

# Annex 4

## Guidelines on procedures and data requirements for changes to approved vaccines

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



## 1. Introduction

Changes to the vaccine manufacturing process or product labelling information often need to be implemented after a new vaccine has been approved (that is, licensed or marketing authorization (MA) received). Changes may be made for a variety of reasons, such as to maintain the routine production of vaccines (for example, replenishment of cell banks, seed lots and reference standards), to improve the quality attributes of the vaccine or the efficiency of manufacture (for example, changes in the manufacturing process, equipment or facility) or to update product labelling information (for example, to add a new indication and/or improve the management of risk by adding a warning, limiting the target population, changing the dosage regimen and adding information on co-administration with other vaccines or medicines).

National regulatory authorities (NRAs) and MA holders should recognize that:

- any change to a vaccine may impact upon the quality, safety and efficacy of that vaccine;
- any change to the information associated with the vaccine (that is, product labelling information) may impact on the safe and effective use of that vaccine.

The regulation of changes to approved vaccines is one of the most important elements in ensuring that vaccines of consistent quality, safety and efficacy are distributed after they receive authorization or licensure. WHO provides support to its Member States through the provision of written standards and guidelines (1–3). However, the NRAs of Member States requested further guidance on the data needed to support changes to approved vaccines to ensure the comparability – with respect to quality, safety and efficacy – of vaccines manufactured with the change. Although it is difficult to provide guidance that applies 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. The categories of such 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, the contents of these WHO Guidelines may be adopted as definitive national requirements. It is possible that modifications to this document may be justified due to risk–benefit and legal considerations specific to each NRA. In such cases, it is recommended that any modifications of the principles and technical specifications set out in this document be made only

on condition that they ensure a level of vaccine quality, safety and efficacy at least equivalent to that which would be achieved by following the guidance provided here (that is, ensure that the risks of introducing vaccines for use in public health programmes are no greater than those that are outlined in this document).

## 2. Scope

This document provides guidance for NRAs and MA holders on the regulation of changes to the original MA dossier or product licence for an approved vaccine in terms of: (a) procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable NRAs to evaluate the impact of the change on the quality, safety and efficacy of the vaccine. Additionally, the purpose of these WHO Guidelines is to assist NRAs in establishing regulatory procedures for post-approval changes to vaccines.

The guidance given below applies to the manufacture and use of approved prophylactic vaccines for humans. However, the general principles set out in this document may also apply to other biological products.

## 3. General considerations

For each change to the original MA dossier or product licence the MA holder should decide if the information in the original MA or product licence needs to be supplemented (that is, requires the official submission of a supplement or a change application dossier to the NRA) based on the guidance provided in this document. Prior to implementing the change, the MA holder should assess the effects of the change and demonstrate through appropriate studies (analytical testing, functional assays, and/or clinical or nonclinical studies) the absence of any negative effect of the change on the quality, safety and efficacy of the vaccine. A supplement requiring approval prior to implementation of a change is referred to as a prior approval supplement (PAS). In general, no change should be implemented without the approval of the NRA unless otherwise indicated in this document (for example, minor quality changes).

Changes to approved vaccines are categorized on the basis of a risk analysis. When a change affects the manufacturing process, this assessment should include evaluation of the effect of the change on the quality (that is, identity, strength, purity and potency) of the final product as it may relate to the safety and/or efficacy of the vaccine. When a change affects the clinical use or product labelling information, this assessment should include evaluation of the effect of the change on the safety and efficacy of the vaccine. Changes that may potentially have a major or moderate impact require submission of a PAS to the NRA. For each change, the supplement should contain information developed

by the MA holder to allow the NRA to assess the effects of the change. When changes may potentially have a minimal impact or no impact on product quality, safety and efficacy, they should be recorded and retained by the manufacturer or MA holder.

Assessment of the extent to which the quality change (also referred to as manufacturing change) affects the quality attributes (that is identity, strength, purity and potency) of the vaccine is generally accomplished by comparing manufacturing steps and test results from in-process and release testing of pre-change and post-change processes, and determining if the test results are comparable (that is, the antigen, intermediate or final product made after the change should be shown to be comparable to and/or to meet the acceptance criteria of the final product made before the change). However, additional supporting data may be required, as noted in Appendices 2–4 below.

An MA holder making a change to an approved vaccine should also conform to other applicable laws and regulations, including good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP). MA holders 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 of equipment used in the manufacturing process generally require installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). 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 may occur routinely, may be required before submission of a supplement for a major manufacturing change such as a move to a new facility, or may be triggered by a major manufacturing change such as a change in production capacity or filtration or purification systems.

Certain major changes, such as changes in the vaccine antigen composition (for example, addition of virus or bacterial types), use of new cell substrates (for example, use of cells unrelated to the established master cell bank (MCB) or pre-MCB material) or changes in the composition of vaccine adjuvants are generally considered to be a new product and as such require the submission of a product licence application for a new MA. In addition, in some countries a change in the quantity of antigen per dose of vaccine also requires a product licence application for a new MA (see section 8.2 for changes to the seasonal influenza virus vaccine composition; and Appendix 2 (changes 9.a and 10.a) for information on changes to the cell banks and seed lots, respectively).

Administrative changes related to acquisitions and mergers, company names or contact information should be submitted directly to the NRA as general correspondence to the MA or product licence. When these changes affect the product labelling information, the revised labelling items should be submitted to the NRA, as described in this document (see section 6.4).

The implementation of new regulations should not affect vaccine supply and access by the public to vaccines. NRAs are therefore strongly encouraged to establish requirements that are commensurate with public health priorities and with their own regulatory capacity and resources. NRAs of vaccine-procuring countries should strongly consider establishing alternative procedures for the expedited approval of changes on the basis of previous expert review and approval of the same changes by the NRAs of countries in which the vaccines are produced and/or licensed, or on the basis of decisions made by 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 to support the change, as outlined in this document. Nevertheless, responsibility for the final regulatory decision on the approval of the change will still lie with the receiving NRA (see section 7 and Appendix 1).

To ensure vaccine supply and encourage adequate reporting of changes by manufacturers, NRAs should also consider establishing procedures for the concurrent (that is, parallel) review of changes to each product. Vaccine production requires the replenishment of biological starting materials such as cell banks, seed lots and reference standards, which are considered routine changes beyond the control of manufacturers. Consequently, these changes often need to be reviewed concurrently with other manufacturing or safety and efficacy changes. Similarly, clinical safety and efficacy changes, such as the addition of a new indication for a vaccine or a new age group for use of a vaccine, require considerable supporting data and review time and should not preclude or impede the review of unrelated manufacturing changes or the immediate implementation of urgent changes to product labelling information. However, multiple related changes may be submitted in the same supplement (see section 7).

The establishment of regional NRA associations or networks that can serve as forums for sharing information and exchanging experience on technical issues and regulatory decisions is highly encouraged. The development of such networks would expand the capacity of individual NRAs through work-sharing and recognition of the decisions of other NRAs in the network, thus avoiding unnecessary repetition of evaluations of the same change by multiple members of the network. NRA associations should establish work-sharing procedures that ensure the protection of confidential proprietary information with the engagement of MA holders and experts on the proprietary laws of each country. Any regional association or network of NRAs should, at a minimum, ensure the confidential nature of the technical information in the MA or licence application, especially information on product quality.

Establishing networks would be part of capacity-building activities for countries in each region. A fully functional regional network would be a

long-term goal, but cooperation can begin in the short term with the sharing of scientific information and experience regarding regulatory decisions on the evaluation of changes to approved products. Meetings should be organized periodically to promote transparency and mutual confidence between the NRAs. Effective regional networks could serve as the foundations for achieving full mutual recognition among NRAs.

In these WHO Guidelines, descriptions of the reporting categories are provided for both quality changes (section 5) and for safety, efficacy and product labelling information changes (section 6). Proposed recommendations on the regulatory procedures for the reporting of changes to NRAs are described in section 7. 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 antigen and intermediates) and Appendix 3 (for the final product). Examples of changes that affect clinical use and product labelling information (safety, efficacy, dosage, administration, vaccine components and expiry date) are provided in Appendix 4.

## 4. Terminology

The definitions given below apply to the terms as used in these WHO Guidelines. They may have different meanings in other contexts, including the compendial references and regulations or guidelines issued by NRAs and by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

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

**Antigen:** the following definitions apply in this document:

- The active ingredient in a vaccine against which the immune response is induced. Antigens may be: (a) live attenuated or inactivated preparations of bacteria, viruses or parasites; (b) crude cellular fractions or purified antigens, including recombinant proteins (that is, those derived from recombinant DNA expressed in a host cell); (c) polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids; (d) synthetic antigens; (e) polynucleotides (such as plasmid DNA vaccines); or (f) living vectored cells expressing specific heterologous antigens. Also referred to as “immunogen” in other documents.

- Also used to describe (a) a component that may undergo chemical change or processing before it becomes the antigen or active ingredient used to formulate the final product (also referred to as an “intermediate” in other documents); or (b) an active ingredient present in an unmodified form in the final product (also referred to as “drug substance” or “active substance” in other documents). For example, in this document the term “antigen” applies, in the case of a polysaccharide conjugated vaccine, to the polysaccharide intermediate as well as to the conjugated polysaccharide that will not undergo further modification prior to formulation.

**Cell bank:** a collection of vials of cells of uniform composition (though not necessarily clonal) derived from a single tissue or cell, and used for the production of a vaccine directly or via a cell bank system. The following terms are used in these Guidelines – **master cell bank (MCB):** a bank of a cell substrate from which all subsequent cell banks used for vaccine production will be derived. The MCB represents a well characterized collection of cells derived from a single tissue or cell; and **working cell bank (WCB):** a cell bank derived by propagation of cells from an MCB under defined conditions and used to initiate production of cell cultures on a lot-by-lot basis. Also referred to as “manufacturer’s working cell bank” in other documents.

**Change:** refers to a change that includes, but is not limited to, the product composition, manufacturing process, quality controls, equipment, facilities or product labelling information made to an approved MA or licence by the MA holder. Also referred to as “variation” in other documents.

**Comparability study:** the activities, including study design, conducting of studies and data evaluation that are designed to investigate whether the pre- and post-change products are comparable. In addition to routine analysis performed during production and control of the antigen or final product, these evaluations typically include a comparison of manufacturing process steps and parameters impacted by the change, characterization studies and an evaluation of product stability following the change. In some cases, nonclinical or clinical data might contribute to the conclusion reached.

