GUIDANCE ON VARIATIONS TO A PREQUALIFIED VACCINE

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1. Introduction

The specifications of medicinal products are defined in a Marketing Authorization (MA) that details which starting materials, manufacturing processes, and quality control tests have been approved by the National Regulatory Authority (NRA). By setting procedures, instructions, specifications, products can be consistently manufactured to the standard shown to be safe and effective in preclinical and clinical studies. However, production, safety, and efficacy parameters evolve with time, and the MA must be updated to reflect the product as it currently exists. Manufacturers are responsible for assessing the impact of planned and proposed changes on their product, and regulatory approval of the changes may be needed to maintain the validity of the MA. However, it is recognized that not all changes affect the product to the same extent. Some, like a change in the active ingredient, are so significant that the altered product is considered a new product, requiring a complete re-assessment and licensing procedure. Others, like the replacement of equipment by another of similar technical characteristics and functioning principles, are considered as occurrences and are unlikely to affect product's quality.

In correspondence with good practices, usually the updating of a manufacturing process is well planned in advance, in such a way that allows an early evaluation of the improvement feasibility and potential impact in the process and product.

The World Health Organization (WHO), through its Department of Essential Medicines and Health products (EMP), provides advice to the United Nations Children's Fund (UNICEF) and other United Nations agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies. This service is called prequalification (PQ). The prequalified vaccines are products that meet WHO recommendations on quality, safety and efficacy, including compliance with WHO's recommended standards for good manufacturing practice (GMP) and good clinical practice (GCP) and meet operational packaging and presentation specifications set by each procuring agency. The aim is to ensure that vaccines provided through the United Nations for use in national immunization services in different countries are safe, effective and suitable for the target populations at the recommended immunization schedules and with appropriate co-administered products.

After the prequalification of a vaccine, it may happen that manufacturers introduce or plan to introduce changes in the manufacturing of the product. These changes are made to a vaccine that has been licensed by the National Regulatory Authority of the producing country and also has been prequalified by WHO for global use. Many of these changes may be introduced to improve the quality of the vaccine, the efficiency of the manufacturing process, or they could be made for marketing reasons. In addition, there may be changes to the labelling system of a vaccine because of a new schedule, improving the management of a potential risk for a product by adding warnings, limiting or expanding the target population, etc.

Due to the implications and impact that these changes may have on the quality, safety and efficacy of the vaccines, as well as to avoid additional regulatory burden, most NRAs have developed and published a scheme to classify these changes. Usually changes are categorized in three groups according to their significance or impact on the attributes of the vaccine. These groups are the following:

I Major changes with a high potential to affect the quality, safety or efficacy of the vaccine.

II Moderate changes with a medium potential to affect the quality, safety, or efficacy.

IIIMinor changes with a low potential to affect quality, safety, or efficacy.

Using this scheme, each change is classified according to how it is to be reported to the responsible NRA, and the amount of supporting information the manufacturer must submit. It is recognized that processing and assessing variations to a MA involves an extensive workload to the responsible NRA.

In the context of the revised prequalification procedure (**Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO TRS 978, ANNEX 6**), a system is needed to ensure that all relevant variations are reported and assessed not only by the responsible NRA but also by the prequalification secretariat at WHO.

This document should be considered as a note for guidance to manufacturers of prequalified vaccines, and as a complement to the **Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO TRS 978, ANNEX 6**. It provides the basis for the reporting of changes introduced to prequalified vaccines and how these should be reported to the prequalification secretariat at WHO. It is a guidance limited to vaccines and it is recognized that it is not an all-inclusive document. As such, both manufacturers and WHO should apply a flexible approach where variations not described in this guidance can be interpreted on a case-by-case basis.

In the context of this document, the words change(s) and variation(s) have the same meaning and / or interpretation.

2. Objectives

This is a guidance document that complements chapters 7 and 8 of the revised **Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO TRS 978, ANNEX 6)**. It is intended to:

- Assist manufacturers with the classification of changes made to a prequalified vaccine;
- Provide guidance on the data package required to support changes that may potentially impact on the quality, safety and efficacy attributes of a prequalified vaccine.

3. Scope and application

This guidance document applies to manufacturers intending to make changes in the production, quality control, indications or other to a prequalified vaccine. This includes the antigenic substance responsible for eliciting an immune response in a human body. It should be read in conjunction with the **Procedure for assessing the acceptability, in principle, of vaccines for purchase by**

United Nations agencies. WHO TRS 978, ANNEX 6 and other documents related with the prequalification process of vaccines.

4. National and WHO reporting requirements

By principle, WHO relies heavily on a well-functioning NRA in the country of manufacture to conduct the day-to-day regulatory oversight of vaccines, and enforce and monitor corrective actions when deficiencies are noted. However, recognizing that regulatory requirements of individual countries may vary, WHO was assigned the responsibility for international standardization. In this regard, the technical specifications for individual vaccines published in the WHO Technical Report Series (TRS), the international standards and reference materials required for testing, the establishment of International Units, as well as the publication of the International Pharmacopoeia and of the WHO Good Manufacture Practices (GMP) code all serve to harmonize requirements globally.

For priority vaccines for global supply, WHO also assesses and prequalifies vaccines that conform to these international standards.

To prequalify vaccines, WHO requires manufacturers to submit a dossier, known as Product Summary File (PSF) that follows a defined format. However, the WHO prequalification Secretariat may accept also a dossier in CTD format (Common Technical Document) used in Europe, accepted by countries like United States, Australia, Japan, and also adopted by several other countries. The dossier contains information on vaccine production, quality control, safety, and efficacy.

For the most part, the dossier required by WHO is an abbreviated version of what usually is submitted to the NRA for national approval. In addition, WHO focuses its review on compliance with the WHO requirements for the specific vaccine, the technical specifications of the UN tender, safety and efficacy data relevant to the target population and compatibility with immunization schedules in user countries. When the result of the WHO assessment is positive (this includes the testing of vaccine samples and site audit(s), the vaccine is granted the prequalification status and is listed as a medicinal product that can be procured by UN agencies.

Thereafter and based on defined risk criteria, WHO will conduct reassessments. For this purpose, WHO needs to be informed of the changes that manufacturers have introduced to their products.

When a vaccine is regulated by a NRA eligible to streamlined prequalification procedure, WHO Prequalification Secretariat will rely on the evaluation performed by the NRA to assess the impact of each change and will base the approval of the variation on the assessment performed by the NRA. However, variations of administrative nature, such as change of address or contact persons etc., are expected to be notified to WHO immediately for their potential implications from the administrative and logistics points of view. These variations pertain therefore to category **"N" Immediate Notification"** further described in Section 5 and Appendix 1 and are listed under the section of administrative changes.

