Annex 3

WHO guidelines on variations to a prequalified product

Introduction

The variation guidelines have been completely updated and expanded, bringing them into line with the principles of the new generic quality guidelines, WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

The guidelines[1] retain the basic structure and function of the previous variation guidelines, and have been expanded to include the classification of additional post-approval/post-prequalification changes and to establish the level of risk inherent to each change.[2] Although the general requirements have not significantly changed, the additional details help the reader to classify changes that may occur related to all the major sections of a quality dossier, to understand the considerations necessary to assess the risk of each change, and to determine the documentation required to support the change.

In some cases, changes that previously were considered major changes by default are now classified minor variations or notifications, and some minor variations have been reclassified as notifications. In addition, for some categories that previously required acceptance of the change prior to implementation, the applicant can now implement the change immediately upon notification.

The change categories are organized according to the structure of the common technical document (CTD). The specific CTD sections associated with individual data requirements have been identified in order to assist in the filing of documentation (reproduced with corresponding numbers in bold). Presentation corresponds to section 1.4 in Annex 4 of WHO Technical Report Series, No. 970.[3]

Changes are classified as major only in those instances where the level of risk is considered to be high and it is deemed necessary to provide the WHO Prequalification of Medicines Programme (WHO/PQP) with adequate time for an assessment of the supporting documentation. Particular circumstances are identified where lower reporting requirements (annual notification (AN), immediate notification (IN) or minor variation (Vmin)) are possible. In all cases where notification to WHO/PQP or acceptance by WHO/PQP is required prior

[1] Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 943), Annex 6.

[2] WHO Guidelines on quality risk management. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report*. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2.

[3] Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 4.

to implementation, assessment timelines will be published in order to provide predictable and reasonable timeframes.

In addition, the guidelines assist in understanding the possible consequences of the listed changes, and may be useful as a risk management tool to promote or enhance best practices within organizations.

A companion Question and Answer document is in preparation to assist in interpretation of the guidelines. This document will address many of the questions raised during the guidelines circulation process.

1. Background

This guidance document is technically and structurally inspired by the European Union Institutions and Bodies Commission's Guideline on the details of the various categories of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products. It is intended to provide supportive information on how to present an application to implement a change to a product.

This guidance supersedes the guidance published in 2007.[4]

An applicant is responsible for the safety, efficacy and quality of a product throughout its life-cycle. Therefore, the applicant is required to make changes to the details of the product in order to accommodate technical and scientific progress, or to improve or introduce additional safeguards for the prequalified product. Such changes, whether administrative or substantive, are referred to as variations and may be subject to acceptance by WHO/PQP prior to implementation.

Technical requirements for the different types of variations are set out in these guidelines in order to facilitate the submission of appropriate documentation by applicants and their assessment by WHO/PQP and to ensure that variations to the medicinal product do not result in health concerns.

The procedure for submitting variations is not within the scope of these guidelines. Advice on the procedure for submitting a variation and current review timelines are set out on the WHO/PQP web site which may be updated from time to time. Applicants are advised to consult information on the web site whenever they are considering the submission of a variation application.

1.1 Objectives

These guidelines are intended to:

- assist applicants with the classification of changes made to the quality part of a prequalified finished pharmaceutical product (FPP);

[4] See footnote 1.

- provide guidance on the technical and other general data requirements to support changes to the quality attributes of the active pharmaceutical ingredient (API) or FPP.

1.2 Scope and application

These guidelines apply to applicants intending to make changes to the quality sections of product dossiers for an API or an FPP. This guidance should be read in conjunction with the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*[5] as well as other related WHO guidelines.

This guidance document is applicable only to APIs and excipients manufactured by chemical synthesis or semi-synthetic processes and FPPs containing such APIs and excipients. APIs produced by fermentation and APIs of biological, biotechnological or herbal origin are treated as special cases. The applicant is requested to contact WHO/PQP regarding planned variations to such products.

The notification requirements for API-related changes differ depending on the manner in which information on the API was submitted in the FPP application, namely, use of a prequalified API, use of a European Pharmacopoeia Certificate of Suitability (CEP), use of the API master file (APIMF) procedure, or as provided in full within the dossier.

The conditions and documentation stipulated in this guidance for API-related variations focus primarily on those FPPs that relied upon the provision of full API information within the FPP dossier. In general FPPs that rely upon the APIMF procedure have reduced reporting requirements because the API manufacturers themselves have notified the relevant API-related change directly to WHO/PQP. Similarly, when an FPP relies upon a CEP or a prequalified API, FPP applicants are required to notify WHO/PQP only when the associated CEP or Confirmation of API Prequalification document has been revised.

Guidance for API manufacturers on the technical and procedural requirements for changes to prequalified APIs and to APIs supported by the APIMF procedure is available on the Prequalification web site. Regardless of whether the API-related change is notified primarily by the API manufacturer (API prequalification (API-PQ) procedure, APIMF procedure or CEP), or the FPP manufacturer (full API information in dossier) the technical requirements are in principle the same as those stipulated in these guidelines.

Whenever FPPs have been prequalified on the basis of approval by a stringent regulatory authority (SRA) (innovator products or generic products), subsequent applications for variations should be approved by the same SRA and

[5] See footnote 3.

WHO/PQP should be notified of the approval of the changes. Applicants are advised to refer to the Letter of Prequalification.

When a variation leads to a revision of the summary of product characteristics (SmPC), the patient information leaflet (PIL), labelling and packaging leaflet and updated product information should be submitted as part of the application.

For variations that require generation of stability data on the API or FPP, the stability studies required, including commitment batches, should always be continued to cover the currently accepted retest or shelf-life period. WHO/PQP should be informed immediately if any problems with the stability of APIs or FPPs occur during storage, e.g. if found to be outside specifications or potentially outside specifications.

Applicants should be aware that some variations may require the submission of additional consequential variations, including where the variation states, "no variation is required, such changes are handled as amendments to the APIMF by the APIMF holder". Therefore, for any given change the applicant should consider whether one or more variations may be required to be submitted.

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation, but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

2. Guidance for implementation

2.1 Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of quality-related changes. Specific examples of changes are provided in these guidelines. However, it should be noted that a change not covered by these guidelines, should be considered as a major change by default. Whenever the applicant is unclear about the classification of a particular change, WHO/PQP should be contacted. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable only under the following circumstances:

- when variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;

- when the same change affects multiple FPPs, e.g. addition of a new API manufacturing site for multiple FPPs;
- when all the changes are annual notification.

For the purposes of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both a minor change and a major change will be classified as a major change.

Applicants are also advised to exercise caution whenever several changes to the same FPP are envisaged. Although each of the individual changes may be classified as a particular reporting type, classification within a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, applicants are advised to contact WHO/PQP prior to submission of the variation application to obtain guidance on classifying such changes.

2.1.1 Notifications

Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Such notifications do not require prior acceptance, but must be notified to WHO/PQP immediately after implementation (immediate notification (IN)), or within 12 months following implementation (annual notification (AN)) of the change.

It should be highlighted that an IN or AN may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

Annual notification (AN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for ANs should be available on request or at the time of inspection. ANs should be submitted to WHO/PQP within 12 months of implementation of the changes. For convenience applicants may group several AN changes as a single submission.

Immediate notification (IN)

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be implemented immediately at the time of submission and they can be considered accepted if an objection is not issued by WHO/PQP within 30 calendar days of the date of acknowledgement of receipt of the application.

2.1.2 Minor variation (Vmin)

Minor variations are changes that may have minor effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

Such variations can be implemented if no objection letter has been issued within a time period indicated on the WHO/PQP web site. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from WHO/PQP.