**Comparability protocol:** establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of a negative effect of specific manufacturing changes on the safety or effectiveness of the product. A comparability protocol is a highly specific, well defined plan for the future implementation of a quality (that is, manufacturing) change. Also referred to as “post-approval change management protocol” in other documents.

**Container closure system:** refers to the following components: (a) a primary container closure system is a packaging component (for example, a vial or pre-filled syringe) that is in, or may come into, direct contact with the final

product dosage form, or components that contribute to the container/closure integrity of the primary packaging material for a sterile product; and (b) a secondary container closure system is a packaging component (for example, a carton or tray) that is not, and will not be, in direct contact with the dosage form.

**Dosage form:** in this document “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.

**Excipient:** any component of the final product other than the active component/antigen and the packaging material. Also referred to as “inactive ingredient” in other documents. In the context of this document, adjuvants are not considered to be excipients.

**Final lot:** a collection of sealed final containers that is homogeneous with respect to the composition of the product and the risk of contamination during filling. A final lot must therefore have been filled from a formulated bulk in one continuous working session.

**Final product:** a finished dosage form (for example, suspension or lyophilized cake) that contains an active ingredient, generally but not necessarily in association with inactive ingredients (excipients) or adjuvants. Also referred to as “finished product” or “drug product” in other documents.

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

**Intermediate:** a material produced during steps in the manufacture of a vaccine that undergoes further processing before it becomes the final product. See the definition for **Antigen** above.

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

**Marketing authorization (MA):** a formal authorization for a medicine to be marketed. Once an NRA approves an MA application for a new medicine, the medicine may be marketed and may be available for physicians to prescribe. Also referred to as “product licence” or “licence” in this and other documents.

**Marketing authorization application (MA application):** a formal application to the NRA for approval to market a new medicine. The purpose of the MA application is to determine whether the medicine meets the statutory standards for safety, effectiveness, product labelling information and manufacturing. Also referred to as “licence application” in other documents.

**Marketing authorization holder (MA holder):** any person or legal entity that has received MA or licensure to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the MA or licence. Also referred to as the “manufacturer” or “applicant” in this and other documents.

**Product labelling information:** printed materials that accompany a prescription medicine and all labelling items, namely: (a) prescribing information (an instruction circular that provides product information on indication, dosage and administration, safety and efficacy, contraindications and warnings, along with a description of the product for health care providers (also referred to as “summary of product characteristics” or “package insert” in various countries); (b) patient labelling or consumer information; (c) inner label or container label; and (d) outer label or carton.

**Quality attribute:** a physical, chemical, biological or microbiological property or characteristic. A critical quality attribute refers to a characteristic or property that should be within an appropriate limit, range or distribution to ensure the desired product quality.

**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 reagents or solvents intended for use in the production of starting materials, intermediates or final products.

**Seed lot:** a preparation of live cells (prokaryotic or eukaryotic) or viruses constituting the starting material for the vaccine antigen. A seed lot is of uniform composition (although not necessarily clonal), is derived from a single culture process and is aliquoted into appropriate storage containers, from which all future vaccine production will be derived either directly or via a seed lot system. The following derived terms are used in these Guidelines – **master seed lot (MSL):** a lot or bank of cells or viruses from which all future vaccine production will be derived. The MSL represents a well characterized collection of cells or viruses of uniform composition. Also referred to as “master virus seed” for virus seeds, “master seed bank” or “master seed antigen” in other documents; and **working seed lot (WSL):** a cell or viral seed lot derived by propagation from the MSL under defined conditions and used to initiate production of vaccines on a lot-by-lot basis. Also referred to as “working virus seed” for virus seeds, “working seed bank” or “working seed antigen” in other documents.

**Specification:** the quality standard (that is, tests, analytical procedures and acceptance criteria) provided in an approved application to confirm the quality of antigens (drug substances), final products (drug products), intermediates, raw materials, reagents, components, in-process materials, container closure systems

and other materials used in the production of the antigen (drug substance) or final product (drug product). For the purpose of this definition, acceptance criteria mean numerical limits, ranges or qualitative criteria for the applied tests.

**Starting material:** any material used at the beginning of the manufacturing process, as described in an MA or product licence. Generally, the term refers to a substance of defined chemical properties and structure that contributes an important and/or significant structural element (or elements) to the active substance (for example in the case of vaccines, synthetic peptides, synthetic glycans and starting materials for adjuvants). The starting material for an antigen (drug substance) obtained from a biological source is considered to consist of: (a) cells; (b) microorganisms; (c) plants, plant parts, macroscopic fungi or algae; or (d) animal tissues, organs or body fluid from which the antigen (drug substance) is derived.

**Supplement:** written request submitted to the NRA to approve a change in the original application for MA (or product licence) or any other notification to add to (that is, supplement) the information in the original MA 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.

**Vaccine:** a preparation containing antigens capable of inducing an active immune response for the prevention, amelioration or treatment of infectious diseases.

**Vaccine efficacy:** the relative reduction in disease incidence or severity in vaccinated individuals compared to unvaccinated individuals measured in a randomized, placebo-controlled clinical trial. In the context of these Guidelines, vaccine efficacy has a broad meaning and relates to all clinical data obtained to ensure vaccine efficacy, immunogenicity or field effectiveness.

## 5. Reporting categories for quality changes

Based on the potential effect of the quality change (for example, manufacturing change) on the quality attributes (that is, identity, strength, purity and potency) of the vaccine, and the potential impact of this on the safety or efficacy of the vaccine, a change should be categorized and identified as:

- a major quality change
- a moderate quality change, or
- a minor quality change.

The implementation of changes in the major or moderate categories requires reporting to the NRA in order to supplement the information in the

original MA or product licence. The major and moderate quality changes should be reviewed and approved by the NRA prior to implementation of the change.

Minor quality changes that are expected to have a potential minimal effect or no effect on the quality, safety or efficacy of the vaccine do not require submission of a supplement. The changes included in this category may be implemented by the MA holder without prior review and approval by the NRA. However, a list of minor changes should be made available by the MA holder upon request by the NRA.

Further information on each category is given below. In addition, Appendices 2 and 3 provide a comprehensive list of major, moderate and minor quality changes, and the information required to support each change. Appendix 2 includes changes to the antigen or intermediates and Appendix 3 includes changes to the final product. 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 or efficacy of the vaccine, 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 based on a change-specific risk assessment using the principles and examples provided in this document. The NRA should consider establishing a mechanism that allows for the updating of its guidelines to address technological changes that require new regulatory category classifications.

### 5.1 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 vaccine. The MA holder should submit a PAS and receive a notification of approval from the NRA before implementing the change. For a change in this category, the supplement should specify the products concerned and should include a detailed description of the proposed change. Additional supporting information is needed, as noted in Appendix 2 for the antigen and in Appendix 3 for the final product, and should include information on: (a) the methods used and studies performed to evaluate the effect of the change on the product's quality attributes; (b) the data derived from those studies; (c) relevant validation protocols and results; (d) updated product labelling information; and (e) summaries of relevant standard operating procedures (SOPs) or a list referencing previously approved relevant SOPs. In some cases, major quality changes may also require nonclinical and/or clinical data. The recommendations given in WHO guidelines on nonclinical evaluation of vaccines (4), Guidelines on clinical evaluation of vaccines: regulatory

expectations (5), Guidelines on stability evaluation of vaccines (6), other related WHO guidance (7–12), and recommendations for specific products and adjuvants should apply.

## 5.2 Moderate quality changes

Moderate quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a moderate potential to have an impact on the quality, safety or efficacy of the vaccine. The MA holder should submit a supplement and receive a notification of approval from the NRA before implementing the change. The requirements for the supplement content of the moderate quality changes are the same as for the major quality changes (see section 5.1 above). However, the amount of supporting data required will generally be less than for major changes and the review time should be shorter.

## 5.3 Minor quality changes

Minor quality changes are changes to the product composition, manufacturing process, quality controls, facilities or equipment that have a minimal potential to have an impact on the quality, safety or efficacy of the vaccine. The changes included in this category may be implemented by the MA holder without prior review by the NRA (that is, such changes do not need to be reported to and approved by the NRA). However, these changes must be retained as part of the product's record by the manufacturer or MA holder, must comply with GMP requirements and must be available for review during GMP inspections.

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

For each approved product, the MA holder or manufacturer should maintain a comprehensive chronological list of all quality changes, including minor quality changes that occur in all production areas. Additionally, this list should include a description of the manufacturing and quality control changes, including the manufacturing site(s) or area(s) involved, the date each change was made, and the references of relevant validations and SOPs. The data to support minor quality changes, as listed in Appendices 2 and 3, should be available to the NRA upon request or during inspections.

When minor quality changes are related to a major or moderate change, they should be described in the supplement for the major or moderate quality change (see section 7.2).

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

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

- 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 before implementation is needed).

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

Further information on each category is provided in the following sections, with examples of efficacy, safety and product labelling information changes considered to be appropriate for each category provided in Appendix 4.

### 6.1 Safety and efficacy changes

Safety and efficacy changes are changes that have an impact on the clinical use of the vaccine in relation to safety, efficacy, dosage and administration, and that require data from clinical studies to support the change. Safety and efficacy changes require supplement submission and approval prior to implementation.

Generally, safety and efficacy changes affect the product labelling information and have the potential to increase or decrease the exposure levels of the vaccine, either by expanding the population that is exposed or by changing dosage or dosing. These changes may relate to the clinical use of the vaccine, for example:

- 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;<sup>1</sup>

<sup>1</sup> Some NRAs consider that changes in the route of administration or strength may require a new MA. Furthermore, in some cases, changes involving the subcutaneous and intramuscular administration routes may not require a new application while others, such as changes from intramuscular to intranasal administration routes, may require a new application.

- change in the recommended dose and/or dosing schedule, including the addition of a booster dose;
- co-administration with other vaccines or medicines;
- deletion or reduction of existing risk-management measures (such as contraindications, adverse events, warnings or cautionary text/statements in the product labelling information).

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

- robustness of the immune response elicited by the vaccine and availability of a correlate of protection (that is, data establishing a threshold level of antibody needed to protect against the development of disease following exposure);
- availability of animal models;
- vaccine attributes (for example, live as opposed to inactivated vaccines).