Unless otherwise specified, changes will be notified to WHO as part of the annual reporting documentation described in chapter 8 of the **Procedure for assessing the acceptability, in**

principle, of vaccines for purchase by United Nations agencies. WHO TRS 978, ANNEX 6, as per the documentation required to be submitted in the Prequalified Vaccine Annual Report (PQVAR).

Manufactures and National Regulatory Authorities of member states may have already established national regulatory requirements in the oversight of variations. However, the current document is aimed at providing additional details to assist manufacturers of prequalified vaccines to classify changes introduced to their products that may affect sections of the dossier (Product Summary File or CTD), and to determine the documentation required to support every change.

5. Reporting categories and procedure for submissions

5.1 General

To better explain what is needed for the reporting of variations introduced in the production and control of WHO prequalified vaccines, this guidance document lists a number of changes likely to occur over the lifespan of a vaccine, the timing for reporting, and required supporting evidence to justify the change.

The reporting of variations in the context of the prequalification of vaccines covers the following categories:

Minor variations, Type **N** – These are changes that must be notified immediately (within one month after approval by the responsible NRA) to WHO PQ Secretariat. "**N"** stands for "**Immediate Notification**".

Moderate variations, Type **R** – Annual reporting system as part of the Prequalified Vaccine Annual Report (PQVAR). "**R"** stands for "**Annual Reporting**".

Major variations, Type **A** – Changes that require WHO approval before implementation for United Nations' supply. "**A"** stands for "**WHO PQ Secretariat approval before implementation of the variation**".

If WHO considers that a change(s) has been inappropriately classified, the manufacturer will be notified accordingly.

The examples of changes presented in Appendix 1 (Administrative changes), Appendix 2 (Manufacturing and Quality Control) and Appendix 3 (Efficacy and Safety) are intended to assist manufacturers with the classification of changes made.

5.2 Pre-Submission Enquiries

The listing of changes presented in this guidance document is not exhaustive, or all inclusive such as to cover all possible situations. When in doubt as to the classification of a change or

about the required supporting documentation, manufacturers are encouraged to seek advice by contacting the WHO Prequalification Secretariat.

To aid in planning the allocation of review resources, sponsors are encouraged to contact WHO regarding the type, number and proposed filing dates for planned changes to existing prequalified vaccines.

5.3 Submissions

5.3.1 Variations Type N

The Prequalification Secretariat (PQ) will review variations Type **N** (Immediate Notification) within 30 days of receipt of the notification and will update the PQ documentation and information available at WHO, accordingly. If WHO PQ Secretariat has not sent the manufacturer a written opinion on t he notification within 30 da ys following the acknowledgement of receipt of a valid notification, the notification shall be deemed acceptable.

The following items should be submitted to the PQ Secretariat where applicable, with the notification:

(a) A cover letter (see Appendix 4).
(b) A variation form (see Appendix 5).
(a) A listing of all Type **N** changes for each vaccine that has been prequalified and that have occurred in the preceding six (6) months, are compiled using the notification Type **N** form;
(b) A copy of the most recent revised label(s) (inner and outer).

Supporting data for the Type **N** changes cited and/or referred to in the associated guidance document should not be submitted; however, the data should be available to WHO PQ Secretariat if requested at any time. Type **N** variations pertaining to the administrative section, and needed in order to keep the product information up-to-date and to facilitate documentation management should be reported, as described in this document.

Any Type **N** changes that have been implemented should be clearly identified in the affected documents (e.g., PSF, labels, package inserts, etc.) with the filing of any subsequent submission to WHO.

5.3.2 Variations type R

Type R changes are those that are reported annually as part of the PQVAR, and are reviewed as part of the assessment of the PQVAR. Variations Type **R** may be submitted by the manufacturer within 12 months after implementation (considering the date of the prequalification of the vaccine). The 12 months deadline is to report minor variations implemented during the previous twelve months, as part of the Prequalified Vaccine Annual Report (PQVAR).

The PQ Secretariat can ask questions as part of the evaluation of the PQVAR and, as a result, complementary information may be requested. PQVAR requirements are defined in Section 8 of the Procedure for assessing the acceptability , in principle, of vaccines for purchase by United Nations agencies WHO TRS 978, ANNEX 6. This information has to be provided within 30 days. In the event the WHO considers that the complementary information is not complete, not sufficient, and/or not satisfactory, the variation may be rejected.

The following items should be included, where applicable, with the variation(s) Type **R**:

(a) A listing of all Type **R** changes for each vaccine that has been prequalified and that have occurred in the preceding twelve (12) months are compiled using the notification Type **R** form;
(b) A copy of the most recent revised label(s) (inner and outer) if a Type **R** label change has been made.

Supporting data for the Type **R** changes recommended in the associated guidance documents must be submitted with the PQVAR.

Any Type **R** changes that have been **implemented should** be annotated in the affected documents (e.g., PSF, labels, package inserts, etc.) with the filing of any subsequent submission to WHO.

5.3.3 Variations type A

For variations categorized as Type **A (Approval before implementation),** approval by the responsible NRA and by PQ Secretariat is required before implementation for lots to be supplied through UN agencies. However, where a vaccine has been assessed for PQ using the streamlined procedure, based on an established data sharing agreement with the NRA of record, provided that variation assessment information from the responsible NRA is supplied, the type A variations can be approved based on the NRA report.

A submission of a type **A** variation must contain the following:

- Cover letter (see Appendix 4).
- A variation form (see Appendix 5).
- Where a variation is the consequence of or related to another variation, a description of the relationship between these variations should be provided in the appropriate section of the form.
- Documentary evidence that the variation meets the conditions referred to in this guidance document, and that relevant supportive documentation is available, as referred in this document.
- Where relevant, a side-by-side comparison of the previously approved product and the proposed information.
- Documents listed in the relevant section of Appendices 2 (Manufacturing and Quality Control) or 3 (Efficacy and Safety) as appropriate.

As a general rule, for variations of Type **A**, a 90 days evaluation timetable will apply.

Within the evaluation period of 90 days the WHO PQ Secretariat may give a positive opinion or ask the manufacturer to provide supplementary information. The clock for the review procedure will then stop for a maximum of 30 days until the supplementary information is received. Should the manufacturer need more than 30 da ys to respond a request for an extension with a justification should be sent to the PQ Secretariat. This request may be accepted or rejected by WHO PQ Secretariat.

