. tests, acceptance criteria or analytical procedures).<br>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.<br>2. The extension of the shelf-life of the reference standard is in accordance with an approved protocol.<br>3. The reference standard is used for a physicochemical test. |
| **Supporting data** |
| 1. Justification for the change in reference standard.<br>2. Information demonstrating qualification of the proposed reference standards or materials (e.g. source, characterization, certificate of analysis, comparability data).<br>3. Justification of the change to the reference standard qualification protocol.<br>4. Updated reference standard qualification protocol.<br>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 (e.g. description, composition, materials of construction of primary packaging components, specifications).<br>2. Data demonstrating the suitability of the container closure system (e.g. extractable/leachable testing) and compliance with pharmacopoeial standards, if applicable.<br>3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (e.g. results of transportation or compatibility studies, and extractable/leachable studies).<br>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 (e.g. 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 (e.g. 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*).<br>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 (e.g. extractable/leachable testing).
2. Information on the proposed container closure system (e.g. description, materials of construction of primary packaging components, specifications).
3. 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 (e.g. 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.
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.<br>2. Rationale for the change.<br>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.<br>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.<br>3. Stability data were generated in accordance with the approved stability protocol.<br>4. Significant changes were not observed in the stability data.<br>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 (e.g. studies conducted, protocols used, results obtained).<br>2. Proposed storage conditions and shelf-life, as appropriate.<br>3. Updated post-approval stability protocol and stability commitment.<br>4. Justification for the change to the post-approval stability protocol or stability commitment.<br>5. Results of stability-testing (i.e. 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 (e.g. *(6)*).

**Supporting data**

1. Copies or summaries of analytical procedures if new analytical procedures are used.
2. Validation results if new analytical procedures are used.
3. Proposed storage conditions and/or shelf-life, as appropriate.
4. Updated post-approval stability protocol including justification for the changes, and stability commitment.
5. If applicable, stability-testing results to support the change to the post-approval stability protocol or stability commitment (e.g. 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 (e.g. 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 (i.e. full real-time/real-temperature stability data covering the proposed shelf-life generated on one commercial-scale batch).
5. Results of stability-testing (i.e. full real time/real temperature stability data covering the proposed shelf-life generated on at least three commercial-scale batches).

# References

1. The common technical document for the registration of pharmaceuticals for human use: quality; M4Q(R1). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 12

September 2002 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf, accessed 14 December 2014).

2. CTD Quality – M4Q Implementation Working Group: Questions & Answers (R1); M4Q(R1). Geneva: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; 17 July 2013 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4_Quality_Questions_Answers_R1.pdf, accessed 14 December 2014).

3. WHO good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: sixty-sixth report. Geneva: World Health Organization; 2016: Annex 2 (WHO Technical Report Series, No. 999; http://www.who.int/biologicals/expert_committee/WHO_TRS_999_FINAL.pdf?ua=1, accessed 8 July 2017).

4. Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology. In: WHO Expert Committee on Biological Standardization: sixty-fourth report. Geneva: World Health Organization; 2014: Annex 4 (WHO Technical Report Series, No. 987; http://apps.who.int/iris/bitstream/10665/129494/1/TRS_987_eng.pdf?ua=1&ua=1, accessed 8 July 2017).

5. ICH Q5E guideline. Comparability of biotechnological/biological products subject to changes in their manufacturing process. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2004 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf, accessed 8 July 2017).

6. ICH Q5C guideline. Stability testing of biotechnological/biological products. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 1995 (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf, accessed 8 July 2017).

7. WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva: World Health Organization; 2003 (WHO/BCT/QSD/2003.01; http://www.who.int/biologicals/publications/en/whotse2003.pdf, accessed 30 November 2014).

8. ICH Q1E guideline. Evaluation of stability data. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2003 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1E/Step4/Q1E_Guideline.pdf, accessed 18 October 2017).

# 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 – e.g. 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 if it may have potential to have an 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 the supporting data are not described. NRAs should establish procedures, with appropriate timelines, on the conduct and the recording of communications between themselves and marketing authorization holders.

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

For additional information on data requirements to support quality changes, WHO's guidelines on GMP requirements and on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology *(3, 4)* should be consulted, as should relevant International Conference on Harmonisation 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 agency and available for inspection.