MA holders are encouraged to consult with NRAs on the adequacy of the clinical 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 may also be consulted on the data required to support such changes.

For nonclinical and clinical studies, the recommendations given in WHO guidelines on nonclinical evaluation of vaccines (4), Guidelines on clinical evaluation of vaccines: regulatory expectations (5) and other related WHO guidance (7–12) should apply.

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

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

## 6.2 Product labelling information changes

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

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

Product labelling information changes require supplement submission and approval prior to distribution of the product. Supplements for product labelling information changes related to clinical use often require data from pharmacovigilance reports (“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 MA holder should submit a supplement to the NRA that may include the following:

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

## 6.3 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 currently approved for use of the vaccine. MA holders should consult with the NRA and agree on the supporting documentation required prior to supplement submission.

## 6.4 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 vaccine. 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 follows:

- Examples of product labelling information changes that require approval by the NRA prior to implementation are changes in the name of the MA holder that are due to a merger, or changes in the proper name or trade name of the vaccine. 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 changes to a distributor's address or minor changes in format. These changes should be reported to the NRA as part of subsequent supplements for safety and efficacy changes or product labelling information changes when updated product labelling information is included.

## 7. Procedures

Establishing procedures and criteria for the 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, to be consulted by MA holders when 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, compared to safety and efficacy changes that do require clinical data. Examples of regulatory categories and review timelines are provided in Appendix 1 below.

MA holders may contact the NRA to determine the appropriate category of a supplement prior to submission of the information in support of a change, especially if the change is not included in Appendices 2–4 of this document. Similarly, MA holders may also consult NRAs for major changes (such as the introduction of new equipment, change in process step or facility expansion) that require the inclusion of a GMP certificate and may trigger a pre-submission inspection, or that may require clinical data to support a change in safety and efficacy or in product labelling information. MA 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 aid NRAs in planning the allocation of review resources. NRAs should establish procedures for the conducting and recording of communications between themselves and MA holders.

To aid in the acceptance of submissions for review, the covering letter accompanying a supplement for a quality change should specify that the change is being reported in the selected category by labelling the submission as either a major quality change or a moderate quality change.

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

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

Major quality change supplements that contain both quality data and revised product labelling information but no clinical 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 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 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. The list should be part of the covering letter. If the submission has been inappropriately classified, the MA holder should be notified. Minor quality changes that are related to a moderate or major quality change should be included in the PAS if they were implemented after the submission of a previous supplement for a moderate or major quality change. For example, a minor change such as the 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 whole regulatory framework which incorporates elements such as MA, GMP inspection, lot release and post-marketing surveillance (PMS). These activities are often performed by different branches of the NRA. It is essential that these different branches – particularly the MA (or regulatory affairs), GMP inspection and lot release branches – interact and exchange information effectively and that the roles and responsibilities of each branch are clearly defined, especially when they operate as separate entities. When multiple branches are involved in the evaluation of a supplement, a formal decision-making process should be in place to discuss, for example, whether a change may require a GMP inspection or may be reviewed

during the next routine inspection. Procedures should also be established so that the outcomes of inspections are verified or taken into account prior to the approval of supplements. Good coordination and communication are pivotal.

### **Expedited review procedures**

NRAs of vaccine-procuring countries that decide to recognize 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 vaccines are produced and/or licensed (see Appendix 1). On the basis of regulatory and regional considerations, regulatory procedures for recognizing the decision of other NRAs on the approval of changes could include:

- The NRA recognizes the decision of other regulatory authorities and does not perform a review of supporting data, but is informed of the change. The submission consists of a covering letter from the MA holder informing the procuring NRA of the change and including as an attachment a copy of the approval letter issued by the NRA of the producing and/or licensing country.
- The NRA performs an assessment of the decision of the NRA from the producing and/or licensing country to determine if recognition of that NRA's decision is appropriate. The submission consists of: (a) the covering letter from the MA holder informing the procuring NRA of the change; (b) a copy of the approval letter issued by the NRA of the producing and/or licensing country; (c) assessment reports and relevant correspondence from the NRA of the producing and/or licensing country (if made available by the NRA); and (d) a detailed description of the change with no supporting data.
- The NRA performs a partial review and evaluation of a complete package of supporting data, as originally submitted in the vaccine-producing and/or -licensing country and/or as recommended in these WHO Guidelines.

Similarly, recognition of inspection activities conducted by the authorities in the place where a vaccine is produced may also be considered 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 7.4 and Appendix 1).

In special or urgent circumstances, an MA holder may ask the NRA to expedite the review of a supplement for public health reasons (for example, a vaccine shortage, or during an epidemic or pandemic) or if a delay in making the change would impose extraordinary hardship on the MA holder or manufacturer.

### Multiple changes

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

Multiple major or moderate quality changes for the same vaccine may be filed in a single submission provided that the changes are related and/or supported by the same information. Minor quality changes that were implemented previously and that are related to a moderate or major quality change should be included in the supplement for the moderate or major quality change. If the changes are related, the MA holder should indicate the association between the proposed changes. Such changes could affect both the antigen and the final 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 MA holder to divide the changes into separate submissions and to re-submit 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 vaccine. This reclassification should be communicated to the MA holder at the start of the assessment.

#### 7.1 Procedures for prior approval supplements

The procedures in this section apply to all changes requiring approval prior to implementation: that is, 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: (a) the type of submission (for example, major quality change, moderate quality change, safety and efficacy change); (b) 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; (c) an indication of the general type of supporting data; and (d) cross-referenced information if applicable (including product name, MA holder's name, submission type control number and date of submission/approval);
- Completed documents or forms based on NRA requirements, such as a medicines submission application form, signed and dated;
- The anticipated date for implementation of the change;
- GMP document information, 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) and the proposed ones (see section 5);
- When relevant, clinical study reports, pharmacovigilance reports, and annotated and clean drafts of product labelling information (see section 6).

In addition to the above common information items, the specific information required to support the various quality changes is outlined in Appendices 2 and 3. It should be noted that the common information items listed above are not included under each of the various changes outlined in these appendices. All data recommended to support a change should be provided with the submission along with all appropriate common information items. When recommended supporting data cannot be submitted, a detailed rationale should be provided.

If the same change is applicable to multiple products, a separate submission is generally required for each product but the data may be cross-referenced. When cross-references are made to information that has been submitted previously, the details of the cross-referenced information should be indicated in the covering letter (for example, brand name of the product, name of manufacturer and/or MA holder, submission type, control number and date approved).

Submissions filed in electronic or paper format should be based upon 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 there are two possible outcomes:

- If the NRA determines that the information in a supplement indicates no adverse impact on the quality, safety or efficacy of the product manufactured with the change, the NRA will issue a written approval notification by which 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 MA holder. If the identified deficiencies are minor, they may be addressed without stopping the review clock. If the deficiencies are major or are not resolved during the allotted review time frame, the NRA may decide to issue a written notification of noncompliance by means of which the review clock 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 information in the MA 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 by which the change can be implemented and the product manufactured with the change can be distributed.
- If the information in the MA 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 by means of which 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 the MA holder's 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 MA holders should be properly recorded.

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

In some cases, following approval, the distribution of a vaccine made with a change may be delayed to allow for depletion of the previously approved vaccine or to allow for global approval. Therefore, the MA holders should provide the anticipated date for implementation of the change. If deemed necessary, any issues related to the implementation dates and distribution of product with the approved manufacturing changes should be communicated to the NRA.

NRAs may consider the following approaches when an MA holder is submitting changes.

### **Comparability protocol**

A comparability protocol (also referred to as a “post-approval change management protocol” in other documents) establishes a framework for a well defined and highly specific plan for the future implementation of a quality change, including the tests to be done and acceptable limits to be achieved to demonstrate the lack of negative effects caused by specific manufacturing changes on the quality, safety or efficacy of a vaccine. For some changes, the routine quality tests performed to release the antigen or final product are not considered adequate for assessing the impact of the change, and additional in-process tests and characterization tests may be needed (for example, addition of bioburden and endotoxin tests to support the removal of preservatives from the manufacturing process). 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 allow for a more expedient distribution of a product by permitting the MA 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. This concept is not discussed in further detail in these Guidelines as the use of a comparability protocol is not currently harmonized among NRAs. It is the decision of the NRA whether or not to include the review and approval of comparability protocols in its approach to regulating changes to approved vaccines. For NRAs currently taking this approach, 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 the comparability protocol in relation to the comparability data should be established by the NRA at the time the comparability protocol is approved.

## Production documents

Production documents (that is, executed lot records) are not required to support changes to the MA dossier or product licence. However, such documents may be requested during review and should be available to the NRA upon request or during inspections.

### 7.2 Procedures for minor quality changes

Minor quality changes do not require notification to, or prior approval from, the NRA for their implementation. However, any minor changes that have been implemented should be noted in the affected documents (for example, SOPs and batch records). As recommended in Appendices 2 and 3 of this document, minor quality changes should be recorded or compiled with related supporting data in a document or file dedicated to minor changes. The documents or files for all minor quality changes should be available to the NRA upon request or during inspections.

Minor quality changes that have previously been implemented and are related 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. In general, changes to SOPs which are not mentioned in Appendices 2 and 3 do not need to be submitted to the NRA for approval.

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 the change or the supporting data are not considered to be acceptable, the MA holder may be requested to file a major or moderate quality change supplement.

For changes that are not reported, if the NRA determines (during an inspection or review of related changes) that the information relating to 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 MA holder. If the NRA finds that the product in distribution poses a danger to public health, or if it determines that there are unresolved issues, it may require the MA 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.

### 7.3 Procedures for urgent product labelling information changes

For urgent changes to product labelling information which address safety updates and have the potential to have an impact on public health (for example, the addition of a contraindication or warning) NRAs should establish a specific

mechanism to allow for the immediate or speedy approval and implementation of such changes on a case-by-case basis after previous agreement between NRAs and MA 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 the vaccines are produced and/or licensed may be implemented immediately upon receipt of the supplement by the NRAs of countries procuring the vaccines. Such accelerated procedures would contribute to the dissemination of the most current information to health care providers, and would also help to mitigate the effects of discrepancies between labelling information in different countries and between the information posted on different web sites.