The evaluation of responses by WHO may take up to 30 days depending on the complexity and amount of data requested to the manufacturer.

The request for supplementary information will be sent to the manufacturer together with a timetable stating the date by when the WHO Prequalification Secretariat expects to receive the requested data, and where appropriate the extended evaluation period.

The Prequalification Secretariat shall inform the manufacturer and the NRA of the concerned country about the approval or rejection of the variation (including the rationale for a negative outcome).

Where several Type **A** variations, or a group of Type **A** variation(s) have been submitted as one application, the Prequalification Secretariat will inform the manufacturer and the corresponding NRA which variation(s) have been accepted or rejected.

It may be the case that a Type **A** variation may imply modifications to labeling or package leaflet of the vaccine, in which case the applicant should submit updates – with the corresponding translations, of the product information texts according to the current prequalification procedure.

Appendix 1
Administrative changes

The examples presented below are intended to assist manufacturers in understanding the reporting categories of changes made to the prequalified vaccines. The information summarized in the tables below provides recommendations for:

(a) the *conditions to be fulfilled* for a given change to be classified as either a Type **A**, Type **R** or Type **N** change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change, unless sufficient justification is provided such as guidance of an NRA in the context of a streamlined prequalification, or a prior discussion and agreement with WHO Secretariat.

For example, if any of the conditions recommended for Type **N** are not fulfilled, the change is considered a Type **A**.

(b) the *supporting data* for a given change, either to be submitted to WHO and/or maintained by the sponsor. Where applicable, the corresponding modules of the dossier (PSF, CTD or hybrid format) for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided; and

(c) the *reporting category* (e.g., **A**, **N**, **R**).

Administrative changes may affect the information provided in Chapter 1 of the Product Summary File of a prequalified vaccine.

As previously mentioned, the WHO PQ Secretariat reserves the right to request additional information as deemed appropriate, or conditions not specifically described in this document.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
A.1 Change in the name and/or address of the marketing authorization holder that was granted the prequalification of the vaccine.	1	1, 2	**N**
Conditions			
1. The marketing authorization holder shall remain the same legal entity.			
Supporting data 1. Approval for change of name as per statutory requirements. 2. Notification of new name in the form of a sponsor signed letter if the manufacturer is sold or merged with another company. Note that if address changes due to manufacturing facility change then PSF needs to be resubmitted with fresh quality; safety and efficacy data according to the manufacturing facility change requirements described in Appendix 2.			
A.2 Company sale, purchase, merger.	1	1, 2, 3	**N**
1. The marketing authorization holder shall remain the same legal entity.			
Supporting data 1. Approval for sale/purchase as per statutory requirements. 2. Notification of new name if the manufacturer is sold or merged with another company.			

3. Revised labeling.			
A.3 Change in the (invented) name of the product.	1	1, 2	**N**
Conditions			
1. The NRA has authorized a new name.			
Supporting data 1. Copy of the NRA letter of acceptance of the new (invented) name. 2. Revised product information.			

Appendix 2
Manufacturing and Quality Control

The examples of changes presented below are intended to assist manufacturers with the classification of changes made to the prequalified vaccines. The information summarized in the tables provides recommendations for:

(a) the *conditions to be fulfilled* for a given change to be classified as either a Type **A**, Type **R** or Type **N** change. If any of the conditions outlined for a given change are not fulfilled, the change is automatically considered the next higher level of change. For example, if any of the conditions recommended for Type **N** are not fulfilled, the change is considered a Type **A or R**.

Similarly, if any of the conditions recommended for a Type **A** notification are not fulfilled, the change would warrant the filing of a new dossier (PSF or CTD) since it would be considered a new product. If this is the case, pre-submission discussions with the WHO Prequalification Secretariat are highly recommended.

(b) the *supporting data* for a given change, either to be submitted to WHO and/or maintained by the sponsor. Where applicable, the corresponding modules of the dossier (PSF, CTD or hybrid format) for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided; and
(c) the *reporting category* (e.g., **A**, **N**, **R**).

Manufacturing and quality control related changes are likely to affect the information provided in Chapters 3, 4, 5, 6, and 7 of the Product Summary File of a prequalified vaccine.

As previously mentioned, the WHO PQ Secretariat reserves the right to request additional information as deemed appropriate, or conditions not specifically described in this document.

For the purpose of this document 'test procedure' has the same meaning as 'analytical procedure' and 'limits' have the same meaning as 'acceptance criteria'. 'Specification parameter' means the quality attribute for which a test procedure and limits are set, e.g. assay, identity and water content. The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

A. Cell banks and seed lots

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
1. Changes to the cell banks: *Note: New cell substrates that are unrelated to the MCB or pre-MCB material generally require a new application for market authorization or license application.*			
a. generation of a new Master Cell Bank	1	1, 2, 5, 7-9	A
b. generation of a new Working Cell Bank (WCB)	*None*	1, 2	A
	2-4	1, 2	N
c. Change in cell bank storage site	7	10	N
2. Changes to the seed lots: *Note: New viral or bacterial seeds that are unrelated to the MSL or pre-MSL material generally require a new application for market authorization or license application.*			
a. generation of a new Master Seed Lot (MSL)	1	1, 5-9, 11	A
b. generation of a new WSL	2, 3	5-9, 11	N
	2-4	5-6, 11	R
c. generation of a new Working Seed Lot (WSL) by extending the passage level of an existing WSL beyond an approved level	None	5-7, 11	A
d. Change in seed lot storage site	7	10	N
3. Change in cell bank/seed lot testing site	5,7	10	R
4. Change in cell bank/seed lot qualification protocol	None	3, 4	A
	7	4	R
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 license. 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 (i.e. addition of new tests or narrowing of acceptance criteria). 7. No changes have been made to the storage conditions used for the cell bank/seed lot and the transport conditions of the cell bank/seed lot has been validated.			
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 the 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 with 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.