In some cases, changes 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 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 (e.g. potency), for changes that have an impact on any items of the product labelling information, and changes that may potentially 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 applies to other types of products, such as plasma-fractionated products. Where post-approval changes to the final product affect the lot release protocol (e.g. 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 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 instance, 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 done 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 (e.g. 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 (e.g. 20 unit/mL versus 20 unit/2 mL) | None | 1, 5, 7, 9, 10 | Major |
| | 2, 4, 5 | 1, 5, 7 | Moderate |

| | | | |
|---|---|---|---|
| d. Addition of a new presentation (e.g. 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 (i.e. linear PK/PD profile of the product from at least three different concentrations over the bracketed range has been demonstrated and the two extreme concentrations of the bracketed range have been shown to be bioequivalent or therapeutically equivalent).

**Supporting data**

1. Revised drug product labelling information, as applicable.
2. Characterization data demonstrating comparability of the new dosage form and/or formulation.
3. Description and composition of the dosage form if there are changes to the composition or dose.
4. Discussion of the components of the drug product, as appropriate (e.g. 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 (e.g. 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 (e.g. 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 (e.g. 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 | None | 1–6 | Moderate |

| | | | |
|---|---|---|---|
| diluent | 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) – i.e. 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, such as:** | | | |
| a. Replacement or addition of a manufacturing | None | 1–7 | Major |

| | | | | |
|---|---|---|---|---|
| | facility for the drug product (including formulation/filling and primary packaging) | 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 (i.e. assembly) facility | 2, 3 | 1–3 | Minor |
| d. | Deletion of a drug product manufacturing facility or packaging site | 6–7 | None | Minor |

**Conditions**

1. The proposed facility is an approved formulation/filling facility (for the same company/marketing authorization holder).
2. There is no change in the composition, manufacturing process and drug product specification.
3. There is no change in the container/closure system and storage conditions.
4. The same validated manufacturing process at critical steps (i.e. 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 (e.g. recurrent out-of-specification events, environmental monitoring failures, etc.).

**Supporting data**

1. Name, address and responsibilities (e.g. formulation, filling, primary/ secondary packaging) of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP-compliant.
3. Confirmation that the description of the manufacturing process of the drug product has not changed (other than the change in facility), or submission of supporting data on the revised description of the manufacturing process if the process has changed.
4. Comparative description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
5. Summary of the process validation studies and results.
6. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
7. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (e.g. 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, such as:** | | | |
| 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 (e.g. formulation tank, filter housing, filling line and head, lyophilizer) | None | 1–7 | Moderate |
| | 5 | 2, 7–8 | Minor |
| c. Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process | None | 1, 3–5 | Moderate |
| | 1–4, 8 | 1, 4 | Minor |
| d. Addition of a new step (e.g. filtration) | 3 | 1–6 | Moderate |
| e. Product-contact equipment change from dedicated to shared (e.g. 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 (e.g. 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" (i.e. 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.
9. 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 (e.g. media fills), as appropriate.
4. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
5. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (e.g. 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, such as:** | | | | |
| 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 |
| 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**<br>*Note: Transfer of in-process control testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections*. | | 1–3, 5, 6 | 9 | Minor |
| **Conditions** | | | | |
| 1. | There is no change in drug product 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 (e.g. content, impurities, any critical physical characteristics or microbial purity). | | | |
| 5. | The replaced analytical procedure maintains or improves precision, accuracy, specificity and sensitivity, if applicable. | | | |
| 6. | There is no change in the in-process control limits outside the approved limits. | | | |
| 7. | The test procedure remains the same, or changes in the test procedure are minor. | | | |
| **Supporting data** | | | | |
| 1. | Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed drug substance. | | | |
| 2. | Updated drug product specification if changed. | | | |