#### 7.4 **Procedures for administrative product labelling information changes**

Administrative product labelling information changes may require approval prior to implementation depending on the scope of the change. For example, changes in the name of the MA holder require approval before implementation while minor formatting changes do not (see Section 6.4).

For an administrative product labelling information change that requires approval prior to implementation, the MA 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 subsequent supplements 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.

## **8. Special considerations**

### 8.1 **Adjuvants**

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

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

## 8.2 Influenza vaccines

To ensure that influenza vaccines are effective against circulating influenza viruses, WHO reviews global virological and epidemiological data twice a year, and if necessary recommends new vaccine strain(s) in accordance with the available evidence for the northern and southern hemispheres (13, 14). WHO and NRAs recommend the use of certain vaccine virus strains on the basis of their antigenic characteristics. Influenza vaccine viruses are usually derived from isolates obtained from laboratories in the WHO Global Influenza Surveillance and Response System.

For seasonal influenza vaccines, annual changes in the vaccine strain composition are considered to be moderate quality changes because of extensive experience with such changes and in order to maximize the flexibility and brevity of the review process. MA holders of approved seasonal vaccines are expected to submit a supplement for a moderate quality change to support annual changes in the influenza strain composition. To allow for the timely distribution of vaccines, NRAs should review the supplement as part of a streamlined and prompt process. The supporting quality information generally consists of: (a) information on the source of the seed viruses; (b) passage history until establishment of working seeds; (c) results of quality release tests performed on working virus seeds (including identity confirmation); and (d) specific validation data (including inactivation kinetics). Generally, stability data for antigen bulks or final drug product produced in the previous influenza season are expected to be submitted to continuously support the approved shelf-life. In addition, updated product labelling information items (package insert and inner and outer labels with relevant strain composition and formula year) should be provided (13).

Changes to the manufacturing processes, posology and product labelling information of influenza vaccines that are not related to the annual update should follow the normal categorization process, as described in Appendices 2–4, and should not be included in the strain change supplements to avoid delays in the approval process. Due to time constraints related to the seasonality of influenza vaccines, changes that are not related to vaccine strain composition should be timed such that approval will allow for vaccines manufactured with the change to be distributed prior to the start of the influenza season.

### 8.3 Bridging studies

Clinical bridging studies are trials in which a parameter of interest (such as manufacturing process, formulation or dosing schedule) is directly compared with a changed version of that parameter with respect to the effect of the change on the product's clinical performance. The comparison of immune responses and safety outcomes (for example, rates of common and serious AEFIs) is often the primary objective. If the immune response and safety profiles are similar, the safety and efficacy of the vaccine can be inferred.

In some cases, safety and efficacy data comparing the approved vaccine to the vaccine produced with the change may be required by NRAs. The following are examples of manufacturing changes that may require clinical bridging studies:

- use of a new or re-derived antigen (that is, re-derived virus seed or bacterial cell bank) or host cell line (that is, re-derived MCB);
- new agents used for inactivation or splitting of the antigen;
- a new dosage form;
- a new formulation (for example, amount of ingredients, adjuvants, preservatives or reactogenic residual components from the manufacturing process).

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# Appendix 1

## Reporting categories and suggested review timelines

It is recommended that NRAs establish review timelines to allow MA holders or applicants to plan the implementation of changes. The review times established will depend upon the capability of the NRA, the impact of the change and the amount of data required to support the change. As a result, the review time frames for major changes should be longer than those for moderate changes. The review times suggested in Table 1 below are shown as examples, based upon 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 MA holder, either by the issuance of an approval notification or a noncompliance notification with a list of comments and deficiencies. In the case of the latter, the MA 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 MA holder. If minor deficiencies are identified during the initial review cycle, the NRA may communicate these to the MA holder without stopping the clock to try to finalize the assessment within the established timeline (see section 7.1).

For product labelling information changes which address urgent safety issues, procedures should be in place to allow for the expedited implementation of such changes (see section 7.4).

For annual updates of influenza virus strain composition, the review timeline of moderate quality change supplements should be as short as possible (around 30 days). This may be achieved by reducing the amount of supporting information required and by clearly describing to MA holders the required content and format of the information to be submitted (see section 8.2).

Table 1  
Examples of review timelines for a prior approval supplement (PAS)

Category	Supplement	Maximum review period
<b>Quality changes</b>		
<b>Major quality changes</b>	PAS	6 months
<b>Moderate quality changes</b>	PAS	3 months

Table 1 *continued*

Category	Supplement	Maximum review period
<b>Quality changes</b>		
Minor quality changes	Do not require notification to the NRA <sup>a</sup>	N/A
<b>Safety, efficacy and product labelling information changes</b>		
Safety and efficacy changes	PAS	10 months
Product labelling information changes	PAS	5 months
Urgent product labelling information changes <sup>b</sup>	PAS for urgent safety restrictions	Immediate implementation on receipt of supplement by the NRA
Administrative product labelling information changes	PAS Do not require approval prior to implementation <sup>c</sup>	30 days N/A

N/A: not applicable.

<sup>a</sup> Minor quality changes that are related to a moderate or major quality change should be included in the PAS if they have been implemented after the submission of a previous supplement for a moderate or major quality change (for example, a minor change such as the narrowing of a specification should be included in a supplement for a moderate or major change which includes updated quality control release information).

<sup>b</sup> 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 MA holders.

<sup>c</sup> 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 supplements for safety and efficacy changes or product labelling information changes.

NRAs of countries that procure vaccines from countries where the vaccines are produced and/or licensed are encouraged to establish alternative regulatory procedures for the expedited approval of changes that have previously been approved by the licensing NRAs. As described in section 7 above, expedited regulatory approval procedures that could be established include:

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

- The NRA performs an assessment of the decision of the NRA of the producing and/or licensing country to determine if recognition of the latter's decision is appropriate. In this case, NRAs could establish abbreviated review timelines, such as 2 months for major quality changes, 4 months for safety and efficacy changes, and immediate implementation upon 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 package of supporting data, as originally submitted in the vaccine producing and/or licensing country and/or as recommended in these WHO Guidelines. In this case, timelines could range from those shown in Table 1 or could be abbreviated as described in the preceding bullet point.

## Appendix 2

### Changes to the antigen

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information for a vaccine antigen. The information summarized in the antigen table below provides recommendations 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 the next higher level of change – for example, if any conditions recommended for a moderate quality change are not fulfilled, the change is considered to be a major quality change);
- the *supporting data* for a given change, either to be submitted to the NRA or maintained by the MA holder (if any of the supporting data outlined for a given change are not provided, are different or are not considered applicable then adequate scientific justification should be provided);
- the *reporting category* (that is, major, moderate or minor quality change).

It is important to note that the NRA reserves the right to request additional information or material, as deemed appropriate, or to define conditions not specifically described in this document in order to allow for adequate assessment of the quality, safety and efficacy of a vaccine. In addition, MA holders should contact the NRA if a change not included in the antigen table below has the potential to impact upon vaccine quality.

Supporting data should be provided according to the submission format accepted by the NRA. For example, for NRAs that accept the ICH common technical document (CTD) and/or ICH eCTD formatted submissions, the supporting data should be provided in the appropriate sections of the CTD modules and not in separate documents. For the placement of data in the appropriate section of the CTD please see the ICH guidelines (1, 2).

For additional information on data requirements to support quality changes, WHO guidelines on GMP requirements and stability evaluation of vaccines (3, 4) should be consulted, together with relevant ICH guidelines.

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

NRAs should make a list of the recognized compendia and/or pharmacopoeia available to MA holders. Manufacturers are expected to comply with the current versions of compendia and/or pharmacopoeia as referenced in the approved MA. Changes in the compendial and/or pharmacopoeial methods or specifications referenced by a particular NRA do not need to be submitted for review, but information on such changes should be available for inspection.

In some cases, changes to comply with recognized compendia and/or pharmacopoeia may require approval by the NRA prior to implementation regardless of the timing of the change with respect to the date 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 (for example, tests for potency), for changes which have an impact on any items of the product labelling information, and for changes which may potentially affect the quality, safety or efficacy of the product.

## Quality changes affecting lot release

Where post-approval changes to the antigen affect the lot release protocol (for example, changes to test procedures, reference standards or laboratory sites) or sample testing requirements for lot release, the MA holder should inform the institution responsible for reviewing the release of vaccine lots. These procedures apply to changes that have been authorized by the NRA in the case of major and moderate quality changes and to changes that have been implemented in the case of minor quality changes. For example, the qualification of a new lot of reference standard against the approved reference standard may be considered a minor quality change if the qualification of a new standard is done in accordance with an approved protocol and specification. Nevertheless, these changes must be reported to the NRA or NCL as appropriate.

## General information

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>1. Change in the name of the antigen</b>	None	1, 2	Moderate
<i>Note: This change generally applies only to influenza vaccines (see section 8.2).</i>			
<b>Conditions</b>			
None			

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>Supporting data</b>			
1. Revised product labelling information (all labelling items).			
2. Information on the proposed nomenclature of the antigen and evidence that the proposed name for the antigen is recognized (for example, proof of acceptance by WHO).			

## Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>2. Change to an antigen manufacturing facility:</b>			
a. replacement or addition of a manufacturing facility for the antigen bulk, or any intermediate of the antigen	None	1–4, 6–8	Major
	1–4	2, 4–8	Moderate
b. deletion of a manufacturing facility or manufacturer of an antigen intermediate, or antigen bulk	5, 6	None	Minor

### Conditions

1. The new manufacturing facility/suite is an approved antigen manufacturing site.
2. Any changes to the manufacturing process and/or controls are considered either moderate or minor.
3. The new facility/suite is under the same quality assurance/quality control (QA/QC) 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 (such as recurrent deviations, recurrent out-of-specification events, environmental monitoring failures and so on).

### Supporting data

1. Evidence that the facility is GMP compliant.
2. Name, address and responsibility of the proposed facility.
3. Process validation study reports.