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B. Manufacture of bulk

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
B.1 Changes to a bulk manufacturing facility, involving:			
a) Replacement or addition of a manufacturing facility for the bulk, or any intermediate of the bulk.	None	1 - 7, 9 – 13, 15	**A**
	1 – 5	3, 7, 9 - 12	**R**
b) Introduction of microbial hosts into a multi - product mammalian cell culture suite or vice versa.	None	13 - 14	**A**
c) Conversion of production and related area(s) from campaign to concurrent for a multiproduct facility.	6	16 - 17	**A**
d) Conversion of a bulk manufacturing facility from single-product to multi-product.	5	12 - 13, 15	**A**
e) Addition of product(s) to an approved multiproduct manufacturing facility.	4 - 5, 7	13, 16	**A**
f) Introduction of a different host/media-type into an approved multi-product facility.	7	8, 15	**R**
g) Deletion of a manufacturing facility or manufacturer for a bulk intermediate, or bulk.	None	None	**R**

Conditions

1. This is an addition of a manufacturing facility/suite to an approved manufacturing site.
2. The process is an equivalent of the approved process and controls.
3. The new facility/suite is under the same Quality Assurance (QA)/Quality Control (QC) oversight.
4. No changes have been made to the approved and validated cleaning and change-over procedures.
5. The proposed change does not involve additional containment requirements.
6. The manufacturing process is a closed process for shared areas.
7. No changes to the cleaning protocol are necessary to support the introduction of new products (no changes in acceptance criteria, and no new materials have been introduced that need to be evaluated for clearance in a cleaning step).

Supporting data

1. Confirmation that the proposed manufacturing site has been inspected and is licensed by the NRA and/or has been audited by WHO.
2. Updated Chapter 3 or new dossier (PSF or CTD).
3. Name, address, and responsibility of the proposed production facility or facility involved in manufacturing and testing.
4. For antigenic substances obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathies (TSEs) agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance). A TSE Certificate of Suitability from a qualified laboratory, if available, is acceptable for raw materials, auxiliary materials, and reagents only. This is also applicable for substances used in conjugation or linkages processes.
5. Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed bulk.
6. Summary of the process validation and/or evaluation studies. Reference to the protocols and validation reports. The complete report with all raw data could be requested during review and/or during a site audit.
7. Comparability of the approved and proposed bulk with respect to physico-chemical characterization, biological activity, and impurity profile (notice that occasionally, the manufacturer may be required to undertake bridging non-clinical or clinical studies, to support the quality data).
8. Information on the in-process control testing to demonstrate lack of carry-over or cross-contamination.

9. 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 bulk (certificates of analysis to be provided).
10. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time / real temperature testing on three (3) commercial scale batches of the proposed bulk, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify WHO of any failures in the on-going long term stability studies. Manufacturer should consider quoting the corresponding procedures or SOPs for on-going studies.
11. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after NRA and WHO approval) and commitment to place the first commercial scale batch of the final product manufactured using the proposed bulk into the stability programme. Manufacturer should consider quoting the corresponding procedures or SOPs for on-going studies.
12. Information on the proposed production facility involved in the manufacture of the bulk, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems), as well as the cleaning and shipping validation, as appropriate.
13. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If this is not the case, a statement from the manufacturer that no changes were made to the change-over procedures.
14. Results of the environmental monitoring studies in critical classified areas.
15. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross- contamination.
16. Data demonstrating lack of carry-over or cross-contamination.
17. Description of the segregation procedures to avoid cross-contamination. Manufacturer should consider quoting the procedures or SOPs in place.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
B.2 Modification to a facility involved in the manufacture of a bulk, such as:			
a) For an intermediate of bulk manufactured in an open system, any changes which have the potential to increase the environmental risk to the product.	None	1 - 2, 5	**R**
b) Relocation of equipment to another room in the same facility, qualification of a new room or change in classification of an existing room.	1 - 3	3 - 5	**R**
c) Modification to a manufacturing area or to an existing service/system (e.g., change to WFI systems or HVAC systems, moving a wall).	1 - 2	3 - 5	**R**
d) Change in the location of steps in the production process within the same facility.	1	4 - 5	**R**

Conditions

1. The change has no impact on the risk of contamination or cross-contamination.
2. The modification has no product impact.
3. Re-qualification of the equipment follows the original qualification protocol, if applicable.

Supporting data

1. Information on the in-process control testing.
2. Process validation and/or evaluation studies (e.g., equipment qualification). The proposed validation protocol is acceptable, but data could be requested.
3. Information demonstrating re-qualification of the equipment or re-qualification of the change (e.g., operational qualification, performance qualification), as appropriate.
4. Information on the modified production facility/area involved in manufacturing, including set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems).
5. Results of the environmental monitoring studies in critical classified areas.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
B.3 Change to the antigen fermentation, viral propagation or cellular propagation process			
a. a critical change (a change with high potential to impact the quality of the antigen or final product) (e.g., incorporation of disposable bioreactor technology)	None	1-7, 9, 11	A
b. a change with moderate potential to impact quality of the antigen or final product (e.g., extension of the *in vitro* cell age beyond validated parameters)	2, 4	1-6, 8, 10	R
c. a non-critical change with minimal potential to impact the quality of the antigen or final product (e.g., 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	R
B.4 Change to the bulk purification process involving:			
a. a critical change (a change with high potential to impact the quality of the antigen or final product) (e.g., change that could potentially impact the viral clearance capacity of the process or the impurity profile of the antigen)	None	1, 2, 5-7, 9, 11, 12	A
b. a change with moderate potential to impact quality of the antigen or final product (e.g., change in the chemical separation method, for example ion-exchange HPLC to reverse phase HPLC)	2, 4	1, 2, 5-7, 10, 11	R
c. a non-critical change with minimal potential to impact the quality of the antigen or final product (e.g., addition of an in-line filtration step equivalent to the approved filtration step)	1-5	1, 2	N
B5. Scale-up of the manufacturing process			
a) At the fermentation stage.	3-6, 11-13	3, 6, 7, 9, 11	A
b) At the purification stage.	1, 3, 5, 7	6, 7, 9, 11	A
B6. Change in supplier of raw materials/reagents of biological origin (e.g., fetal calf serum, insulin, human serum albumin)	None	4, 8, 12, 13	R
	8	4, 8	R

B7. Change in source of raw materials / reagents of biological origin	None	4, 7, 12, 13	R
	8	4, 7	R
B8. Introduction of reprocessing steps	14	8, 10, 11, 14	N

Conditions

1. No change in the principle of the sterilization procedures of the antigen.
2. The change does not impact the viral clearance data or the chemical nature of an inactivating agent.
3. No change in the antigen specification outside of the approved limits.
4. No change in the impurity profile of the antigen outside of the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The change in scale is linear.
8. The change is for compendial raw materials 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.
12. No change in the proportionality of the raw materials (i.e., the change in scale is linear).
13. The change in scale involves the use of the same bioreactor (i.e., does not involve the use of a larger bioreactor).
14. The need for reprocessing is not due to recurrent deviations from the validated process and the root cause triggering reprocessing is identified.