2.1.3 Major variation (Vmaj)

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by WHO/PQP is required before the changes can be implemented. A letter of acceptance will be issued for all major variations if and when the variation is considered acceptable.

2.1.4 New applications and extension applications

Certain changes are so fundamental that they alter the terms of the accepted dossier and consequently cannot be considered as changes. In these cases a new dossier must be submitted. Examples of such changes are listed in Appendix 1.

2.1.5 Labelling information

For any change to labelling information (SmPC, PIL, labels) not covered by the variation categories described in this document, WHO/PQP must be notified and submission of the revised labelling information is expected as per the guidance on the WHO/PQP web site.

2.2 Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower reporting requirements (IN, AN or Vmin) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a Vmaj.

In some circumstances Vmaj categories have been specifically stated for a given variation. This has been done to indicate to applicants what documents should be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy or quality of the FPP.

2.3 Documentation required

Examples of variations are organized according to the structure of the CTD. For each variation, certain documents have been identified as supporting data and are organized according to CTD structure. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation.

Where applicable, the following should be included in the application:

- a variation application form (a template can be downloaded from the web site). All sections of this form should be completed and the document signed. Electronic versions of the application form, both as a Word document and a scanned signed PDF, should be provided in addition to the printed version;
- an updated quality information summary (QIS) (if applicable);
- replacement of the relevant sections of the dossier as per CTD format;
- copies of SmPC, PIL and labels, if relevant.

It should be noted that WHO/PQP reserves the right to request further information not explicitly described in these guidelines.

The QIS provides a summary of the key quality information from the product dossier. For FPPs that have an agreed-upon QIS, the QIS should be revised and submitted (in Word format only) with every variation application. Any revised sections within the QIS should be highlighted. If there is no change to the QIS as a result of the variation, a statement should be made in the covering letter to this effect.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that WHO/PQP may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the safety, efficacy and quality of an FPP.

3. Glossary

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient (API)

A substance used in the FPP, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

active pharmaceutical ingredient (API) starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

applicant

For the purposes of this document, the term applicant refers to any person or entity who has participated in the procedure for prequalification of FPPs by submission of the required documentation on a product that has been listed after evaluation as prequalified.

biobatch

The batch used to establish bioequivalence or similarity to the comparator product as determined in bioequivalence or biowaiver studies, respectively.

final intermediate

The last reaction intermediate in the synthetic pathway that undergoes synthetic transformation to the API or the crude API. Purification is not considered to be a synthetic transformation.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labelling.

in-process control

Check performed during manufacture to monitor or to adjust the process in order to ensure that the final product conforms to its specifications.

manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.

officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized in the WHO/PQP (i.e. *The International Pharmacopoeia* (Ph. Int.), the *European Pharmacopoeia* (Ph. Eur.), the *British Pharmacopoeia* (BP), the *Japanese Pharmacopoeia* (JP) and the *United States Pharmacopeia* (USP)).

pilot-scale batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth

that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.[6]

production batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

stringent regulatory authority (SRA)

A stringent regulatory authority is:

- the medicines regulatory authority in a country which is: (a) a member of the International Conference on Harmonisation (ICH) (European Union (EU), Japan and the United States of America); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);
- only in relation to good manufacturing practices (GMP) inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as specified at http://www.picscheme.org

4. Administrative changes

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1 Change in the name and/ or corporate address of the supplier of the FPP.	1	1	IN
Conditions to be fulfilled 1. Confirmation that the supplier of the product remains the same legal entity.			
Documentation required 1. A formal document from a relevant official body (e.g. the national medicines regulatory authority (NMRA)) in which the new name and/or address is mentioned.			

continues

[6] Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 953), Annex 3.

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2	Change in the name or address of a manufacturer of an API that is not a supplier of a prequalified API or that is not supported by a CEP.	1	1–2	IN
Conditions to be fulfilled 1. No change in the location of the manufacturing site and in the manufacturing operations.				
Documentation required 1. A formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned. 2. An updated Letter of Access in case of change in the name of the holder of the APIMF.				

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3	Change in the name and/or address of a manufacturer of the FPP.	1	1	IN
Conditions to be fulfilled 1. No change in the location of the manufacturing site and in the manufacturing operations.				
Documentation required 1. Copy of the modified manufacturing authorization or a formal document from a relevant official body (e.g. NMRA) in which the new name and/or address is mentioned.				

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
4	Deletion of a manufacturing site or manufacturer involving:			
4a	production of the API starting material	1	1	AN
4b	production or testing of the API intermediate or API	1–2	1	IN
4c	production, packaging or testing of the intermediate or FPP	1–2	1	IN

continues

Table *continued*

Conditions to be fulfilled

1. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.
2. The deletion of the site is not a result of critical deficiencies in manufacturing.

Documentation required

1. Clear identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.

5. Changes to a CEP or to a confirmation of API-prequalification document

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
5	Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API:			
5a.1	from a currently accepted manufacturer	1–5	1–5	AN
5a.2		1–4	1–6	IN
5a.3		1, 3–4	1–6	Vmin
5b.1	from a new manufacturer	1–4	1–6	IN
5b.2		1, 3– 4	1–6	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for any impurities including organic, inorganic and genotoxic impurities and residual solvents, with the exception of residual solvents when the limits stipulated comply with ICH requirements.
3. The manufacturing process of the API, starting material or intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4. For low solubility APIs the polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
5. No revision of the FPP manufacturer's API specifications is required.

continues

Table *continued*

Documentation required

1. Copy of the current (updated) CEP, including any annexes and a declaration of access for the CEP to be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the WHO/PQP who refers to the CEP.
2. A written commitment that the applicant will inform WHO/PQP in the event that the CEP is withdrawn and an acknowledgement that withdrawal of the CEP will require additional consideration of the API data requirements to support the product dossier.
3. Replacement of the relevant pages of the dossier with the revised information for the CEP submission option stipulated under section 3.2.S of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.
4. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation data.
5. (P.8.2) In the case of the submission of a CEP for an API, if the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of the FPP of at least pilot-scale, and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to WHO/PQP.
6. (S.4.1) Copy of FPP manufacturer's revised API specifications.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
6	Submission of a new or updated confirmation of API-prequalification document			
6a.1	from a currently accepted manufacturer	1–3	1–3, 5	AN
6a.2		1–2	1–5	Vmin
6b.1	from a new manufacturer	1–3	1–3, 5	IN
6b.2		1–2	1–5	Vmin

Conditions to be fulfilled

1. No change in the FPP release and shelf-life specifications.
2. For low solubility APIs the API polymorph is the same, and whenever particle size is critical (including low solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
3. There is no difference in impurity profile of the proposed API to be supplied, including organic, inorganic, genotoxic impurities and residual solvents, compared to that of the API currently supplied. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.

continues

Table *continued*

Documentation required

1. Copy of the current (updated) confirmation of API-PQ document. The API manufacturer should duly fill out the authorization box with the name of the applicant or FPP manufacturer seeking to use the document.
2. Replacement of the relevant pages of the dossier with the revised information for the API-PQ procedure submission option (*Option 1: confirmation of API Prequalification document*) stipulated under section 3.2.S. of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.
3. (S.2.5) For sterile APIs, data on the sterilization process of the API, including validation.
4. (S.4.1) Copy of FPP manufacturer's revised API specifications.
5. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one batch of at least pilot-scale of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out-of-specification results to WHO/PQP.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
7	Submission of a new or updated transmissible spongiform encephalopathy (TSE) CEP for an excipient or API (addition or replacement)	None	1	AN

Conditions to be fulfilled

None

Documentation required

1. Copy of the current (updated) TSE CEP.

6. Quality changes

3.2. S Drug substance (or API)

3.2. S.2 Manufacture

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
8	Replacement or addition of a new manufacturing site or manufacturer of an API involving:			