Table continued

**Supporting data**

4. Comparability of the pre- and post-change antigen 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 vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine 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 and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
7. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen 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, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
8. Updated post-approval stability protocol.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>3. Change to the antigen fermentation, viral propagation or cellular propagation process:</b>			
a. a critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, incorporation of disposable bioreactor technology)	None	1–7, 9, 11	Major

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
b. a change with moderate potential to have an impact on the quality of the antigen or final product (for example, extension of the in vitro cell age beyond validated parameters)	2, 4	1–6, 8, 10	Moderate
c. a noncritical change with minimal potential to have an impact on the quality of the antigen or final product (for example, 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; or duplication of a fermentation train)	1–6, 9–11	1–4	Minor
<b>4. Change to the antigen purification process involving:</b>			
a. a critical change (a change with high potential to have an impact on the quality of the antigen or final product) (for example, a change that could potentially have an impact on the viral clearance capacity of the process or the impurity profile of the antigen)	None	1, 2, 5–7, 9, 11, 12	Major
b. a change with moderate potential to have an impact on the quality of the antigen or final product (for example, a change in the chemical separation method, such as from ion-exchange HPLC to reverse-phase HPLC)	2, 4	1, 2, 5–7, 10, 11	Moderate

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
c. a noncritical change with minimal potential to have an impact on the quality of the antigen or final product (for example, addition of an in-line filtration step equivalent to the approved filtration step)	1–5	1, 2	Minor
<b>5. Change in scale of the manufacturing process:</b>			
a. at the fermentation, viral propagation or cellular propagation stage	3–6, 11–13	2, 3, 5–7, 9, 11	Moderate
b. at the purification stage	1, 3, 5, 7	2, 5–7, 9, 11	Moderate
<b>6. Change in supplier of raw materials of biological origin (for example, fetal calf serum, human serum albumin, trypsin)</b>			
	None	4, 8, 12, 13	Moderate
	8	4, 8	Minor
<b>7. Change in source of raw materials of biological origin</b>			
	None	4, 7, 12, 13	Moderate
	8	4, 7	Minor
<b>8. Introduction of reprocessing steps</b>	14	8, 10, 11, 14	Moderate

**Conditions**

1. No change in the principle of the sterilization procedures of the antigen.
2. The change does not have an impact on the viral clearance data or the chemical nature of an inactivating agent.
3. No change in the antigen specification outside the approved limits.
4. No change in the impurity profile of the antigen outside the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The change in scale is linear with respect to the proportionality of production parameters and materials.
8. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).
9. The new fermentation train is identical to the approved fermentation train(s).
10. No change in the approved in vitro cell age.
11. The change is not expected to have an impact on the quality, safety or efficacy of the final product.

Table *continued*

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**Conditions**

12. No change in the proportionality of the raw materials (that is, the change in scale is linear).
  13. The change in scale involves the use of the same bioreactor (that is, it does not involve the use of a larger bioreactor).
  14. The need for reprocessing is not due to recurrent deviations from the validated process and the root cause triggering reprocessing is identified.
- 

**Supporting data**

1. Justification for the classification of the change(s) as critical, moderate or noncritical as this relates to the impact on the quality of the antigen.
  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 antigen for non-recombinant product.
  4. For antigens obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, and use and previous acceptance of the material) (5).
  5. Process validation study reports.
  6. Comparability of the pre- and post-change antigen 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 vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
  7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
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Table continued

### Supporting data

8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. 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 MA holder if outside the specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen 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, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least one (1) commercial-scale antigen batch produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months of testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen 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 and agreed by the NRA.
11. Updated post-approval stability protocol and stability commitment to place the first commercial-scale batch of the final product manufactured using the post-change antigen into the stability programme.
12. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on viral clearance studies and BSE/TSE risk) (5).
13. Information demonstrating comparability of the raw materials/reagents of both sources.
14. Data describing the root cause triggering the reprocessing, as well as validation data (for example, extended hold-times and resistance to additional mechanical stress) to help prevent the reprocessing from having an impact on the antigen.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>9. Change to the cell banks:</b>			
<i>Note: New cell substrates that are unrelated to the licensed master cell bank (MCB) or pre-MCB material generally require a new application for MA or licence application.</i>			
a. generation of a new MCB	1	1, 2, 5, 7–9	Moderate
b. generation of a new working cell bank (WCB)	None	1, 2	Moderate
	2–4	1, 2	Minor
c. change in cell bank storage site	7	10	Minor
<b>10. Change to the seed lots:</b>			
<i>Note: New viral or bacterial seeds that are unrelated to the master seed lot (MSL) or pre-MSL material generally require a new application for MA or licence application.</i>			
a. generation of a new MSL	1	1, 5–9, 11	Major
b. generation of a new working seed lot (WSL)	2, 3	5–9, 11	Moderate
	2–4	5–6	Minor
c. generation of a new WSL by extending the passage level of an existing WSL beyond an approved level	None	5–7, 11	Moderate
d. change in seed lot storage site	7	10	Minor
<b>11. Change in cell bank/seed lot testing/storage site</b>	5, 7	10	Minor
<b>12. Change in cell bank/seed lot qualification protocol</b>	None	3, 4	Moderate
	6	4	Minor

**Conditions**

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

Table continued

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**Supporting data**

1. Qualification of the cell bank or seed lot 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/seed lot qualification protocol.
  4. Updated cell bank/seed lot qualification protocol.
  5. Comparability of the pre- and post-change antigen 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 vaccine, existing relevant nonclinical and clinical data, and aspects of vaccine use.
  6. Quality control test results as quantitative data in tabular format for the new seed lot.
  7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the antigen derived from the new cell bank/seed lot. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
  8. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen 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, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
  9. Updated post-approval stability protocol.
  10. Evidence that the new company/facility is GMP compliant.
  11. Revised information on the quality and controls of critical starting materials (for example, specific pathogen-free eggs and chickens) used in the generation of the new WSL, where applicable.
-

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>13. Change in equipment used in the antigen manufacturing process, such as:</b>			
a. introduction of new equipment with different operating principles and different product contact material	None	1–6	Moderate
b. introduction of new equipment with the same operating principles but different product contact material	None	1, 3–6	Moderate
c. introduction of new equipment with different operating principles but the same product contact material	None	1–3, 5, 6	Moderate
d. replacement of equipment with equivalent equipment (including filter)	None	1, 5–7	Minor
<b>Conditions</b>			
None			
<b>Supporting data</b>			
1. Information on the in-process control testing.			
2. Process validation study reports.			
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the antigen 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 MA holder if outside specification (with proposed action).			
4. Information on leachables and extractables.			
5. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.			
6. Information demonstrating requalification of the equipment or requalification of the change.			
7. Rationale for regarding the equipment as similar/comparable, as applicable.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>14. Change in specification for the materials, involving:</b>			
a. raw materials/intermediates: widening of the approved specification limits for starting materials/intermediates, which may have a significant effect on the overall quality of the antigen and/or final product and are not changes to the cell banks or seed lots	None	1, 3–6, 8, 11	Moderate
b. raw materials/intermediates: narrowing of the approved specification limits for starting materials/intermediates	1–4	1, 3–7	Minor
<b>15. Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen, involving:</b>			
a. narrowing of in-process limits	3, 5, 8, 9	2, 6	Minor
b. addition of new in-process test and limits	4, 5, 10, 11	2–6, 8, 10	Minor
c. deletion of a non-significant in-process test	4–6	2, 6, 9	Minor
d. widening of the approved in-process limits	None	2–6, 8, 10, 11	Moderate
	3–5	2, 6, 8, 10, 11	Minor
e. deletion of an in-process test which may have a significant effect on the overall quality of the antigen	None	2, 6, 8, 10	Moderate
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	2–6, 8, 10	Moderate
<b>16. Change in in-process controls testing site</b>	3–5, 7, 8	12	Minor

**Conditions**

1. The change in specification for the materials is within the approved limits.
2. The grade of the materials is the same or is of higher quality, where appropriate.
3. No change in the antigen specification outside the approved limits.
4. No change in the impurity profile of the antigen outside the approved limits.

Table *continued*

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**Conditions**

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

**Supporting data**

1. Revised information on the quality and controls of the materials (for example, raw materials, starting materials, solvents, reagents and catalysts) used in the manufacture of the post-change antigen.
  2. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen.
  3. Updated antigen specification, if changed.
  4. Copies or summaries of analytical procedures, if new analytical procedures are used.
  5. Validation study reports, if new analytical procedures are used.
  6. Comparative table or description, where applicable, of pre- and post-change in-process tests/limits.
  7. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial-scale batch of the pre- and post-change antigen. 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 MA holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified and agreed by the NRA.
  8. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change antigen. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Matrixing, bracketing, the use of smaller-scale batches and/or the use of fewer than 3 batches may be acceptable where justified and agreed by the NRA.
  9. Justification/risk assessment showing that the attribute is non-significant.
-

Table continued

### Supporting data

10. Justification for the new in-process test and limits.
11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
12. Evidence that the new company/facility is GMP compliant.

## Control of the antigen

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>17. Change affecting the quality control (QC) (release and stability) testing of the antigen, involving:</b>			
a. transfer of the QC testing activities for a non-pharmacopoeial assay to a new company not approved in the current MA or licence	1–3	1, 2	Minor
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company not approved in the current MA or licence	1	1, 2	Minor

### Conditions

1. The transferred QC test is not a potency assay (for example, the test may be a bioassay such as an endotoxin assay or sterility assay).
2. No changes to the test method.
3. Transfer within a site approved in the current MA for the performance of other tests.

### Supporting data

1. Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>18. Change in the specification used to release the antigen, involving:</b>			
a. deletion of a test	None	1, 5, 8	Moderate
b. addition of a test	1–3	1–3, 5	Minor
c. replacement of an analytical procedure	None	1–5	Moderate
d. change in animal species/strains for a test (for example, new species/strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)	None	6, 7	Moderate
e. minor changes to an approved analytical procedure	4–7	1, 4, 5	Minor
f. change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure	4, 7	1–3	Minor
g. widening of an acceptance criterion	None	1, 5, 8	Moderate
h. narrowing of an acceptance criterion	1, 8, 9	1	Minor

**Conditions**

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

Table continued

**Supporting data**

1. Updated antigen specification.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Validation reports, if new analytical procedures are used.
4. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.
5. Justification for deletion of the test or for the proposed antigen specification (for example, tests, acceptance criteria or analytical procedures).
6. Data demonstrating that the change in animals/strains give results comparable to those obtained using the approved animals/strains.
7. Copies of relevant certificate of fitness for use (for example, veterinary certificate).
8. Declaration/evidence that consistency of quality and of the production process is maintained.