Supporting data

1. Justification for the classification of the change(s) as critical, moderate or non-critical as it relates to the impact on the quality of the 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 BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance).
5. Process validation study reports.
6. Comparability of the pre and post-change antigen with respect to physico-chemical characterization, biological activity, and impurity profile. Occasionally, bridging non-clinical and/or clinical studies may be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis taking into consideration the quality comparability findings, the nature and level of the 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 less than 3 batches may be acceptable where justified and agreed upon 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 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 upon 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 upon by the NRA.
9. Comparative pre and post-change test results for the manufacturer's characterised key stability indicating

attributes with 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 shall 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 less than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed upon by the NRA.

10. Comparative pre and post-change test results for the manufacturer's characterised key stability indicating attributes with at least 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 testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the 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 upon 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 program.
12. Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk).
13. Information demonstrating comparability of the raw materials/reagents of both sources.
14. Data describing the root cause triggering the reprocessing as well as validation data (e.g., extended hold times, resistance to additional mechanical stress) to support that the reprocessing does not have an impact on the antigen.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Categories
B9. Change in equipment used in the antigen manufacturing process, such as:			
a. introduction of new equipment with different operating principles and different product contact materials	None	1-6	R
b. introduction of new equipment with the same operating principles but different product contact material	None	1, 3-6	R
c. introduction of new equipment with different operating principles but the same product contact material	None	1-3,5,6	R
d. Replacement of equipment with equivalent equipment (including filter)	None	1,5-7	R

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 Categories**
B10. Change in specifications for the materials, involving:			
a. raw materials/intermediates: widening of the approved specifications 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	R
b. raw materials/intermediates: narrowing of the approved specification limits for starting materials/intermediates	1-4	1, 3-7	R
B11. Change to in-process tests or limits applied during manufacture of the antigen, involving:			
a. narrowing of in-process limits	3,5,8,9	2,6	R
b. addition of new in-process test and limits	4, 5, 10, 11	2-6,8,10	R
c. deletion of a non-significant in-process test	4-6	2, 6, 9	R
d. widening of the approved in-process limits, which may have a significant effect on the overall quality of the antigen	None	2-6,8,10,11	R
	3-5	2,6,8,10,11	R
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	R
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	2-6,8,10	R

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.
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 (e.g. content, impurity, any critical physical characteristics or microbial purity).
7. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
8. No change in the in-process 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 (e.g. raw materials, starting materials, solvents, reagents, 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 three (3) 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. 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. 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 with at least three (3) commercial-scale final product batches produced with the proposed changes under real-time/real-temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on 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.

C. Control of the bulk

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
C1. 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 market authorization or license.	1-3	1,2	**R**
b) transfer of the QC testing activities for a pharmacopoeial assay to a new company not approved in the current market authorization or license	1	1,2	**R**
Conditions			
1. The transferred QC test is not a potency assay (e.g. 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 market authorization for the performance of other tests.			
Supporting data			
1. Information demonstrating technology transfer qualification. 2. Evidence that the new company / facility is GMP compliant.			
C2. Change in the specifications used to release the bulk, involving:			
a. deletion of a test	None	1, 5, 8	**A**
b. addition of a test	1-3	1-3, 5	**R**
c. replacement of an analytical procedure	None	1-5	**A**
d. change in animal species/strains for a test (e.g., new species/strains, animals of different age, new supplier where genotype of the animal cannot be confirmed)	None	6, 7	**A**
e. minor changes to an approved analytical procedure	4-7	1, 4, 5	**R**
f. a change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure	4, 7	1-3	**R**
g. widening of an acceptance criterion	None	1, 5, 8	**R**
h. narrowing of an acceptance criterion	1, 8, 9	1	**R**
Conditions			
1. The change does not result from unexpected events arising during manufacture (e.g., new unqualified impurity, change in total impurity limits). 2. No change in the limits/acceptance criteria outside of the approved limits for the approved assays. 3. The addition of test is not to monitor new impurity species. 4. No change in the acceptance criteria outside of the approved limits. 5. The method of analysis is the same and is based on the same analytical technique or principle (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected. 6. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. 7. The change does not concern potency testing. 8. Acceptance criterion for residuals are within recognized or approved acceptance limits, e.g., within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements. 9. The analytical procedure remains the same, or changes to the analytical procedure are minor.			
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 (e.g., tests, acceptance criteria, or analytical procedures). 6. Data demonstrating that the change in animals/strains give comparable results with those obtained using the approved animals/strains. 7. Copies of relevant certificate of fitness for use (e.g., veterinary certificate). 8. Declaration/evidences that consistency of quality and of the production process is maintained.			

D. Reference Standards or Materials

Description of the change	Conditions to	Supporting	Reporting

	be fulfilled	data	category
a. Qualification of a new reference standard against a new primary international standard	None	1, 2	**R**
b. Change in the reference standard from in-house (no relationship with international standard) to pharmacopoeial or international standard	None	1, 2	**R**
c. Qualification of a new lot of reference standard against the approved reference standard (including qualification of a new lot of a secondary reference standard against the approved primary standard)	1	1, 2	**R**
d. Change to reference standard qualification protocol	None	3, 4	**R**
e. Extension of reference standard shelf life	2	5	**R**
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 (e.g., source, characterization, certificate of analysis, comparability data). 3. Justification of the change to reference standard qualification protocol. 4. Updated reference standard qualification protocol. 5. Summary of stability testing and results to support the extension of reference standard shelf life.			

E. Container closure system (for bulk)

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
a) Change in the primary container closure system(s) for the storage and shipment of the bulk.	None	1 – 2, 4	**A**
	1	1, 3	**R**
Conditions			
1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.			
Supporting data			
1. Information on the proposed container closure system (e.g., description, specifications). 2. Demonstration of compatibility with the bulk. 3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (e.g., results of transportation or interaction studies, extractable/leachable studies). 4. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time / real temperature testing on three (3) commercial scale batches of the proposed bulk or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the NRA and WHO Prequalification Secretariat of any failures in the ongoing long term stability studies. Results from one (1) batch may be sufficient based on rationale.			