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

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

**Conditions**

| | |
|---|---|
| 1. | Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure. |
| 2. | The replaced analytical procedure maintains or improves precision, accuracy, specificity and sensitivity. |
| 3. | The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient. |
| 4. | Acceptance criteria for residual solvents are within recognized or approved acceptance limits (e.g. 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 (e.g. 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.<br>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.<br>3. Justification of the proposed excipient specification (e.g. 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 (i.e. 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.<br>2. The change is made exclusively to comply with a pharmacopoeial standard/monograph.<br>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.<br>4. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph.<br>5. There is no deletion or change to any analytical procedures, except to comply with a pharmacopoeial standard/monograph. | | | |
| **Supporting data** | | | |
| 1. Updated excipient specifications.<br>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.<br>3. Justification of the proposed excipient specifications (e.g. demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product).<br>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 (e.g. 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 (e.g. 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 (e.g. human serum albumin)** | None | 3–8 | Major |
| | 3, 4 | 5, 6, 9 | Moderate |

| | | | |
|---|---|---|---|
| **49. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient)** | None | 2, 3, 5–7 | Moderate |
| | 1, 5, 6 | 3 | Minor |
| **50. Change in excipient testing site**<br>*Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and 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 (e.g. animal species, country of origin) and the steps undertaken during processing to minimize the risk of TSE exposure *(7)*.
3. Information demonstrating comparability in terms of physicochemical properties, and the impurity profile of the proposed excipient compared to the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process, and on the intermediate of the proposed excipient.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three commercial-scale batches of the proposed excipient.
6. Comparative pre-change and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three commercial-scale drug product batches produced with the proposed changes and stored under accelerated and/or stress conditions for a minimum of 3 months. Test results that cover a minimum of 6 months in real-time/real-temperature conditions should also be provided. A possibility of 3 months of real-time data could be acceptable if properly justified (e.g. 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 (e.g. 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:**<br>*Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and 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 |
| 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.<br>2. There are no changes to the test method.<br>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.<br>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 (i.e. specifications) claimed for the drug product, involving the following:** | | | |
| a. A change from a pharmacopoeial standard/monograph to an in-house standard | None | 1–5 | Moderate |
| b. A change from an in-house standard to a pharmacopoeial standard/monograph or from one pharmacopoeial standard/ monograph to a different pharmacopoeial standard/monograph | 1–4 | 1–3 | Minor |
| **53. Change in the specifications for the drug product to comply with an updated pharmacopoeial standard/monograph** | 1–2 | 1–3 | Minor |
| **Conditions** | | | |
| 1. The change is made exclusively to comply with a pharmacopoeial monograph.<br>2. There is no change in drug product specifications outside the approved ranges.<br>3. There is no deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeial standard/monograph.<br>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) (e.g. 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.<br>2. An updated copy of the proposed drug product specifications.<br>3. Copies or summaries of analytical procedures if new analytical procedures are used.<br>4. Copies or summaries of validation reports if new analytical procedures are used to monitor the new critical quality attribute at release.<br>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.<br>2. The additional test is not intended to monitor new impurity species.<br>3. The method of analysis is the same (e.g. a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.<br>4. The modified analytical procedure maintains or improves the performance parameters of the method.<br>5. The change does not concern potency-testing.<br>6. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (e.g. within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).<br>7. The change does not result from unexpected events arising during manufacture (e.g. new unqualified impurity, or impurity content outside the approved limits).<br>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.<br>2. Copies or summaries of analytical procedures if new analytical procedures are used.<br>3. Validation/qualification results if new analytical procedures are used.<br>4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.<br>5. Justification for the change to the analytical procedure (e.g. demonstration of the suitability of the analytical procedure in monitoring the drug product, including the degradation products) or for the change to the specification (e.g. demonstration of the suitability of the revised acceptance criterion to control the drug product).<br>6. Justification for the deletion of the test (e.g. demonstration of the suitability of the revised specification in controlling the final product).<br>7. Documented evidence that consistency of quality and of the production process is maintained. | | | |

## Reference standards

| Description of change | Conditions to be fulfilled | Supporting data | Reporting category |
|---|---|---|---|
| **56. Replacement of a primary reference standard** | None | 1-2 | Moderate |
| **57. Change of the reference standards from a pharmacopoeial or international standard to in-house (no relationship with international standard)** | None | 1, 2 | Moderate |
| **58. Change of the reference standard from in-house (no relationship with international standard) to a pharmacopoeial or international standard** | 3 | 1, 2 | Minor |
| **59. Qualification of a new batch of reference standard against the approved reference standard (including qualification of a new batch of a secondary reference standard against the approved primary standard)** | 1 | 2 | Minor |
| **60. Change to the reference standard qualification protocol** | None | 3, 4 | Moderate |
| **61. Extension of the reference standard shelf-life or re-test period** | 2 | 5 | Minor |