**Reference standards or materials**

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
19. Qualification of a new reference standard against a new primary international standard	None	1, 2	Moderate
20. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	Moderate
21. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	1, 2	Minor
22. Change to reference standard qualification protocol	None	3, 4	Moderate
23. Extension of reference standard shelf-life	2	5	Minor

Table *continued***Conditions**

1. Qualification of the new reference standard is according to an approved protocol.
2. The extension of the shelf-life is according to an approved protocol.

**Supporting data**

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

**Container closure system**

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>24. Change in the primary container closure system(s) for the storage and shipment of the antigen</b>	None	1, 2, 4, 5	Moderate
	1	1, 3, 5	Minor

**Conditions**

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.

**Supporting data**

1. Information on the proposed container closure system (for example, description, composition, materials of construction of primary packaging components and specification).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (for example, results of transportation or interaction studies, and extractable/leachable studies).

Table continued

### Supporting data

4. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale antigen batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the antigen 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, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
5. Comparative table of pre- and post-change specifications.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>25. Change in the specification of the primary container closure system for the antigen, involving:</b>			
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 nor result in a potential impact on the performance of the antigen.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.

Table continued

**Conditions**

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 and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect a new pharmacopoeial monograph specification for the container closure component.

**Supporting data**

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

**Stability**

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>26. Change in the shelf-life/hold-time for the antigen or for a stored intermediate of the antigen, involving:</b>			
a. extension	None	1–5	Moderate
	1–5	1, 2, 5	Minor
b. reduction	None	1–5	Moderate
	6	2–4	Minor

**Conditions**

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

Table continued

**Supporting data**

1. Summary of stability testing and results (for example, studies conducted, protocols used and results obtained).
2. Proposed storage conditions and shelf-life, as appropriate.
3. Updated post-approval stability protocol and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the antigen. Under special circumstances and with prior agreement of the NRA, interim stability testing results and a commitment to notify the NRA of any failures in the ongoing long-term stability studies may be provided.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>27. Change in the post-approval stability protocol of the antigen, involving:</b>			
a. significant 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	1–6	Moderate
	1	1, 2, 4–6	Minor
b. addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c. addition of test(s) into the post-approval stability protocol	2	1, 2, 4, 6	Minor
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	3	4, 6	Minor

**Conditions**

1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

Table continued

**Conditions**

2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
3. The approved antigen shelf-life is at least 24 months.

**Supporting data**

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>28. Change in the storage conditions for the antigen, involving:</b>			
a. addition or change of storage condition for the antigen (for example, widening or narrowing of a temperature criterion)	None	1–4	Moderate
	1, 2	1–3	Minor

**Conditions**

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change consists in the 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 labelled storage conditions/cautionary statement.
4. Results of stability testing (that is, full real-time/real-temperature stability data covering the proposed shelf-life generated on at least three (3) commercial-scale batches).

## References

1. The common technical document for the registration of pharmaceuticals for human use: quality – M4Q(R1) (Step 4 version, 12 September 2002). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2002 ([http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/CTD/M4\\_R1\\_Quality/M4Q\\_\\_R1\\_.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf), accessed 14 December 2014).
2. M4Q Implementation Working Group. Questions & Answers (R1) (Current version, 17 July 2003). 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/CTD/M4\\_R1\\_Quality/M4\\_Quality\\_Questions\\_Answers\\_R1.pdf](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. Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: forty-second report. Geneva: World Health Organization; 1992: Annex 1 (WHO Technical Report Series, No. 822; [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_822.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf?ua=1), accessed 2 December 2014).
4. Guidelines on stability evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: fifty-seventh report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 962; [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_962\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_962_eng.pdf?ua=1), accessed 2 December 2014).
5. 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).

## Appendix 3

### Changes to the final product

The examples presented in this appendix are intended to assist with the classification of changes made to the quality information of the final product. The information summarized in the final product table below provides recommendations 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 the next higher level of change – for example, if any conditions recommended for a moderate quality change are not fulfilled, the change is considered to be a major quality change);
- the *supporting data* for a given change, either to be submitted to the NRA or maintained by the MA holder (if any of the supporting data outlined for a given change are not provided, are different or are not considered applicable then adequate scientific justification should be provided);
- the *reporting category* (that is, major, moderate or minor quality change).

It is important to note that the NRA reserves the right to request additional information or material, as deemed appropriate, or to define conditions not specifically described in this document in order to allow for adequate assessment of the quality, safety and efficacy of a vaccine. In addition, MA holders should contact the NRA if a change not included in the final product table below has the potential to impact upon vaccine quality.

Supporting data should be provided according to the submission format accepted by the NRA. For example, for NRAs that accept the ICH common technical document (CTD) and/or ICH eCTD formatted submissions, the supporting data should be provided in the appropriate sections of the CTD modules and not in separate documents. For the placement of data in the appropriate section of the CTD please see the ICH guidelines (1, 2).

For additional information on data requirements to support quality changes, WHO guidelines on GMP requirements and stability evaluation of vaccines (3, 4) should be consulted, together with relevant ICH guidelines.

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

NRAs should make a list of the recognized compendia and/or pharmacopoeia available to MA holders. Manufacturers are expected to comply with the current versions of compendia and/or pharmacopoeia as referenced in the approved MA. Changes in the compendial and/or pharmacopoeial methods or specifications referenced by a particular NRA do not need to be submitted for review, but information on such changes should be available for inspection.

In some cases, changes to comply with recognized compendia and/or pharmacopoeia may require approval by the NRA prior to implementation regardless of the timing of the change with respect to the date 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 (for example, tests for potency), for changes which have an impact on any items of the product labelling information, and for changes which may potentially affect the quality, safety or efficacy of the product.

## Quality changes affecting lot release

Where post-approval changes to the final product affect the lot release protocol (for example, changes to test procedures, reference standards or laboratory sites) or sample testing requirements for lot release, the MA holder should inform the institution responsible for reviewing the release of vaccine lots. These procedures apply to changes that have been authorized by the NRA in the case of major and moderate quality changes and to changes that have been implemented in the case of minor quality changes. For example, the qualification of a new lot of reference standard against the approved reference standard may be considered a minor quality change if the qualification of a new standard is done in accordance with an approved protocol and specification. Nevertheless, these changes must be reported to the NRA or NCL as appropriate.

## Description and composition of the final product

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

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Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>29. Change in the description or composition of the final product, involving:</b>			
a. addition of a dosage form or change in the formulation (for example, lyophilized powder to liquid, change in the amount of excipient or new diluent for lyophilized product)	None	1–10	Major
<i>Note: Change in formulation does not include changes in antigen(s) or adjuvants. A change in antigen(s) or adjuvant(s) requires the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.</i>			
b. change in fill volume (that is, same concentration, different volume)	None	1, 5, 7, 10	Major
	1, 2	1, 5, 7	Moderate
	1–3	5, 7	Minor
c. addition of a new presentation (for example, addition of a new pre-filled syringe where the approved presentation is a vial for a vaccine in a liquid dosage form)	None	1, 5, 7–10	Major

**Conditions**

1. No changes classified as major in the manufacturing process to accommodate the new fill volume.
2. No change in the dose recommended.
3. Narrowing of fill volume while maintaining the lower limit of extractable volume.

**Supporting data**

1. Revised final product labelling information (as applicable).
2. Characterization data demonstrating that the conformation and immunogenicity of the antigen is comparable in the new dosage form and/or formulation.
3. Description and composition of the dosage form if there are changes to the composition or dose.
4. Discussion of the components of the final product, as appropriate (for example, choice of excipients, compatibility of antigen and excipients, leachates or compatibility with new container closure system, as appropriate).

Table continued

### Supporting data

5. Information on the batch formula, manufacturing process and process controls, control of critical steps and intermediates, and process validation study reports.
6. Control of excipients, if new excipients are proposed (for example, specification).
7. Information on specification, analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three (3) consecutive commercial-scale batches should be provided). Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
8. Information on the container closure system and leachables and extractables, if any of the components have changed (for example, description, materials of construction and summary of specification).
9. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
10. Supporting clinical data or a justification for why such studies are not needed.

## Description and composition of the final product: change to an adjuvant

Note:

- *Change in type/structure of a chemical adjuvant, in the type of a biological adjuvant or in a component of a biological adjuvant may necessitate the filing of a new application for MA or licensure. MA holders are encouraged to contact the NRA for further guidance.*
- *For additional guidance on the required supporting data for quality changes for chemical and biological adjuvants, see recommendations for other changes to the final product, such as changes to facilities, equipment, manufacturing process, quality control, shelf-life, and so on, as applicable.*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>30. Change involving an approved chemical/synthetic adjuvant:</b>			
a. change in supplier of a chemical/synthetic adjuvant	None	4, 5, 10, 11	Moderate
	1–3	5	Minor
b. change in manufacture of a chemical/synthetic adjuvant	None	3–5, 10, 11	Moderate
c. change in specification of a chemical/synthetic adjuvant (including tests and/or the analytical procedures)	None	7–11	Moderate
	1, 3	7–9	Minor
<b>31. Change involving a biological adjuvant:</b>			
a. change in supplier of a biological adjuvant	None	1–7, 10–13	Major
b. change in manufacture of a biological adjuvant	None	1–7, 10–12	Major
	4	1–7, 10–12	Moderate
c. change in specification of a biological adjuvant (including tests and/or the analytical procedures)	None	6–10	Moderate
	1, 3	7–8	Minor
<b>Conditions</b>			
1. The specification of the adjuvant is equal to or narrower than the approved limits (that is, narrowing of acceptance criterion).			
2. The adjuvant is an aluminium salt.			
3. The change in specification consists of the addition of a new test or of a minor change to an analytical procedure.			
4. There is no change in the manufacturer and/or supplier of the adjuvant.			
<b>Supporting data</b>			
1. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, BSE/TSE risk) (5).			
2. Information on the quality and controls of the materials (for example, raw materials, starting materials) used in the manufacture of the proposed adjuvant.			
3. Flow diagram of the proposed manufacturing process(es), a brief narrative description of the proposed manufacturing process(es), and information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.			