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
8a.1	API testing only	1, 2, 4	1, 3–4	IN
8a.2		2, 4	1, 3–4	Vmin
8b.1	production of API starting material	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8b.2		4–5	1–2, 12	IN
8b.3		None	1,2,5, 7–8,12, 13	Vmaj
8c.1	production of API intermediate	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
8c.2		4, 6	1–2, 12	IN
8c.3		None	1, 2, 5, 7–8, 12, 13	Vmaj
8d.1	production of API (APIMF procedure)	3, 7–9	1, 2, 6, 8	IN
8d.2		3, 7, 9	1, 2, 6–8	Vmin
8e.1	production of API (full dossier)	1, 9–11	1–2, 4, 8–9	IN
8e.2		None	1, 2, 4, 5, 7–8, 10–11, 13	Vmaj

Conditions to be fulfilled

1. The API is non-sterile.
2. The transfer of analytical methods has been successfully undertaken.
3. The new site is supported by an APIMF that is currently accepted through the APIMF procedure and the FPP manufacturer holds a valid Letter of Access.
4. No change in the FPP manufacturer's API specifications.
5. The impurity profile of the API starting material is essentially the same as other accepted sources. The introduction of the new supplier does not require the revision of the API manufacturer's API starting material specifications. The route of synthesis is verified as identical to that already accepted.
6. Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require the revision of the API manufacturer's API intermediate specifications.

continues

Table *continued*

Conditions to be fulfilled

7. No change in the FPP release and end-of-shelf-life specifications.
8. No difference in impurity profile of the proposed API to be supplied, including organic, inorganic and genotoxic impurities and residual solvents. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications.
9. For low-solubility APIs the API polymorph is the same, and whenever particle size is critical (including low-solubility APIs) there is no significant difference in particle size distribution, compared to the API lot used in the preparation of the biobatch.
10. Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or a new contract manufacturing site with evidence of an acceptable and similar quality system to that of the main manufacturer).
11. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or equivalent guidelines of the ICH region and associated countries.

Documentation required

1. (S.2.1) Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s)). A valid testing authorization or a certificate of GMP compliance, if applicable.
2. (S.2.2) A side-by-side comparison of the manufacturing flowcharts for production of the API, intermediate, or API starting material (as applicable) at the parent and proposed sites and a tabulated summary of the differences.
3. (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalence of analytical procedures to be used at the proposed testing site.
4. (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed manufacturers and/or sites.
5. Relevant sections of (S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.[7]

continues

[7] See footnote 3.

Table *continued*

Documentation required

6. The open part of the new APIMF (with a Letter of Access provided in Module 1) and documentation in fulfilment of requirements for the APIMF option under section 3.2.S of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.[8]
7. (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO/PQP.
8. (S.4.1) A copy of the FPP manufacturer's API specifications.
9. (S.2) A declaration from the supplier of the prequalified FPP that the route of synthesis, materials, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
10. A discussion of the impact of the new API on the safety, efficacy and quality of the FPP.
11. For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low-solubility APIs) where there is a significant difference in particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.
12. Certificates of analysis for at least one batch of API starting material or intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material or intermediate (as applicable) from the new source and from a previously accepted source. For an alternative source of plant-derived starting material, control of pesticide residues must be established. This can either be in the form of an attestation from the starting material supplier that no pesticides are used during the growth of the plant material, or by providing the results of pesticide screening from one batch of the starting material.
13. An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary.

continues

[8] See footnote 3.

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
9a	change or addition of a manufacturing block or unit at a currently accepted site of API manufacture	1–5	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder.	
9b		1, 3–5	1–4	IN

Conditions to be fulfilled

1. The API is non-sterile.
2. The API manufacturing block or unit is currently accepted through the APIMF procedure.
3. The same quality system covers currently accepted and proposed units or blocks.
4. For low-solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API lot used in the preparation of the biobatch.
5. No change in the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable). Minor changes in the equipment are acceptable.

Documentation required

1. (S.2) A declaration from the supplier of the FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
2. (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s)). A valid manufacturing and/or testing authorization and a certificate of GMP compliance, if available.
3. (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed units or blocks.
4. (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
10a	change in the manufacturing process of the API	1–3, 9	1–2, 8	AN
10b.1		1–2, 4, 6–9	3–4, 11–12	IN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
10b.2	change in the manufacturing process of the API	1–2, 4, 6–8, 10	3–4, 11–12	Vmin
10c		1–2, 4–7	3–4, 11–12	Vmin
10d		None	2–14	Vmaj

Conditions to be fulfilled

1. No change in the physical state (e.g. crystalline, amorphous) of the API.
2. For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change in the particle size distribution compared to that of the API lot used in the preparation of the biobatch.
3. The API manufacturing site is currently accepted through the APIMF procedure.
4. Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required.
5. No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process.
6. No change in qualitative and quantitative impurity profile or in physicochemical properties of the API.
7. The change does not affect the sterilization procedures of a sterile API.
8. The change involves only steps before the final intermediate.
9. The change does not require revision of the starting material, intermediate or API specifications.
10. The change does not require revision of the API specifications.

Documentation required

1. A copy of the APIMF amendment acceptance letter.
2. (P.8.2) If the quality characteristics of the API are changed in a way that may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to WHO/PQP.
3. (S.2.2) A side-by-side comparison of the current process and the new process.
4. (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
5. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.

continues

Table *continued*

Documentation required

6. (S.2.3) Either a TSE CEP for any new source of material or, where applicable, documented evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent authority and shown to comply with the current *WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or equivalent guidelines of the ICH region and associated countries.
7. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
8. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.
9. (S.3.1) Evidence for elucidation of structure, where applicable.
10. (S.3.2) Information on impurities.
11. (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable).
12. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) manufactured according to the current and proposed processes.
13. (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API.
14. For low-solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low-solubility APIs) where there is dissimilar particle size distribution compared to the lot used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
11	Change in the in-process tests or limits applied during the manufacture of the API:			
11a	any change in the manufacturing process controls	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
11b	tightening of in-process limits	2–4	1	AN
11c	addition of a new in-process test and limit	2, 5	1–5	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
11d	addition or replacement of an in-process test as a result of a safety or quality issue	None	1–5, 7, 8–10	Vmin
11e.1	deletion of an in-process test	2, 6–7	1–3, 6	AN
11e.2		None	1–3, 7–10	Vmaj
11f	relaxation of the in-process test limits	None	1–3, 5, 7–10	Vmaj

Conditions to be fulfilled

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by unexpected events arising during manufacture e.g. a new unqualified impurity or a change in total impurity limits.
3. The change is within the range of currently accepted limits.
4. The analytical procedure remains the same, or changes to the analytical procedure are minor.
5. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The affected parameter is non-significant.
7. The change does not affect the sterilization procedures of a sterile API.

Documentation required

1. A comparison of the currently accepted and the proposed in-process tests.
2. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
3. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.
4. Details of any new non-pharmacopoeial analytical method and validation data where relevant.
5. Justification for the new in-process test and/or limits.
6. Justification and/or risk-assessment showing that the parameter is non-significant.
7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, where applicable.
8. (S.3.2) Information on impurities, if applicable.
9. (S.4.1) Copy of currently accepted specifications of API (and intermediates, if applicable).
10. (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) for all specification parameters.

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
12	Change in batch size of the API or intermediate involving:			
12a	up to 10-fold compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	AN
12b.1	downscaling	1–4	1, 3–4	AN
12b.2		1–3	1–4	IN
12c	any change in scale (APIMF procedure)	5	1–2, 4–5	AN
12d	more than 10-fold increase compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	Vmin

Conditions to be fulfilled

1. No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of a different size of equipment).
2. The change does not affect the reproducibility of the process.
3. The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.
4. The change does not concern a sterile API.
5. The API manufacturing site and batch size is currently accepted through the APIMF procedure.
6. The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation.