F. Stability of the bulk

Description of the change	Conditions to	Supporting	Reporting

	be fulfilled	data	category
F1. Change in the shelf life for the bulk or for a stored intermediate of the bulk, involving:			
a) Extension.	None	1 - 4, 6	**A**
	1 - 5	1 - 2, 5	**R**
b) Reduction.	None	1 - 5	**R**
	6	2 - 4	**R**
Conditions			
1. No changes to the container closure system in direct contact with the bulk with the potential of impact on the bulk; or to the recommended storage conditions of the bulk. 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 (i.e.: problems arising during manufacturing or stability concerns should be reported for evaluation).			
Supporting data			
1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained). 2. Proposed storage conditions and shelf life, as appropriate. 3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment. 4. Justification of the change to the post-approval stability protocol or stability commitment. 5. Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches). For intermediates, data to show that the extension of shelf life has no negative impact on the production of the bulk. 6. Interim stability testing results and a commitment to notify NRA and WHO of any failures in the ongoing long term stability studies. Extrapolation of shelf life should be made in accordance with current regulations and must be justified.			
F2. Change in the post-approval stability protocol of the bulk, involving:			
a) Major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature.	None	3 - 6	**A**
	1 - 2	1 - 2, 4 - 5	**R**
b) Addition of time point(s) into the post-approval stability protocol.	None	4 - 5	**R**
c) Addition of test(s) into the post-approval stability protocol.	3	4 - 5	**R**
d) Deletion of time point(s) from the post approval stability protocol beyond the approved shelf life.	None	4 - 5	**R**
e) Deletion of time point(s) from the post approval stability protocol within the approved shelf life.	4	4 - 5	**R**
Conditions			
1. For the replacement of an analytical procedure, the results of method validation demonstrate that the new analytical procedure is at least equivalent to the approved analytical procedure. 2. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. 3. The addition of test(s) is not due to stability concerns or to the identification of new impurities. 4. The approved bulk shelf life is at least 24 months.			
Supporting data			
1. Copies or summaries of analytical procedures, if new analytical procedures are used.			

2. Copies or summaries of validation reports, if new analytical procedures are used. 3. Proposed storage conditions and or shelf life, as appropriate. 4. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment (according to established SOPs; reference to it should be done). 5. Justification of the change to the post-approval stability protocol or stability commitment. 6. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).

G. Storage of the bulk

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
G1. Change in the labeled storage conditions for the bulk, involving:			
a) Addition or change storage condition for the bulk (e.g., widening or tightening of a temperature criterion).	None	1 – 5	**R**
	1 - 2	1 - 4	**R**
Conditions			
1. Change is not necessitated by recurring events arising during manufacture or because of stability concerns. 2. The change consists in the tightening of a temperature criterion within the approved ranges.			
Supporting data			
1. Revised product monograph (e.g., where applicable, title page, composition and packaging and pharmaceutical information section) and inner and outer labels, as applicable. 2. Proposed storage conditions and shelf life. 3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment. 4. Justification of the change in the labeled storage conditions/cautionary statement. 5. Results of stability testing (i.e.: full real time/real temperature stability data covering the proposed shelf life generated on one (1) commercial scale batch).			

H. In process control and process validation

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
H2. Major change to the following process validation protocols used during the manufacture of the final product: introduction of product into an approved multiproduct facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process:.	None	1 - 2	**R**
Conditions			
None.			
Supporting data			
1. Proposed validation protocol (code, date of approval, plan, etc.). Process validation and/or evaluation studies could be requested. The WHO Prequalification Secretariat, at any time, may ask for documented evidences. 2. Rationale for the change in the validation protocol.			

I. Final product characteristics

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
I1. Change in the description or composition of the final product, involving:			
a) Addition of a dosage form or change in the formulation (e.g., lyophilized powder to liquid, change in the amount of excipient, new diluents for lyophilized product).	None	1 - 10	**A**
b) Change in fill volume (same concentration, different volume).	None	1 - 3, 5, 7 - 9	**A**
	1, 3	2 - 4, 6, 9	**A**
c) Change in the concentration of the active ingredient (e.g., 20 unit/mL .vs. 10 unit/mL).	None	2 - 4, 6, 8- 10	**A**
	2 - 3	2 - 4, 6, 8	**A**
d) Addition of a new presentation (e.g., addition of syringes to vials).	None	2 - 3, 6, 8 - 10	**A**

Conditions

1. No major changes in the manufacturing process to accommodate the new fill volume.
2. The new concentration is bracketed by existing approved concentrations.
3. No change in the dose recommended.

Supporting data

1. Chapters of the dossier (PSF / CTD, hybrid format) should be updated according to what is recommended by WHO (dossier content, format. See also document WHO TRS 978, ANNEX 6).
2. Confirmation that information on the bulk has not changed as a result of the submission (e.g., cross reference(s) should be provided to the previously approved dossier (PSF / CTD) or revised information on the bulk, if any of the attributes have changed.
3. Description and composition of the finished form.
4. Discussion of the components of the finished product, as appropriate (e.g., choice of excipients, compatibility of bulk and excipients, the leachates, compatibility with new container closure system (as appropriate)).
5. Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation and/or evaluation studies. Manufacturer may refer to these documents in the variation submission. WHO Prequalification Secretariat may request to review one or more of these documents if deemed necessary.
6. Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the NRA or banned by international organizations (like WHO).
7. Specification(s), analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), and batch analyses (certificate of analysis for three (3) consecutive commercial scale batches. Bracketing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.
8. Information on the container closure system, if any of the components have changed (e.g., description, materials of construction, summary of specifications).
9. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time / real temperature testing on three (3) commercial scale batches of the proposed final product, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the NRA and WHO of any failures in the ongoing long term stability studies.
10. Supporting clinical data or a request for a waiver of in vivo studies.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
I2. Change involving a chemical / synthetic adjuvant:			
a) Change in supplier/manufacturer of a chemical / synthetic adjuvant.	None	4, 5, 9, 10	**R**
	1, 2	5	**R**
b) Change in manufacture process of a chemical / synthetic adjuvant.	None	3-5, 9, 10	**R**
	None	6-10	**R**
c) Change in release specifications of a chemical / synthetic adjuvant (including the tests and / or the analytical procedures).	1, 3	6-8	**R**
	None	4, 5, 9, 10	**R**
I3. Change involving a biological adjuvant			
a) Change in supplier of a biological adjuvant.	None	1-6, 9-12	**N**
b) Change in manufacture of a biological adjuvant.	None	1-6, 9-11	**A**
	4	1-6, 9-11	**A**
c) Change in release specifications of a biological adjuvant (the tests and/or the analytical procedures).	None	6-10	**R**
	1, 3	6-8	**R**

Conditions

1. Any change in specification of the adjuvant is within the approved limits (i.e., narrowing of acceptance criterion).
2. The adjuvant is an aluminium salt.
3. The change in specification consists in the addition of a new test or in a minor change to an analytical procedure.
4. 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 (e.g., impact on the viral clearance studies, BSE/TSE risk).
2. Information on the quality and controls of the materials (e.g., raw materials, starting materials) used in the manufacture of the proposed adjuvant.
3. Flow diagram of the proposed manufacturing process(es) and 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.
4. Process validation study reports (e.g., for manufacturing of the adjuvant) unless justified.
5. Description of the general properties including stability, characteristic features and characterization data of the adjuvant, as appropriate.
6. Updated copy of the proposed specification for the adjuvant (and updated analytical procedures if applicable).
7. Copies or summaries of analytical procedures, if new analytical procedures are used.
8. Validation study reports, if new analytical procedures are used.
9. 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.
10. Comparative pre- and post-change test results for the manufacturer's characterised key stability indicating attributes with at least 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 shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to the NRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed upon by the NRA.