Table continued

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**Supporting data**

4. Process validation study reports (for example, for manufacture of the adjuvant) unless otherwise justified.
  5. Description of the general properties, including stability, characteristic features and characterization data of the adjuvant, as appropriate.
  6. Comparability of the pre- and post-change adjuvant 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 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 adjuvant, existing relevant nonclinical and clinical data, and aspects of vaccine use.
  7. Updated copy of the proposed specification for the adjuvant (and updated analytical procedures if applicable).
  8. Copies or summaries of analytical procedures, if new analytical procedures are used.
  9. Validation study reports, if new analytical procedures are used.
  10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the final product with the pre-change (approved) and post-change (proposed) adjuvant, as applicable. Comparative test results for the approved adjuvant do not need to be generated concurrently; relevant historical testing results are acceptable.
  11. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
  12. Supporting nonclinical and clinical data, if applicable.
  13. Evidence that the facility is GMP compliant.
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## Description and composition of the final product: change to a diluent

*Note: Changes to diluents containing adjuvants and/or antigens are considered final products and as such the corresponding changes to final product (not diluent) should be applied.*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>32. Change to the diluent, involving:</b>			
a. change in manufacturing process	None	1–5	Moderate
	1, 3	1–4	Minor
b. replacement of or addition to the source of a diluent	None	1–5	Moderate
	1–3	1–3	Minor
c. change in facility used to manufacture a diluent (same company)	1, 2	1, 3, 5	Minor
d. addition of a diluent filling line	1, 2, 4	1, 3, 5	Minor
e. addition of a diluent into an approved filling line	1, 2	1, 3, 5	Minor
f. deletion of a diluent	None	None	Minor

### Conditions

1. The diluent is water for injection or a salt solution (including buffered salt solutions) – that is, it does not include an ingredient with a functional activity (such as a preservative) and there is no change to its composition.
2. After reconstitution, there is no change in the final product specification outside the approved limits.
3. The proposed diluent is commercially available in the NRA country/jurisdiction.
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 (3) consecutive commercial-scale batches of the approved and proposed diluent. Comparative test results for the approved diluent do not need to be generated concurrently; relevant historical testing results are acceptable.

Table continued

### Supporting data

4. Updated stability data on the product reconstituted with the new diluent.
5. Evidence that the facility is GMP compliant.

## Manufacture

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>33. Change involving a final product manufacturer/ manufacturing facility, such as:</b>			
a. replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)	None	1–7	Major
	1–5	1–3, 5–8	Moderate
b. replacement or addition of a secondary packaging facility, a labelling/storage facility or a distribution facility	2, 3	1–3	Minor
c. deletion of a final product manufacturing facility	None	None	Minor

### Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
2. There is no change in the composition, manufacturing process and final product specification.
3. There is no change in the container/closure system and storage conditions.
4. The same validated manufacturing process is used.
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the products already approved at the site, and also uses the same filling process/equipment.

### Supporting data

1. Name, address and responsibility of the proposed production facility involved in manufacturing and testing.
2. Evidence that the facility is GMP compliant.
3. Confirmation that the manufacturing process description of the final product has not changed as a result of the submission (other than the change in facility), or revised description of the manufacturing process.
4. Comparative description of the manufacturing process if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.

Table continued

**Supporting data**

5. Process validation study reports. The data should include transport between sites, if relevant.
6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
7. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
8. Rationale for considering the proposed formulation/filling facility as equivalent.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>34. Change in the final product manufacturing process, such as:</b>			
a. scale-up of the manufacturing process at the formulation/filling stage	1–4	1–6	Moderate
b. addition or replacement of equipment (for example, formulation tank, filter housing, filling line and head, and lyophilizer); see change 13 above.	None	1–8	Moderate
	5	2, 7–9	Minor
c. addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process	1–4	1, 4	Minor

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
d. addition of a new step (for example, filtration)	3	1–6	Moderate

**Conditions**

1. The proposed scale uses similar/comparable equipment to the approved equipment. Note: Change in equipment size is not considered as using similar/comparable equipment.
2. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch size (for example, the same formulation, controls and SOPs are utilized).
3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the final product.
5. Replacement of equipment with equivalent equipment; the change is considered "like for like" (that is, in terms of product contact material, equipment size and operating principles).

**Supporting data**

1. Description of the manufacturing process, if different from the approved process, and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
2. Information on the in-process control testing, as applicable.
3. Process validation study reports (for example, media fills), as appropriate.
4. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final 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- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

Table continued

**Supporting data**

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. Information demonstrating requalification of the equipment or requalification of the change.
9. Rationale for regarding the equipment as similar/comparable, as applicable.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>35. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:</b>			
a. narrowing of in-process limits	2, 3, 7	1, 5	Minor
b. addition of new in-process test and limits	2, 3, 8, 9	1–6, 8	Minor
c. deletion of a non-significant in-process test	2–4	1, 5, 7	Minor
d. widening of the approved in-process limits	None	1–6, 8, 9	Major
	1–3	1, 5, 6, 8, 9	Moderate
e. deletion of an in-process test which may have a significant effect on the overall quality of the final product	None	1, 5, 6, 8	Major
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	1–6, 8	Moderate
<b>36. Change in in-process controls testing site</b>	1–3, 5, 6	10	Minor

**Conditions**

1. No change in final product specification outside the approved limits.
2. No change in the impurity profile of the final product outside the approved limits.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. The test does not concern a critical attribute (for example, content, impurities, any critical physical characteristics or microbial purity).

Table continued

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**Conditions**

5. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
  6. 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.
  8. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
  9. The new test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)
- 

**Supporting data**

1. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen.
  2. Updated final product specification if changed.
  3. Copies or summaries of analytical procedures, if new analytical procedures are used.
  4. Validation study reports, if new analytical procedures are used.
  5. Comparative table or description, where applicable, of current and proposed in-process tests.
  6. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final 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. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
  10. Evidence that the new company/facility is GMP compliant.
-

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>37. Change in the specification used to release the excipient, involving:</b>			
<i>Note: This change excludes adjuvants. See adjuvant-specific changes above for details (changes 30 and 31).</i>			
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 acceptance criterion	None	1, 3	Moderate
g. narrowing of an acceptance criterion	3, 4, 6, 7	1	Minor

**Conditions**

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient.
4. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements).
5. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
6. The analytical procedure remains the same, or changes in the test procedure are minor.
7. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity or 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.

Table continued

<b>Supporting data</b>			
<ol style="list-style-type: none"> <li>1. Updated excipient specification.</li> <li>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.</li> <li>3. Justification of the proposed excipient specification (for example, demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the final product).</li> </ol>			
Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>38. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk</b>	None	2–7	Major
<b>39. Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source</b>	None	1, 3, 5, 6	Moderate
<b>40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source</b>	5, 6	2–7	Minor
<b>41. Change in manufacture of a biological excipient</b>	None	2–7	Major
<i>Note: This change excludes biological adjuvants; see adjuvant-specific changes above for details (changes 30 and 31).</i>	2	2–7	Moderate
	1, 2	2–7	Minor
<b>42. Change in supplier for a plasma-derived excipient (for example, human serum albumin)</b>	None	3–8	Major
	3, 4	5, 6, 9	Moderate
<b>43. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient)</b>	None	2, 3, 5–7	Moderate
	1, 5, 6	3	Minor
<i>Note: This change excludes adjuvants; see adjuvant-specific changes above for details (changes 30 and 31).</i>			

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
44. Change in excipient testing site	1	10	Minor

**Conditions**

1. No change in the specification of the excipient or final 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 (5).
6. Any new excipient does not require the assessment of viral safety data.

**Supporting data**

1. Declaration from the manufacturer of the excipient that the excipient is entirely of vegetable or synthetic origin.
2. Details of the source of the excipient (for example, animal species, country of origin) and the steps undertaken during processing to minimize the risk of TSE exposure (5).
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 (3) commercial-scale batches of the proposed excipient.
6. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.

Table continued

#### Supporting data

7. Information assessing the risk with respect to potential contamination with adventitious agents (for example, impact on the viral clearance studies, or BSE/TSE risk (5)) including viral safety documentation where necessary.
8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient.
9. Letter from the supplier certifying that no changes were made to the plasma-derived excipient compared to the currently approved corresponding medicinal product.
10. Evidence that the new company/facility is GMP compliant.

### Control of the final product

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>45. Change affecting the QC testing of the final product (release and stability), involving:</b>			
<i>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 reviewed during inspections.</i>			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company or to a different site within the same company	None	1, 2	Moderate
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company	1	1, 2	Minor
<b>Conditions</b>			
1. The transferred QC test is not a potency assay or a bioassay.			
<b>Supporting data</b>			
1. Information demonstrating technology transfer qualification.			
2. Evidence that the new company/facility is GMP compliant.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>46. Change in the specification used to release the final product, involving:</b>			
a. for products or components subject to terminal sterilization by heat (for example, diluent for reconstitution of lyophilized vaccines), replacing the sterility test with process parametric release	None	1, 2, 6, 8, 10	Major
b. deletion of a test	None	2, 9, 10	Moderate
c. addition of a test	1, 2, 9	2–4, 8	Minor
d. change in animal species/strains for a test (for example, new species/strains, animals of different ages, and/or new supplier where genotype of the animal cannot be confirmed)	None	5, 11	Moderate
e. replacement of an analytical procedure	None	2–4, 7, 8	Moderate
f. minor changes to an approved analytical procedure	3–6	3, 8	Minor
g. change from an in-house analytical procedure to a recognized compendial analytical procedure	3, 6	2–4	Minor
h. widening of an acceptance criterion	None	2, 8, 10	Moderate
i. narrowing of an acceptance criterion	7–10	2	Minor
<b>Conditions</b>			
1. No change in the limits/acceptance criteria outside the approved limits for the approved assays.			
2. The additional test is not intended to monitor new impurity species.			
3. No change in the acceptance criteria outside the approved limits.			
4. The method of analysis is the same (for example, a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.			

Table *continued*

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**Conditions**

5. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
6. The change does not concern potency testing.
7. The change is within the range of approved acceptance criteria.
8. Acceptance criteria for residual solvents are within recognized or approved acceptance limits (for example, within ICH limits for a Class 3 residual solvent, or pharmacopoeial requirements).
9. The change does not result from unexpected events arising during manufacture (for example, new unqualified impurity, or impurity content outside of the approved limits).
10. The analytical procedure remains the same, or changes to the analytical procedure are minor.