Documentation required

1. (S2.2) A brief narrative description of the manufacturing process.
2. (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.
3. (S.4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable).
4. (S.4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size.
5. A copy of the APIMF amendment acceptance letter.

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
13	Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. raw materials, starting materials, reaction intermediates, solvents, reagents, catalysts) involving:			
13a	any change	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
13b	tightening of the specification limits	2–4	1–3	AN
13c	minor change to an analytical procedure	5–7	2–3	AN
13d	addition of a new specification parameter and a corresponding analytical procedure where necessary	2, 7–9	1–3	AN
13e	deletion of a specification parameter or deletion of an analytical procedure	2, 10	1–4	AN
13f	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1–3, 5	Vmin
13g	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	4, 7, 9–10	1, 3–4	IN
13h	relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1–3, 5	Vmaj

continues

Table *continued*

Conditions to be fulfilled

1. API manufacturing site is currently accepted through the APIMF procedure.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any change is within the range of currently accepted limits.
4. The analytical procedure remains the same.
5. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments, to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
6. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
7. No change to the total impurity limits; no new impurities are detected.
8. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
9. The change does not concern a genotoxic impurity.
10. The affected parameter is non-significant or the alternative analytical procedure has been previously accepted.

Documentation required

1. Comparative table of currently accepted and proposed specifications.
2. (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable.
3. (S.2.4) Information on intermediates, where applicable.
4. Justification and/or risk assessment showing that the parameter is non-significant.
5. (S.3.2) Information on impurities, where applicable.

3.2. S.4 Control of the API by the API manufacturer

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
14	Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturer's API specifications involving:			
14a	a. API supported through the APIMF procedure.	1–2	No variation is required; such changes are handled as amendments to the associated APIMF	

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
14b	b. API not supported through the APIMF procedure.	2	1–4	IN

Conditions to be fulfilled

1. The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APIMF and accepted.
2. The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer's API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API is maintained.

Documentation required

1. (S.4.1) Copy of the current and proposed API specifications dated and signed by the API manufacturer.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable.
4. Justification as to why the change does not affect the FPP manufacturer's specifications.

3.2. S.4 Control of the API by the FPP manufacturer

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
15	Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:			
15a	updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.	11	1–5	AN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
15b.1	deletion of a test parameter	1–2	1, 6	AN
15b.2		10	1, 6, 8	IN
15b.3		None	1, 6	Vmaj
15c.1	addition of a test parameter	1, 4–8	1–6	AN
15c.2		1, 5–6, 10	1–6, 8	IN
15c.3		1, 5–6	1–6	Vmin
15c.4		None	1–7	Vmaj
15d.1	replacement of a test parameter	1, 5–8	1–6	IN
15d.2		5, 7, 10	1–6, 8	Vmin
15d.3		None	1–7	Vmaj
15e.1	tightening of an acceptance criterion	1, 3, 9	1, 6	AN
15f.1	relaxation of an acceptance criterion	1, 5–9	1, 6	IN
15f.2		5, 7, 10	1, 6, 8	Vmin
15f.3		None	1, 6–7	Vmaj

Conditions to be fulfilled

1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
2. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
3. The change is within the range of currently accepted acceptance criteria.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. For insoluble APIs there is no change in the polymorphic form and whenever particle size is critical (including low-solubility APIs) there is no change in particle size distribution acceptance criteria.
6. No additional impurity found over the ICH identification threshold.
7. The change does not concern sterility testing.
8. The change does not involve the control of a genotoxic impurity.
9. The associated analytical procedure remains the same.
10. The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF amendment.
11. No change is required in FPP release and shelf-life specifications.

continues

Table *continued*

Documentation required

1. (S.4.1) A copy of the proposed API specifications (of the FPP manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer, if new analytical procedures are used.
4. (S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented.
6. (S.4.5) Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
7. (P.2) Where changes have occurred to the particle size criteria of an insoluble API or wherever particle size is critical, evidence is provided that the changes do not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batch used in the registration bioequivalence study. However, if the routine dissolution medium contains a surfactant, the applicant should contact WHO/PQP for advice. For changes to the polymorph of an insoluble API the applicant should contact WHO/PQP for advice before embarking upon any investigation.
8. Copy of the APIMF amendment acceptance letter.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
16	Change to the analytical procedures used to control the API by the FPP manufacturer involving:			
16a	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.	None	1–3	AN

continues

Table *continued*

16b	change from a currently accepted in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another official recognized pharmacopoeia	None	1–4	IN
16c.1	addition of an analytical procedure	1–3	1–3	AN
16c.2		3, 8	1–3, 5	AN
16c.3		8	1–3, 5	Vmin
16c.4		None	1–3	Vmaj
16d.1	modification or replacement of an analytical procedure	1–6	1–4	AN
16d.2		2–3, 5–6, 8	1–5	AN
16d.3		1–3, 5–6	1–4	Vmin
16d.4		5–6, 8	1–5	Vmin
16d.5		None	1–4	Vmaj
16e.1	deletion of an analytical procedure	6–7	1, 6	AN
16e.2		6, 8	1, 5, 6	IN
16e.3		None	1, 6	Vmaj

Conditions to be fulfilled

1. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. No new impurities have been detected as a result of the use of the new analytical method.
4. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.

continues

Table *continued*

Conditions to be fulfilled

5. Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
6. The change does not concern sterility testing.
7. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.
8. The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF.

Documentation required

1. (S.4.1) Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (S.4.2) Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used.
3. (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or significantly modified analytical procedures are used.
4. (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures.
5. A copy of the APIMF acceptance letter.
6. (S.4.5) Justification for the deletion of the analytical procedure, with supporting data.

3.2. S.6 Container-closure system

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
17a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	3, 4	1–2, 4	AN
17b		1–2, 4	2–3	IN
17c		4	1–3	Vmin

Conditions to be fulfilled

1. Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, and moisture permeability among others).
2. The change does not concern a sterile API.
3. The change has previously been accepted through the APIMF procedure.
4. The change is not the result of stability issues.

continues

Table *continued*

Documentation required

1. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process.
2. (S.6) Information on the proposed primary packaging (e.g. description and specifications) and data in fulfillment of condition 1.
3. (S.7.1) Results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing of the API in the proposed primary packaging type.
4. A copy of the APIMF amendment acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
18	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
18a	tightening of specification limits	1–2	1	AN
18b	addition of a test parameter	2–3	1–3	AN
18c	deletion of a non-critical parameter	2	1, 4	AN
18d	any change (APIMF procedure)	4	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.
2. (S.4.2) Details of method and summary of validation of new analytical procedure.
3. (S.6) Certificate of analysis for one batch.
4. Justification to demonstrate that the parameter is not critical.

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
19	Change to an analytical procedure on the immediate packaging of the API involving:			
19a	minor change to an analytical procedure	1–3	1	AN
19b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
19c	deletion of an analytical procedure	5	2	AN
19d	any change (APIMF procedure)	6	No variation is required; such changes are handled as amendments to the associated APIMF	

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3. Comparative studies indicate the new analytical procedure to be at least equivalent to the currently accepted procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.
6. The change has previously been accepted through the APIMF procedure.

Documentation required

1. (S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent.
2. Justification for deletion of the analytical procedure.