| **Conditions** |
|---|
| 1. The qualification of a new standard is carried out in accordance with an approved protocol.<br>2. The extension of the shelf-life of the reference standard is carried out in accordance with an approved protocol.<br>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.<br>2. Qualification data of the proposed reference standards or materials (e.g. source, characterization, certificate of analysis).<br>3. Justification of the change to the reference standard qualification protocol.<br>4. Updated reference standard qualification protocol.<br>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 (e.g. new coating, adhesive, stopper, type of glass)**<br>*Note: The addition of a new container closure system (e.g. 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 (e.g. change from reusable pen to disposable pen)** | None | 1, 3, 6 | Moderate |
| **64. Deletion of a container closure system**<br>*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.<br>2. There is no change in the shape or dimensions of the container closure.<br>3. The change is made only to improve the quality of the container and does not modify the product contact material (e.g. increased thickness of the glass vial without changing interior dimensions).<br>4. The modified part is not in contact with the drug product. |
| **Supporting data** |
| 1. Revised product labelling information, as appropriate.<br>2. For sterilized products, process validation results, unless otherwise justified.<br>3. Update dossier containing information on the proposed container closure system, as appropriate (e.g. description, materials of construction of primary packaging components).<br>4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and biological reactivity tests.<br>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 (e.g. 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 (e.g. 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<br>*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.<br>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.<br>2. Certificate of analysis, or equivalent, for the container provided by the new supplier and comparison with the certificate of analysis, or equivalent, for the approved container. | | | |

| **Description of change** | **Conditions to be fulfilled** | **Supporting data** | **Reporting category** |
|---|---|---|---|
| **66. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving the following:** | | | |
| a. Deletion of a test | 1, 2 | 1, 2 | Minor |
| b. Addition of a test | 3 | 1, 2 | Minor |

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

**Conditions**

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a 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 |
| 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 | 1, 2, 4, 5 | Moderate |
| | 3 | 4, 5 | Minor |
| **Conditions** | | | |
| 1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities.<br>2. Deletion of time point(s) is done according to relevant guidelines (e.g. *(6)*).<br>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.<br>2. Validation results if new analytical procedures are used.<br>3. Proposed storage conditions and or shelf-life, as appropriate.<br>4. Updated post-approval stability protocol, including justification for the change, and stability commitment.<br>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 (e.g. 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 (e.g. “Do not freeze”) | None | 1, 2, 4, 5 | Moderate |
| c. Deletion of a cautionary statement (e.g. “Do not freeze”) | None | 1, 2, 4, 6 | Moderate |
| **Conditions** | | | |
| None | | | |
| **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.

# References

1. The common technical document for the registration of pharmaceuticals for human use: quality; M4Q(R1). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 12 September 2002 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf, accessed 14 December 2014).

2. CTD Quality – M4Q Implementation Working Group, Questions & Answers (R1); M4Q(R1). Geneva: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; 17 July 2003. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4_Quality_Questions_Answers_R1.pdf, accessed 14 December 2014).

3. WHO good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: sixty-sixth report. Geneva: World Health Organization; 2016: Annex 2 (WHO Technical Report Series, No. 999; http://www.who.int/biologicals/expert_committee/WHO_TRS_999_FINAL.pdf?ua=1, accessed 8 July 2017).

4. Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology. In: WHO Expert Committee on Biological Standardization: sixty-fourth report. Geneva: World Health Organization; 2014: Annex 4 (WHO Technical Report Series, No. 987; http://apps.who.int/iris/bitstream/10665/129494/1/TRS_987_eng.pdf?ua=1&ua=1, accessed 8 July 2017).

5. ICH Q5E guideline. Comparability of biotechnological/biological products subject to changes in their manufacturing process. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2004 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf, accessed 8 July 2017).

6. ICH Q5C guideline. Stability testing of biotechnological/biological products. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 1995 (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf, accessed 8 July 2017).

7. WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva: World Health Organization; 2003 (WHO/BCT/QSD/2003.01; http://www.who.int/biologicals/publications/en/whotse2003.pdf, accessed 26 July 2014).

# Appendix 4

## Safety, efficacy and product labelling information changes

The examples of safety and efficacy changes, product labelling information changes and administrative product labelling information changes in this appendix are provided for clarification. However, such changes are not limited to those included in this appendix. They may also result in changes to the product labelling information for health-care providers and patients, and inner and outer labels.