11. Supporting non-clinical and clinical data, if in vitro tests are insufficient to prove comparability
12. Evidence of facility GMP compliance.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
I4. Change to diluent, involving:			
a. change in manufacturing process	None	1 - 5	**A**
	1	1-5	**R**
b. replacement of or addition to the source of a diluent	None	1-3	**R**
	1-3	1-3,5	**R**
c. change in facility used to manufacture a diluent (same company)	1,2	1,3,5	**R**
d. addition of a diluent filling line	1,2,4	1,3,5	**R**
e. addition of a diluent into an approved filling line	1,2	1,3,5	**R**

Conditions

1. The diluent is water for injection (WFI) or a salt solution approved for parenteral human use (i.e., does not include an ingredient with a functional activity, e.g., a preservative) and there is no change to its composition.
2. After reconstitution, there is no change in the final product specification outside of 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.
4. Updated stability data on the product reconstituted with the new diluent.
5. Evidence of facility GMP compliance.

J. Manufacture of the finished product

J1. 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	**A**
	1 - 5	1-3, 5-8	**A**

b. replacement or addition of a secondary packaging facility; a labeling/storage facility; or a distribution facility	2, 3	1-3	**R**
c) deletion of a final product manufacturing facility	None	None	**R**

Conditions

1. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
2. No change in the composition, manufacturing process and final product specification.
3. 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 one of those already approved at the site and uses the same filling process/equipment.

Supporting data

1. Name, address, and responsibility of the proposed production facility involved in manufacturing and testing.
2. Evidence of facility GMP compliance.
3. Confirmation that the manufacturing process description of the final product has not changed as a result of the submission (e.g., other than 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.
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 characterised key stability indicating attributes with at least three (3) commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to the NRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed upon by the NRA.
8. Rationale for considering the proposed formulation/filling suite as equivalent.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
J2. Effect on the existing finished products in a finished product manufacturing facility involving introduction of a new product or change in concurrence*:			
a) Conversion of a finished product manufacturing facility from single-product to multi-product).	None	1 - 3	**A**
b) Conversion of formulation and filling area(s) from campaign to concurrent for multiple product manufacturing areas.	1	1 - 2	**R**

c) Introduction of new product into an approved multi-product formulation/filling suite.	2 - 4	1 - 3	**R**

Conditions

1. The manufacturing process is a closed process for shared areas.
2. The newly introduced product does not introduce significantly different risk issues.
3. The newly introduced product is not of significantly different strength (i.e., mg .vs. µg).
4. The maximum allowable carry-over is not affected by the introduction of the new product.

Supporting data

1. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products) demonstrating lack of carry-over or cross-contamination.
2. Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as appropriate. If no revisions, a signed attestation that no changes were made to the change-over procedures.
3. Information on the product(s) which share the same equipment (e.g., therapeutic classification).

Manufacturer may refer to this data in the variation submission. WHO Prequalification Secretariat may request to review one or more of the documented evidence (SOP of an analytical procedure, validation protocols / reports, change-over and segregation procedures, floor plans and charts, etc.) if deemed necessary.

J3. Change in the final product manufacturing process, such as:			
a) Scale-up of the manufacturing process at the formulation/filling stage.	1 - 4	1, 3, 5 - 6, 8, 10	**R**
b) Addition or replacement of equipment (e.g., formulation tank, filter housing, filling line and head, and lyophilizer).	None	1 - 4, 7, 9	**R**
	5	3 - 4	**N**
c) Product-contact equipment change from dedicated to shared (e.g., formulation tank, filter housing, filling line and head, lyophilizer).	None	9	**R**
d) Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process.	1 – 4	1 - 3, 5, 7, 10	**R**
e) Change in process flow or procedures.	None	1 - 3, 5 - 6, 8	**R**

Conditions

1. The proposed scale uses similar / comparable equipment to that approved (N.B. change in equipment size is not considered as using similar / comparable equipment).
2. Any changes to the manufacturing process and / or to the in-process controls are only those necessitated by the change in batch size (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized).
3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the final product.
5. For product-contact equipment, the change is considered ‘like for like’ (i.e., in term of product-contact material/equipment size).

Supporting data

1. Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
2. Information on the in-process control testing, as applicable.
3. Process validation and/or evaluation studies (e.g., equipment qualification, media fills, as appropriate). The proposed validation protocol is acceptable, but data could be requested.
4. Information demonstrating qualification of the equipment (operational qualification, performance, qualification), or qualification of the change, as applicable.
5. Description of the batches and summary of results, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed product (certificates of analysis to be provided). Bracketing for multiple strength products, container sizes and/or fills may be acceptable if justified.
6. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
7. Commitment to place the first commercial scale batch of the final product manufactured using the proposed formulation / filling suite into the stability programme, and to notify the NRA and WHO Prequalification Secretariat of any failure in the ongoing stability studies.
8. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time / real temperature testing on three (3) commercial scale batches of the proposed product, or longer if less than three (3) time points are available (including the zero time point). Commitment to notify the NRA and WHO Prequalification Secretariat of any failure in the ongoing long term stability studies. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.
9. Cleaning procedures (summary validation report) demonstrating lack of carry-over or cross-contamination.
10. Rationale for regarding the equipment as similar / comparable, as applicable.

Manufacturer may refer to this data in the variation submission. WHO PQ Secretariat may request to review one or more of the documented evidence (SOP of analytical procedures, validation protocols / reports; evaluation studies, report of the qualification of equipment; media fill report, floor plans / drawing of equipment, summary lot protocols, certificates, stability report, charts, etc.) if deemed necessary.