3.2. S.7 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
20	Change in the retest period or shelf-life of the API involving:			
20a	any change (APIMF procedure)	4	4	IN
20b	reduction	3	1–2	IN
20c	extension	1–2	1–3	Vmin

Conditions to be fulfilled

1. No change to the primary packaging in direct contact with the API or to the recommended condition of storage.
2. Stability data were generated in accordance with the currently accepted stability protocol.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
4. The revised retest period has previously been accepted through the APIMF procedure.

Documentation required

1. (S.7.1) Proposed retest period or shelf-life, summary of stability testing according to currently accepted protocol and test results.
2. (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.
3. (S.7.3) Stability data to support the change.
4. A copy of the APIMF acceptance letter.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
21	Change in the labelled storage conditions of the API involving:			
21a	any change in storage conditions (APIMF procedure)	1	1	IN
21b	any change in storage conditions	2	2	Vmin

Conditions to be fulfilled

1. The revised storage conditions have previously been accepted through the APIMF procedure.

continues

Table *continued*

Conditions to be fulfilled

2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

1. A copy of the APIMF acceptance letter.
2. (S.7.1) Stability and/or compatibility test results to support the change to the storage conditions.

3.2. P Drug product (or FPP)

3.2. P.1 Description and composition of the FPP

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
22a	Change in the composition of a solution dosage form	1–6	2, 4, 7, 9–10	IN
22b		None	1–10	Vmaj

Conditions to be fulfilled

1. The affected excipient(s) does/do not function to affect the solubility and/or the absorption of the API.
2. The affected excipient(s) does/do not function as a preservative or preservative enhancer.
3. No change in the specifications of the affected excipient(s) or the FPP.
4. No change in the physical characteristics of the FPP (e.g. viscosity, osmolality, pH).
5. The change does not concern a sterile FPP.
6. The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within ±10% of the amount (or concentration) of each excipient in the originally prequalified product.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.1) Description and composition of the FPP.
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, suitability studies on the packaging system for the changed product).
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.

continues

Table *continued*

5. (P.4) Control of excipients, if new excipients are proposed.
6. (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.
7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
23	Change in the colouring system or the flavouring system currently used in the FPP involving:			
23a	reduction or increase of one or more components of the colouring or the flavouring system	1–3, 6	1, 4, 6–7	AN
23b	deletion, addition or replacement of one or more components of the colouring or the flavouring system	1–6	1–7	IN

Conditions to be fulfilled

1. No change in the functional characteristics of the pharmaceutical form e.g. disintegration time or dissolution profile.

continues

Table *continued*

Conditions to be fulfilled

2. Any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
3. Specifications for the FPP are updated only with respect to appearance, odour and/or taste or if relevant, deletion or addition of a test for identification.
4. Any new component must comply with section 3.2.P.4 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.[9]
5. Any new component does not include the use of materials of human or animal origin for which assessment of viral safety data is required, or is in compliance with the current *WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or an equivalent guide from the ICH region and associated countries.
6. Where applicable, the change does not affect the differentiation between strengths and for paediatric formulations it does not require submission of results of taste acceptability studies.

Documentation required

1. Sample of the FPP.
2. (P.2) Discussion on the components of the FPP (e.g. compatibility of API and qualitative composition of the colouring or flavouring system if purchased as a mixture, with specifications, if relevant).
3. (P.4.5) Either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.
4. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches.
5. (P.5.3) If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
6. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

continues

[9] See footnote 3.

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
24	Change in weight of tablet coatings or capsule shells involving:			
24a	immediate-release oral FPPs	1–3	2–5	AN
24b	gastro-resistant, modified or prolonged release FPPs	None	1–5	Vmaj

Conditions to be fulfilled

1. Multipoint in vitro dissolution profiles of the proposed version of the product (determined in the routine release medium on at least two batches of pilot- or production-scale), are similar to the dissolution profiles of the biobatch.
2. Coating is not a critical factor for the release mechanism.
3. Specifications for the FPP are updated only with respect to weight and dimensions, if applicable.

Documentation required

1. Justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence (*Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*, WHO Technical Report Series, No. 937, 2006, Annex 8).
2. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch.
3. (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot- or production-scale batch.
4. (P.8.1) Results of stability testing generated on at least one pilot- or production-scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
5. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
25	Change in the composition of an immediate-release solid oral dosage form including:			
25a.1	replacement of a single excipient with a comparable excipient at a similar concentration	1–5	1–10	Vmin
25a.2		None	1–10	Vmaj

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
25b.1	quantitative changes in excipients	1–4	1–4, 7–10	Vmin
25b.2		None	1–4, 7–10	Vmaj

Conditions to be fulfilled

1. No change in functional characteristics of the pharmaceutical form.
2. Only minor adjustments (see Appendix 2) are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation.
3. Stability studies have been started under conditions according to WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*[10] (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot- or production-scale batches, satisfactory stability data covering at least 3 months are at the disposal of the applicant, and the stability profile is similar to that of the currently accepted product.
4. The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch.
5. The change is not the result of stability issues and/or does not result in potential safety concerns, i.e. differentiation between strengths.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.1) Description and composition of the FPP.
3. (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles obtained on at least two batches of pilot- or production-scale of the proposed product and the biobatch (depending on the solubility and permeability of the drug, dissolution in the routine release medium or in multiple media covering the physiological pH range).
4. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
5. (P.4) Control of excipients, if new excipients are proposed.

continues

[10] See footnote 3.

Table *continued*

Documentation required

6. (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals and its use.
7. (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP.
8. (P.8.1) Results of stability testing generated on at least two pilot- or production-scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
9. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
10. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch**,** and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
26	Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving:			
26a	changes in imprints, embossing or other markings	1–3	1–2, 5–6	IN
26b	deletion of a scoreline	2–5	1, 5–6	IN
26c.1	addition of a scoreline	2–4	1, 3, 5–6	Vmin
26c.2		None	1, 3–6	Vmaj

continues

Table *continued*

Conditions to be fulfilled

1. Any ink complies with section 3.2.P.4 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.[11]
2. The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP.
3. Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring.
4. Addition or deletion of a score line from a generic product is consistent with a similar change in the comparator product or was requested by WHO/PQP.
5. The scoring is not intended to divide the FPP into equal doses.

Documentation required

1. Sample of the FPP.
2. (P.1.) Qualitative composition of the ink, if purchased as a mixture.
3. (P.2) Demonstration of the uniformity of the dosage units of the tablet portions, where the scoring is intended to divide the FPP into equal doses.
4. (P.2) Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified or prolonged release products.
5. (P.5) Copies of revised FPP release and shelf-life specifications.
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
27	Change in dimensions without change in qualitative or quantitative composition and mean mass of:			
27a	tablets, capsules, suppositories and pessaries other than those stated in change no. 27b	1–2	2–6	IN
27b	gastro-resistant, modified or prolonged-release FPPs and scored tablets	1–2	1–6	Vmin

continues

[11] See footnote 3.

Table *continued*

Conditions to be fulfilled 1. Specifications for the FPP are updated only with respect to dimensions of the FPP. 2. Multipoint in vitro dissolution profiles of the current and proposed versions of the product (determined in the routine release medium, on at least one batch of pilot- or production-scale), are comparable.
Documentation required 1. For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions. 2. Sample of the FPP. 3. (P.2) Discussion on the differences in manufacturing process(es) between the currently accepted and proposed products and the potential impact on product performance. 4. (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium, on at least one batch of pilot- or production-scale of the current and proposed products. 5. (P.5) Copies of revised FPP release and shelf-life specifications. 6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted.