Because the amount of safety and efficacy data needed to support a change may vary according to the impact of the change, risk–benefit considerations and product-specific characteristics (i.e. there is no "one size fits all"), this appendix provides a list of examples of changes in the various categories rather than a detailed table linking each change with the required data needed to support that change (as is provided in Appendices 2 and 3 for quality changes). Marketing authorization holders or applicants are encouraged to contact the NRA for guidance on the data needed to support major changes if deemed necessary.

**Safety and efficacy changes**
Safety and efficacy change supplements require approval prior to implementation of the change and are generally submitted for changes related to clinical practice, safety and indication claims.

The following are examples of safety and efficacy changes requiring data from clinical studies and/or nonclinical studies, post-marketing observational studies or extensive post-marketing safety data:

1. Change to the indication:
    a. addition of a new indication (e.g. treatment of a previously unspecified disease);
    b. modification of an approved indication (e.g. expansion of the age of use or restriction of an indication based on clinical studies demonstrating lack of efficacy).
2. Change in the recommended dose and/or dosing schedule.
3. Change to the use in specific at-risk groups (e.g. addition of information on use in pregnant women or immunocompromised patients).
4. Change to add information on co-administration with other medicines.
5. Change to add a new route of administration.[1]
6. Change to add a new dosage form[1] (e.g. replacement of a suspension for injection with a lyophilized cake).

[1] Some NRAs consider that these changes may require a new application for a marketing authorization or licence.

7. Change to add a new strength.[1]
8. Change to add a new delivery device[1] (e.g. adding a prefilled syringe or pen).
9. Change in existing risk-management measures:
    a. deletion of an existing route of administration, dosage form and/or strength due to safety reasons;
    b. deletion of a contraindication (e.g. use in pregnant women);
    c. changing a contraindication to a precaution.

**Product labelling information changes**

Supplements on product labelling information change should be submitted for changes which do not require clinical efficacy and/or safety data from clinical studies but normally require extensive pharmacovigilance (safety surveillance) data. Product labelling information changes require approval prior to implementation.

The following are examples of product labelling information changes that are associated with changes that have an impact on the clinical use of a product:

1. Addition of an adverse event that is identified as consistent with a causal association with administration of the biotherapeutic concerned.
2. Change in the frequency of occurrence of a given adverse reaction.
3. Addition of a contraindication or warning (e.g. identification of a specific subpopulation as being at greater risk, such as persons with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include provision of recommended risk-management actions (e.g. ensuring patient awareness of certain risks).
4. Strengthening, clarification or amendment of text of the product labelling information relating to contraindications, warnings, precautions and adverse reactions.
5. Revisions to the instructions for use, including dosage, administration and preparation for administration, to optimize the safe use of the biotherapeutic product.

In some cases, the ***safety-related changes*** listed above may be urgent and may require rapid implementation (e.g. addition of a contraindication or warning). To allow for speedy processing of such requests, the supplements for these changes should be labelled as "Urgent product labelling information changes" and should be submitted after prior agreement between the NRA and the marketing authorization holder (see section 8.3 and Appendix 1).

**Administrative product labelling information changes**

Administrative product labelling information changes are changes to any of the labelling items which are not expected to have an impact on the safe and efficacious use of the biotherapeutic. 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, as described below.

Example of changes which require reporting to the NRA and receipt of approval prior to implementation by the marketing authorization holder include:

1. Change in the proper/ non-proprietary name or trade name of the biotherapeutic product.

Examples of changes which ***may not*** require approval by the NRA prior to implementation include:

1. Change in the name of the marketing authorization holder and/or manufacturer (e.g. change of name due to a merger).
2. Update of the marketing authorization holder's contact information (e.g. customer service number, website addresses) or distributor's name.
3. Minor changes to the layout of the product labelling information items or revision of typographical errors without changing the content of the label.
4. Update of the existing information for referenced literature without adding or removing references.
5. Changes made to comply with an official compendium (e.g. change of the common name).
6. Minor changes to the text to add clarity in relation to maintaining consistency with common label phrase standards (e.g. change from "not recommended for children" to "not for use in children").

These administrative product labelling information changes (i.e. changes not subject to prior approval that have been implemented since the last approved product labelling information) should be included when submitting subsequent PAS for safety and efficacy changes or for product labelling information changes (see section 8.4).

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