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**Supporting data**

1. Process validation study reports on the proposed final product.
  2. Updated copy of the proposed final product specification.
  3. Copies or summaries of analytical procedures, if new analytical procedures are used.
  4. Validation study reports, if new analytical procedures are used.
  5. Data demonstrating that the change in animals gives results comparable to those obtained using the approved animals.
  6. Description of the batches and summary of results as quantitative data for a sufficient number of batches to support the process parametric release.
  7. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial-scale batches of the final product.
  8. Justification for the change to the analytical procedure (for example, demonstration of the suitability of the analytical procedure in monitoring the final product, including the degradation products) or for the change to the specification (for example, demonstration of the suitability of the revised acceptance criterion in controlling the final product).
  9. Justification for the deletion of the test (for example, demonstration of the suitability of the revised specification in controlling the final product).
  10. Declaration/evidence that consistency of quality and of the production process is maintained.
  11. Copies of relevant certificates of fitness for use (for example, veterinary certificate).
-

## Reference standards or materials

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

### Conditions

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

### Supporting data

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

## Container closure system

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>52. Modification of a primary container closure system (for example, new coating, adhesive, stopper or type of glass)</b>	None	1–7	Moderate
	1–3	3	Minor
<p><i>Note: The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation; see <b>change 29.c</b> above.</i></p>			
<b>53. Change from a reusable container to a disposable container with no changes in product contact material (for example, change from reusable pen to disposable pen)</b>	None	1, 3, 6	Moderate
<b>54. Deletion of a container closure system</b>	None	1	Minor
<p><i>Note: The NRA should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate.</i></p>			

### Conditions

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

### Supporting data

1. Revised product labelling information, as appropriate.
2. For sterile products, process validation study reports, or providing equivalency rationale. For a secondary functional container closure system, validation testing report.
3. Information on the proposed container closure system, as appropriate (for example, description, materials of construction of primary/secondary packaging components, performance specification).

Table continued

**Supporting data**

4. Results demonstrating protection against leakage, no leaching of undesirable substance and compatibility with the product, and results from the toxicity and biological reactivity tests.
5. Summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial-scale batches of the pre- and post-change final 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- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
7. Information demonstrating the suitability of the proposed container/closure system with respect to its relevant properties (for example, results from last media fills; results of transportation and/or interaction studies demonstrating the preservation of protein integrity and maintenance of sterility for sterile products; results of maintenance of sterility in multidose containers and results of user testing).

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>55. Change in the supplier for a primary container closure component, involving:</b>			
a. replacement or addition of a supplier	1, 2	4, 5	Minor
<i>Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data such as is shown for <b>change 52</b> above.</i>			
b. deletion of a supplier	None	None	Minor

Table continued

### Conditions

1. No change in the type of container closure, materials of construction, shape and dimensions, or in the sterilization process for a sterile container closure component.
2. No change in the specification of the container closure component outside the approved limits.

### Supporting data

1. Information on the supplier and make of the proposed container closure system (for example, certificate of analysis, description, materials of construction of primary packaging components, specification).
2. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing).
3. Comparative pre- and post-change test results for the manufacturer's characterized key stability-indicating attributes for at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer should commit to undertake real-time stability studies to support the full shelf-life/hold-time of the final product under its normal storage conditions and to report to the NRA any failures in these ongoing long-term stability studies. Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed by the NRA.
5. Letter from the MA holder certifying that there are no changes to the container closure system.
6. Certificate of analysis for the container provided by the new supplier and comparison with the certificate of analysis for the approved container.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>56. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving:</b>			
a. deletion of a test	1, 2	1, 2	Minor
b. addition of a test	3	1, 2	Minor
c. replacement of an analytical procedure	6, 7	1–3	Minor
d. minor changes to an analytical procedure	4–7	1–3	Minor

Table continued

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

**Conditions**

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the final product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. 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 and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the container closure component.

**Supporting data**

1. Updated copy of the proposed 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
<b>57. Change in the shelf-life of the final product, involving:</b>			
a. extension (includes extension of shelf-life of the final product as packaged for sale, and hold-time after opening and after dilution or reconstitution)	None	1–5	Moderate

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
b. reduction (includes reduction as packaged for sale, after opening, and after dilution or reconstitution)	None	1–5	Moderate
<b>Conditions</b>			
None			
<b>Supporting data</b>			
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 (3) commercial-scale batches.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>58. Change in the post-approval stability protocol of the final product, involving:</b>			
a. major 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	1–6	Moderate
b. addition of time point(s) into the post-approval stability protocol	None	4, 6	Minor
c. addition of test(s) into the post-approval stability protocol	1	4, 6	Minor
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf-life	None	4, 6	Minor
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf-life	2	4, 6	Minor

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
f. replacement of the sterility testing by the container/closure system integrity testing	None	1, 2, 4, 6	Moderate
	3	4, 6	Minor

**Conditions**

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

**Supporting data**

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
<b>59. Change in the labelled storage conditions for the final product or the diluted or reconstituted vaccine, involving:</b>			
a. addition or change of storage condition(s) for the final product, or for diluted or reconstituted vaccine (for example, widening or narrowing of a temperature criterion, or addition of or change to controlled temperature chain conditions)	None	1–4, 6	Moderate
b. addition of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 5	Moderate

Table continued

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
c. deletion of a cautionary statement (for example, "Do not freeze")	None	1, 2, 4, 6	Moderate
<b>Conditions</b>			
None			
<b>Supporting data</b>			
<ol style="list-style-type: none"> <li>1. Revised product labelling information, as applicable.</li> <li>2. Proposed storage conditions and shelf-life.</li> <li>3. Updated post-approval stability protocol and stability commitment.</li> <li>4. Justification of the change in the labelled storage conditions/cautionary statement.</li> <li>5. Results of stability testing under appropriate stability conditions covering the proposed shelf-life, generated on one (1) commercial-scale batch unless otherwise justified.</li> <li>6. Results of stability testing under appropriate conditions covering the proposed shelf-life, generated on at least three (3) commercial-scale batches unless otherwise justified.</li> </ol>			

## References

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2. M4Q Implementation Working Group. Questions & Answers (R1) (Current version, 17 July 2003). 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/CTD/M4\\_R1\\_Quality/M4\\_Quality\\_Questions\\_Answers\\_R1.pdf](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. Good manufacturing practices for biological products. In: WHO Expert Committee on Biological Standardization: forty-second report. Geneva: World Health Organization; 1992: Annex 1 (WHO Technical Report Series, No. 822; [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_822.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf?ua=1), accessed 2 December 2014).
4. Guidelines on stability evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: fifty-seventh report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 962; [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_962\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_962_eng.pdf?ua=1), accessed 2 December 2014).
5. 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).

## 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 given in this appendix are provided for clarification. However, such changes are not limited to those included in this appendix. They may also result in changes to the product labelling information for health care providers and patients, and inner and outer vaccine labels.

The amount of safety and efficacy data needed to support a change may vary according to the impact of the change, risk–benefit considerations and product-specific characteristics (that is, there is no “one size fits all” approach). This appendix therefore provides a list of examples of changes in the various categories rather than a detailed table linking each change with the data required to support that change (as provided in Appendices 2 and 3 for quality changes). MA 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.

In some cases, safety and efficacy data comparing the approved clinical use (for example, indications or dosing regimens) of a vaccine with a new one may be required. Such studies, often referred to as clinical bridging studies, are trials in which a parameter of interest (such as formulation, dosing schedule or population group) is directly compared with a changed version of that parameter to assess the effect of the change on the product’s clinical performance. Comparisons of immune responses and safety outcomes (for example, rates of common and serious AEFIs) are often the primary objectives. If the immune response and safety profiles are non-inferior, then the efficacy and safety of the vaccine can be inferred.

Examples of safety and efficacy changes that require data from clinical studies, post-marketing observational studies or extensive post-marketing safety data include:

- change to the indication:
  - (a) addition of a new indication (such as prevention of a previously unspecified disease);

- (b) modification of an approved indication (such as expansion of the age of use or restriction of an indication based on clinical studies demonstrating lack of efficacy).
- Change in the recommended dose and/or dosing schedule:
  - (a) addition of a new vaccination regimen (such as addition of accelerated vaccination regimens);
  - (b) addition or modification of the existing vaccination regimen (such as addition of a booster dose or modification of the recommended time interval for booster vaccinations).
- Change to add information on shedding and transmission.
- Change to the use in specific at-risk groups (such as addition of information on use in pregnant women or immunocompromised patients).
- Change to add information on co-administration with other vaccines or medicines.
- Change to add a new route of administration.<sup>1</sup>
- Change to add a new dosage form<sup>1</sup> (such as replacement of a suspension for injection with a lyophilized cake).
- Change to add a new strength.<sup>1</sup>
- Change to add a new delivery device.<sup>1</sup> (such as adding a needle-free jet injector).
- 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 (such as use in pregnant women).

## Product labelling information changes

Supplements on product labelling information change should be submitted for changes which do not require clinical efficacy data, safety data or extensive pharmacovigilance (safety surveillance) data. Product labelling information changes require approval prior to implementation of the change.

Examples of product labelling information changes associated with changes that have an impact on clinical use include:

- Addition of an adverse event identified as consistent with a causal association with immunization with the vaccine concerned.

<sup>1</sup> Some NRAs consider that these changes may require a new application for MA or licence.

- Change in the frequency of occurrence of a given adverse reaction.
- Addition of a contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example, required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks).
- Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions.
- Revisions to the instructions for use, including dosage, administration and preparation for administration to optimize the safe use of the vaccine.

In some cases, the safety-related changes listed above may be urgent and may require rapid implementation (for example, the addition of a contraindication or warning). To allow for the rapid 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 MA holder (see section 7.3 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 vaccine. In some cases, these changes may need to be reported to the NRA and approval received prior to implementation, while in other cases reporting may not be required.

Examples of changes which *do* require reporting to the NRA and approval prior to implementation by the MA holder include:

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

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

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

- Update of the MA holder's contact information (for example, customer service number or web site addresses) or the distributor's name.
- Update of the existing information for referenced literature without adding or removing references.
- Changes made to comply with an official compendium (such as change of common name).
- Minor changes to the text to add clarity in relation to maintaining consistency with common label phrase standards (for example, a change from "not recommended for children" to "not for use in children").

These administrative product labelling information changes (that is, changes that have been implemented since the time of the last approved product labelling information not subject to prior approval) should be included when submitting subsequent supplements for safety and efficacy changes, or for product labelling information changes (see section 7.4).