3.2. P.3 Manufacture

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
28	Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving:			
28a	secondary packaging of all types of FPPs	2–3	1	IN
28b	primary packaging site of:			
28b.1	solid FPPs (e.g. tablets, capsules), semi-solid FPPs (e.g. ointments, creams) and solution liquid FPPs	2–4	1, 8	IN
28b.2	other liquid FPPs (suspensions, emulsions)	2–5	1, 5, 8	IN

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
28c	all other manufacturing operations except batch control and/or release testing	1–3, 5	1–9	Vmin

Conditions to be fulfilled

1. No change in the batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, or FPP specifications.
2. Satisfactory inspection in the last three years either by WHO or an SRA.
3. Site appropriately authorized by an NMRA (to manufacture the pharmaceutical form and the product concerned).
4. The change does not concern a sterile FPP.
5. Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production-scale batches in accordance with the current protocol.

Documentation required

1. Evidence that the proposed site has been appropriately authorized in the last three years, for the pharmaceutical form and the product concerned:
    - a copy of the current manufacturing authorization, a GMP certificate or equivalent document issued by the NMRA;
    - a GMP statement or equivalent issued by WHO or an SRA;
    - date of the last satisfactory inspection concerning the packaging facilities by WHO or an SRA in the last three years.
2. Date and scope (with indication as to whether scope was e.g. product-specific or related to a specific pharmaceutical form) of the last satisfactory inspection.
3. (P.2) Where applicable, for semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.
4. (P.2) For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches.
5. (P.3.5) Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f2 calculation as necessary.
6. (P.5.1) Copies of release and shelf-life specifications.
7. (P.5.4) Batch analysis data on one production-scale batch from the proposed site and comparative data on the last three batches from the previous site.

continues

Table *continued*

Documentation required

8. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the FPP produced at the new site into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
9. (R.1) Executed production documents for one batch of the FPP manufactured at the new site.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
29	Replacement or addition of a site involving batch control testing	1–2	1–3	AN

Conditions to be fulfilled

1. Site is appropriately authorized by the NMRA and satisfactorily inspected either by WHO or an SRA.
2. Transfer of methods from the current testing site to the proposed testing site has been successfully completed.

Documentation required

1. Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application.
2. Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected either by WHO or an SRA.
3. (P.5.3) Documented evidence of successful transfer of analytical procedures from the current to the proposed site.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
30	Change in the batch size of the FPP involving:			
30a	up to and including a factor of 10 compared to the biobatch	1–7	2, 5–6	IN
30b	downscaling	1–5	2, 6	AN
30c	other situations	1–7	1–7	Vmin

Conditions to be fulfilled

1. The change does not affect the reproducibility and/or consistency of the product.

continues

Table *continued*

Conditions to be fulfilled

2. The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
3. Changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different-sized equipment.
4. A validation protocol is available or validation of the manufacture of three production-scale batches has been successfully undertaken in accordance with the current validation protocol.
5. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6. The change does not require supporting in vivo data.
7. The biobatch size was at least 100 000 units in the case of solid oral dosage forms.

Documentation required

1. (P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next two full production-scale batches should be available on request and should be reported if they do not meet dissolution profile similarity (f2) requirements. For semi-solid dosage forms (e.g. lotions, gels, creams and ointments), containing the API in the dissolved or non-dissolved form, comparative in vitro data on membrane diffusion (membrane release testing) should be submitted or be available on request.
2. (P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme).
3. (P.5.1) Copies of release and shelf-life specifications.
4. (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production-scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two full production-scale batches should be available on request and should be reported immediately by the supplier of the product, if outside specifications (with proposed remedial action).
5. (P.8.2) Updated post-acceptance stability protocol (approved by authorized personnel) and stability commitment to place the first production-scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified).
6. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch (if manufactured as required by documentation 4) (above) and confirmation that there are no changes to the production documents other than those highlighted.
7. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
31a	Change in the manufacturing process of the FPP	1–9	1–4, 6–7	AN
31b		1–3, 5–9	1–7	Vmin

Conditions to be fulfilled

1. The change does not require supporting in vivo data.
2. No change in qualitative and quantitative impurity profile or in physicochemical properties; dissolution profiles are similar to those of the biobatch.
3. The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet or dry granulation or vice versa would be considered a change in manufacturing principle), the same processing intermediates and there are no changes to any manufacturing solvent used in the process.
4. The same classes of equipment, operating procedures, in-process controls (with no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters.
5. No change in the specifications of the intermediates or the FPP.
6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. The change does not involve packaging or labelling where the primary packaging provides a metering and/or delivery function.
8. The change does not concern a gastro-resistant, modified or prolonged-release FPP.
9. The change does not affect the sterilization parameters of a sterile FPP.

Documentation required

1. Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current WHO guidelines on bioequivalence.
2. (P.2) Discussion on the development of the manufacturing process; where applicable:
    - comparative in vitro testing, e.g. multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification);
    - comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be submitted or be available on request);

continues

Table *continued*

Documentation required

- microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the API is present in non-dissolved form.

3. (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation.
4. (P.5) Specification(s) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the proposed process.
5. (P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products, one pilot batch; the other one can be smaller) with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme.
7. (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
32	Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:			
32a	tightening of in-process limits	1–2, 5	1	AN
32b	deletion of a test	2, 4	1, 6	AN
32c	addition of new tests and limits	2–3	1–6	AN
32d	revision or replacement of a test	2–3	1–6	IN

Conditions to be fulfilled

1. The change is within the range of acceptance limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

continues

Table *continued*

Conditions to be fulfilled

3. Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. colour) and does not affect the critical quality attributes of the product (e.g. blend uniformity, weight variation).
5. No change in the analytical procedure.

Documentation required

1. (P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented.
6. (P.5.6) Justification for the addition or deletion of the tests and limits.

3.2. P.4 Control of excipients

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
33	Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin.	1	1	AN

Conditions to be fulfilled

1. No change in the excipient and FPP release and shelf-life specifications.

Documentation required

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
34	Change in the specifications or analytical procedures for an excipient involving:			
34a	deletion of a non-significant in-house parameter	2	1–3	AN
34b	addition of a new test parameter or analytical procedure	2–3	1–2	AN
34c	tightening of specification limits	1–2, 4	1–2	AN
34d	change or replacement of an analytical procedure	2–3	1–2	Vmin

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the analytical procedure.

Documentation required

1. Justification for the change.
2. (P.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable).
3. Justification to demonstrate that the parameter is not critical.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
35	Change in specifications of an excipient to comply with an officially recognized pharmacopoeia	1	1	AN

Conditions to be fulfilled

1. No change to the specifications other than those required to comply with the pharmacopoeia (e.g. no change in particle size distribution).

Documentation required

1. Comparative table of currently accepted and proposed specifications for the excipient.

3.2. P.5 Control of FPP

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
36a	Change in the standard claimed for the FPP from an in-house to an officially recognized pharmacopoeial standard	1–3	1–5	AN
36b	Update to the specifications to comply with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the FPP is controlled	None	1, 3, 5	AN

Conditions to be fulfilled

1. The change is made exclusively to comply with the officially recognized pharmacopoeia.
2. No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test).
3. No deletion of or relaxation of any of the tests, analytical procedures or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 37a or 37d and should follow the corresponding reporting types.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
3. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented.
4. (P.5.6) Justification for the proposed FPP specifications.
5. (P.5.3) Demonstration of the suitability of the monograph to control the FPP.

continues

Table *continued*

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
37	Change in the specifications of the FPP involving test parameters and acceptance criteria:			
37a	deletion of a test parameter	5	1, 6	AN
37b	addition of a test parameter	2–4, 7	1–6	AN
37c	tightening of an acceptance criterion	1–2	1, 6	AN
37d	relaxation of an acceptance criterion	2, 4, 6–7	1, 5–6	IN
37e	replacement of a test parameter	2–4, 6-7	1–6	IN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No additional impurity found over the ICH identification threshold.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The change to the specifications does not affect the stability and the performance of the product.
7. The change does not concern sterility testing.

Documentation required

1. (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.

continues

Table *continued*

Documentation required

5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed procedures, if new analytical procedures are implemented.
6. (P.5.6) Justification for the proposed FPP specifications.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
38	Change in the analytical procedures for the FPP involving:			
38a	deletion of an analytical procedure	5	1, 6	AN
38b	addition of an analytical procedureref	3–4, 6–7	1–5	AN
38c.1	modification or replacement of an analytical procedure	1–4, 6–7	1–5	AN
38c.2		2–4, 6–7	1–5	Vmin
38d	updating the analytical procedure with an officially recognized pharmacopoeial monograph as a result of an update to that monograph	None	1–5	AN
38e	change from an in-house analytical procedure to an analytical procedure in an officially recognized pharmacopoeial monograph or from the analytical procedure in one officially recognized pharmacopoeial monograph to an analytical procedure in another officially recognized pharmacopoeial monograph	2, 7	1–3, 5	IN

continues

Table *continued*

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected.
2. Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. The change does not concern sterility testing.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted analytical procedure.
6. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
7. No new impurities have been detected.

Documentation required

1. (P.5.1) A copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications.
2. (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used.
3. (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used.
4. (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods.
5. (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed analytical procedures.
6. Justification for the deletion of the analytical procedure, with supporting data.

3.2. P.7 Container-closure system

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
39a	Replacement or addition of a primary packaging type	1	1–2, 4–6	Vmin
39b		None	1–6	Vmaj

continues

Table *continued*

Conditions to be fulfilled

1. The change does not concern a sterile FPP.

Documentation required

1. Samples of the product as packaged in the new container-closure system.
2. (P.2) Data on the suitability of the container-closure system (e.g. extractable/leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging.
3. (P.3.5) For sterile FPPs, process validation and/or evaluation studies.
4. (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, and results of transportation studies, if appropriate).
5. (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photostability studies.
6. (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation 5.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
40	Change in the package size involving:			
40a	change in the number of units (e.g. tablets, ampoules, etc.) in a package	1–2	1–2	IN
40b.1	change in the fill weight or fill volume of non-parenteral multidose products	1–3	1–2	IN
40b.2		1–2	1–2	Vmin

Conditions to be fulfilled

1. The change is consistent with the posology and treatment duration accepted in the SmPC.
2. No change in the primary packaging material.
3. No increase in the headspace or surface/volume ratio.

Documentation required

1. Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SmPC.

continues

Table *continued*

Documentation required

2. (P.8.2) A written commitment that stability studies will be conducted in accordance with the WHO guidelines for products where stability parameters could be affected.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
41	Change in the shape or dimensions of the container or closure for:			
41a	non-sterile FPPs	1–2	1–3	AN
41b	sterile FPPs	1–2	1–4	Vmin

Conditions to be fulfilled

1. No change in the qualitative or quantitative composition of the container and/or closure.
2. The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP.

Documentation required

1. Samples of the product packaged in the new container-closure system.
2. (P.7) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications).
3. (P.8.1) In the case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies.
4. (P.3.5) Evidence of revalidation studies in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
42	Change in qualitative and/or quantitative composition of the immediate packaging material for:			
42a	solid FPPs	1–3	1–3	IN
42b	semisolid and liquid FPPs	1–3	1–3	Vmin

continues

Table *continued*

Conditions to be fulfilled

1. The change does not concern a sterile FPP.
2. No change in the packaging type and material (an example of an allowable change is blister to blister).
3. The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material.

Documentation required

1. (P.2) Data demonstrating the suitability of the proposed packaging material (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, and moisture).
2. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).
3. (P.8.1) Stability summary and conclusions, results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
43	Change in the specifications of the immediate packaging involving:			
43a	tightening of specification limits	1–2	1	AN
43b	addition of a test parameter	2–3	1–2	AN
43c	deletion of a non-critical parameter	2	1, 3	AN

Conditions to be fulfilled

1. The change is within the range of currently accepted limits.
2. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

Documentation required

1. (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications.

continues

Table *continued*

Documentation required

2. (P.7) Description of the analytical procedure and summary of validation of the new analytical procedure.
3. Documentation to demonstrate that the parameter is not critical.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
44	Change to an analytical procedure on the immediate packaging involving:			
44a	minor change to an analytical procedure	1–3	1	AN
44b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	AN
44c	deletion of an analytical procedure	5	2	AN

Conditions to be fulfilled

1. The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method).
2. Appropriate (re)validation studies have been performed in accordance with the relevant guidelines.
3. Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method.

Documentation required

1. (P.7) Description of the method and comparative validation results demonstrating that the currently accepted and proposed methods are at least equivalent.
2. Documentation to demonstrate the equivalence of the deleted method and a currently accepted method.

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
45	Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, or change of needle shield).	1	1–2	IN

Conditions to be fulfilled

1. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the FPP.

Documentation required

1. (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications).
2. Sample of the FPP.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
46	Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers) involving:			
46a	addition or replacement	1, 2	1–2	IN
46b	deletion	3	3	IN

Conditions to be fulfilled

1. The proposed measuring device is designed to accurately deliver the required dose for the product concerned in line with the posology, and results of such studies are available.
2. The proposed device is compatible with the FPP.
3. The FPP can be accurately delivered in the absence of the device.

Documentation required

1. (P.2) Data to demonstrate accuracy, precision and compatibility of the device.
2. Sample of the device.
3. Justification for the deletion of the device.

3.2. P.8 Stability

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
47	Change in the shelf-life of the FPP (as packaged for sale) involving:			
47a	reduction	3	1–3	IN
47b	extension	1–2	1–3	Vmin

Conditions to be fulfilled

1. No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage.
2. Stability data were generated in accordance with the currently accepted stability protocol.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

1. (P.5.1) Copy of the currently accepted shelf-life specifications.
2. (P 8.1) Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two pilot- or production-scale batches for a period sufficient to support the proposed shelf-life.
3. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
48	Change in the in-use period of the FPP (after first opening or after reconstitution or dilution):			
48a	reduction	1	1	IN
48b	extension	None	1–2	Vmin

Conditions to be fulfilled

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Documentation required

1. (P 8) Proposed in-use period, test results and justification of change.
2. (P 5.1) Copy of currently accepted end of shelf-life FPP specifications and, where applicable, specifications after dilution or reconstitution.

continues

Table *continued*

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
49	Change in the labelled storage conditions of the FPP (as packaged for sale), the product during the in-use period or the product after reconstitution or dilution	1	1–2	Vmin

Conditions to be fulfilled

1. The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns.

Documentation required

1. (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage conditions.
2. (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change.

Appendix 1

Examples of changes that make a new application or extension application necessary

Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1. Change of the API to a different API 2. Inclusion of an additional API in a multicomponent product 3. Removal of one API from a multicomponent product 4. Change in the dose and/or strength of one or more APIs 5. Change from an immediate-release product to an extended or delayed-release dosage form or vice versa 6. Change from a liquid to a powder for reconstitution or vice versa 7. Changes in the route of administration	None	1	New application/ extension application
Conditions to be fulfilled None			
Documentation required 1. Documents in fulfilment of the requirements outlined in the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.[12]			

[12] See footnote 3.

Appendix 2

Changes to excipients

Excipient	Percentage excipient (w/w) out of total target dosage form core weight
Filler	± 5.0
Disintegrant	
• starch	± 3.0
• other	± 1.0
Binder	± 0.5
Lubricant	
• Ca or Mg Stearate	± 0.25
• other	± 1.0
Glidant	
• talc	± 1.0
• other	± 0.1

- These percentages are based on the assumption that the active pharmaceutical ingredient (API) in the finished pharmaceutical product (FPP) is formulated to 100.0% of label/potency declaration. The total additive effect of all changes to excipients should be not more than 5.0% relative to the target dosage form weight (e.g. in a product consisting of API, lactose, microcrystalline cellulose and magnesium stearate, the lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%).
- If an excipient serves multiple functions (e.g. microcrystalline cellulose as a filler and as a disintegrant), then the most conservative recommended range should be applied (e.g. ± 1.0% for microcrystalline cellulose should be applied in this example). If a wider range is proposed, scientific justification and supporting data should be provided to demonstrate that the wider range will not affect the other function of the excipient.

Annex 4

Guidelines on procedures and data requirements for changes to approved vaccines

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;[1]

[1] 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).

9. Authors and acknowledgements

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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
	Quality changes	
Major quality changes	PAS	6 months
Moderate quality changes	PAS	3 months

Table 1 *continued*

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

N/A: not applicable.

[a] 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).

[b] 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.

[c] 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
1. Change in the name of the antigen *Note: This change generally applies only to influenza vaccines (see section 8.2).*	None	1, 2	Moderate
Conditions None			

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
Supporting data 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
2. Change to an antigen manufacturing facility:			
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
3. Change to the antigen fermentation, viral propagation or cellular propagation process:			
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
4. Change to the antigen purification process involving:			
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
5. Change in scale of the manufacturing process:			
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
6. Change in supplier of raw materials of biological origin (for example, fetal calf serum, human serum albumin, trypsin)	None	4, 8, 12, 13	Moderate
	8	4, 8	Minor
7. Change in source of raw materials of biological origin	None	4, 7, 12, 13	Moderate
	8	4, 7	Minor
8. Introduction of reprocessing steps	14	8, 10, 11, 14	Moderate

Conditions

1. No change in the principle of the 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*

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.

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
9. Change to the cell banks:			
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.			
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
10. Change to the seed lots:			
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.			
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
11. Change in cell bank/seed lot testing/storage site	5, 7	10	Minor
12. Change in cell bank/seed lot qualification protocol	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*

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
13. Change in equipment used in the antigen manufacturing process, such as:			
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

Conditions

None

Supporting data

1. Information on the in-process control testing.
2. Process validation study reports.
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (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
14. Change in specification for the materials, involving:			
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
15. Change to in-process tests and/or acceptance criteria applied during manufacture of the antigen, involving:			
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
16. Change in in-process controls testing site	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*

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
17. Change affecting the quality control (QC) (release and stability) testing of the antigen, involving:			
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
18. Change in the specification used to release the antigen, involving:			
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
24. Change in the primary container closure system(s) for the storage and shipment of the antigen	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
25. Change in the specification of the primary container closure system for the antigen, involving:			
a. deletion of a test	1, 2	1, 2	Minor
b. addition of a test	3	1–3	Minor
c. replacement of an analytical procedure	6, 7	1–3	Minor
d. minor changes to an analytical procedure	4–7	1–3	Minor
e. widening of an acceptance criterion	None	1, 2	Moderate
f. 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
26. Change in the shelf-life/hold-time for the antigen or for a stored intermediate of the antigen, involving:			
a. extension	None	1–5	Moderate
	1–5	1, 2, 5	Minor
b. reduction	None	1–5	Moderate
	6	2–4	Minor

Conditions

1. No changes to the container closure system in direct contact with the 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
27. Change in the post-approval stability protocol of the antigen, involving:			
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
28. Change in the storage conditions for the antigen, involving:			
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, 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, 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, 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, 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

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.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
29. Change in the description or composition of the final product, involving:			
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) *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.*	None	1–10	Major
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
30. Change involving an approved chemical/synthetic adjuvant:			
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
31. Change involving a biological adjuvant:			
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

Conditions

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.

Supporting data

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*

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.

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
32. Change to the diluent, involving:			
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
33. Change involving a final product manufacturer/ manufacturing facility, such as:			
a. replacement or addition of a manufacturing facility for the final product (including formulation/ filling and primary packaging)	None	1–7	Major
	1–5	1–3, 5–8	Moderate
b. 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
34. Change in the final product manufacturing process, such as:			
a. scale-up of the manufacturing process at the formulation/filling stage	1–4	1–6	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
35. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:			
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
36. Change in in-process controls testing site	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*

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
37. Change in the specification used to release the excipient, involving: *Note: This change excludes adjuvants. See adjuvant-specific changes above for details (**changes 30** and **31**).*			
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*

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
38. Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk	None	2–7	Major
39. Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source	None	1, 3, 5, 6	Moderate
40. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5, 6	2–7	Minor
41. Change in manufacture of a biological excipient *Note: This change excludes biological adjuvants; see adjuvant-specific changes above for details (**changes 30** and **31**).*	None	2–7	Major
	2	2–7	Moderate
	1, 2	2–7	Minor
42. Change in supplier for a plasma-derived excipient (for example, human serum albumin)	None	3–8	Major
	3, 4	5, 6, 9	Moderate
43. Change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient) *Note: This change excludes adjuvants; see adjuvant-specific changes above for details (**changes 30** and **31**).*	None	2, 3, 5–7	Moderate
	1, 5, 6	3	Minor

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
45. Change affecting the QC testing of the final product (release and stability), involving:			
Note: Transfer of testing to a different facility within a GMP-approved site is not considered to be a reportable change but is treated as a minor GMP change and reviewed during inspections.			
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

Conditions

1. The transferred QC test is not a potency assay or a bioassay.

Supporting data

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

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
46. Change in the specification used to release the final product, involving:			
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

Conditions

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*

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.

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
52. Modification of a primary container closure system (for example, new coating, adhesive, stopper or type of glass) *Note: The addition of a new container closure system (for example, addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation; see **change 29.c** above.*	None	1–7	Moderate
	1–3	3	Minor
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)	None	1, 3, 6	Moderate
54. Deletion of a container closure system *Note: The NRA should be notified of the deletion of a container closure system, and product labelling information should be updated, as appropriate.*	None	1	Minor

Conditions

1. 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
55. Change in the supplier for a primary container closure component, involving:			
a. replacement or addition of a supplier	1, 2	4, 5	Minor
*Note: A change in container closure system involving new materials of construction, shape or dimensions would require supporting data such as is shown for **change 52** above.*			
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
56. Change in the specification used to release a primary container closure component or functional secondary container closure component, involving:			
a. deletion of a test	1, 2	1, 2	Minor
b. addition of a test	3	1, 2	Minor
c. replacement of an analytical procedure	6, 7	1–3	Minor
d. minor changes to an analytical procedure	4–7	1–3	Minor

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
57. Change in the shelf-life of the final product, involving:			
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
Conditions None			
Supporting data 1. Updated product labelling information, as appropriate. 2. Proposed storage conditions and shelf-life, as appropriate. 3. Updated post-approval stability protocol. 4. Justification of the change to the post-approval stability protocol or stability commitment. 5. Results of stability testing under real-time/real-temperature conditions covering the proposed shelf-life generated on at least three (3) commercial-scale batches.			

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
58. Change in the post-approval stability protocol of the final product, involving:			
a. major change to the post-approval stability protocol or stability commitment, such as deletion of a test, replacement of an analytical procedure 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
59. Change in the labelled storage conditions for the final product or the diluted or reconstituted vaccine, involving:			
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

Conditions

None

Supporting data

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

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, 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, 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, accessed 2 December 2014).
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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.[1]
- Change to add a new dosage form[1] (such as replacement of a suspension for injection with a lyophilized cake).
- Change to add a new strength.[1]
- Change to add a new delivery device.[1] (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.

[1] 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).