K. Control of excipients

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
K1. Change in the specifications used to release the excipient, involving:			
a) Deletion of a test.	5,8	1, 3	**R**
b) Addition of a test.	4	1 - 3	**R**
c) Replacement of an analytical procedure.	1 - 3	1,2	**R**
d) Minor changes to an approved analytical procedure.	None	1,2	**R**
e) A change from a house/professed analytical procedure to a recognized compendial analytical procedure.	None	1,2	**R**
f) Widening of an acceptance criterion	None	1,3	**R**
g) Narrowing of an acceptance criterion	3,4,6,7	1	**R**
Conditions			

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the excipient.
4. Acceptance criterion for residual solvents are within recognized or approved acceptance limits, e.g., within ICH limits for a Class 3 residual solvent or pharmacopoeial requirements.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
6. The analytical procedure remains the same, or changes in the test procedure are minor
7. The change does not result from unexpected events arising during manufacture, e.g., new unqualified impurity; change in total impurity limits
8. An alternative test analytical procedure is already authorized for the specification attribute/test and this procedure has not been added through a Minor change submission.

Supporting data

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

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
K2. 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	**A**
K3. Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	None	1, 3, 5,6	**N**
K4. Replacement in the source of an excipient from a TSE risk source to a different TSE risk source	5,6	2-7	**R**
K.5 Change in manufacture of a biological excipient *Note: excludes biological adjuvants, refer to adjuvant specific changes for details.*	None	2-7	A
	2	2-7	N
	1, 2	2-7	R
K6. Change in supplier for plasma - derived excipient (e.g., human serum albumin).	None	4 - 8	**A**
	3,4	5,6,9	**N**
K7. Change in supplier of an excipient of non-biological origin or of biological origin (exclude human plasma derived excipient). *Note: excludes chemical/synthetic adjuvants, refer to adjuvant specific changes for details.*	None	3,5-7	**N**
	1,5,6	3	**R**
K8. Change in excipient testing site	1	10	**R**

Conditions
1. No change in the specifications of the excipient or final product outside of 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 NRA country/jurisdiction. 4. The excipient does not influence the structure/conformation of the active ingredient. 5. The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk compared to the previously approved material. 6. Any new excipient does not require the assessment of viral safety data..

Supporting data
1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin. 2. Details of the source of the excipient (e.g., animal species, country of origin) and the steps undertaken in processing to minimize the risk of TSE exposure. 3. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the proposed excipient with the approved excipient. 4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed excipient. 5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the proposed excipient. 6. Comparative pre and post-change test results for the manufacturer's characterised key stability indicating attributes with at least three (3) commercial scale final product batches produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified. Additionally, the manufacturer shall commit to undertake real time stability studies to support the full shelf life/hold-time of the final product under its normal storage conditions and to report to the NRA of any failures in these ongoing long term stability studies. Matrixing, bracketing, the use of smaller scale batches, the use of less than 3 batches and/or use of forced degradation or accelerated temperature conditions for stability testing may be acceptable where justified and agreed upon by the NRA. 7. Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk) including viral safety documentation where necessary. 8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma-derived excipient. 9. Letter from the supplier certifying that no changes were made to the plasma derived excipient compared to the currently approved corresponding medicinal product. **10.** Evidence that the new company/facility work under acceptable quality standards.

L. Control of the final product

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
L1. Change affecting the quality control (QC) testing of the finished product, involving:			
a) Transfer of the QC testing activities for a non pharmacopoeial assay (in-house) to a new company or to a different facility within the same company.	None	1,2	**R**

b) transfer of the QC testing activities for a pharmacopoeial assay to a new company	1	1,2	**R**

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.

Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation protocols / reports, studies on the technology transfer, etc.). However, the WHO Prequalification Secretariat may request documented evidence.

L2. Change in the specifications used to release the finished product, involving:

a) For sterile products, replacing the sterility test with process parametric release.	None	1 - 2, 6, 8 - 9	**N**
b) Deletion of a test.	None	2, 8, 9	**A**
c) Addition of a test.	1 - 2	2 - 4, 8	**N**
d) Change in animal species/strains for a test (e.g., new species/ strains, animals of different age, new supplier where genotype of the animal cannot be confirmed).	None	5, 10	**N**
e) Replacement of an analytical procedure.	6	2 - 4, 7	**R**
f) Minor changes to an approved analytical procedure.	3 - 6	3 - 4, 7	**R**
g) Widening of an acceptance criterion.	None	2, 8, 9	**N**
h) Tightening of an acceptance criterion.	7 - 8	2	**R**

Conditions

1. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The addition of test is not to monitor new impurity species.
3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
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 criterion for any residual solvent is within the international recommended specification (e.g., based on harmonized ICH limits).
9. The change does not result from unexpected events arising in the manufacturing process (e.g.: with impact on the impurity profile of the product).
10. The analytical procedure remains the same or changes to the procedure are minor.

Supporting data

1. Process validation and / or evaluation studies or validation protocol of the proposed finished product.
2. Updated, QC approved finished product specifications (final version to be signed by QC).
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Copies or summaries of validation reports, if new analytical procedures are used.
5. Data showing that change in animals gives comparable results with those obtained using approved animals.
6.Description of the batches and summary of results as quantitative data of a sufficient number of batches to support process parametric release (certificate of analysis should be provided)
7. Justification for the change to the analytical procedure (e.g., demonstration of the suitability of the analytical procedure to monitor the finished product, including the degradation products).
8. Justification of the proposed finished product specifications (e.g., demonstration of the suitability of the monograph to control the finished product, including degradation products).
9. Declaration that consistency of quality and of the production process is maintained.

10. Copies of relevant certificate of fitness for use (e.g., veterinary certificate). Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation protocols / reports, studies of consistency, etc.). However, the WHO Prequalification Secretariat may request documented evidence.

M. Reference standards or materials

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
Change affecting the quality control (QC) testing of the finished product, involving:			
M1. Change the reference standards from pharmacopoeial to in-house.	None	1 - 2	**R**
M2. Change the reference standards from in-house / professed to pharmacopoeial.	None	1 - 2	**R**
M3. Qualification of a new lot of reference standard against the approved reference standard.	None	2	**R**
M4. Extension of reference standard shelf life.	None	3	**R**
Conditions			
None			
Supporting data			
1. Revised Product monograph to reflect the change in reference standard. 2. Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis). 3. Summary of stability testing and results to support the extension of reference standard shelf life. Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation and stability protocols / reports, and other studies). However, the WHO Prequalification Secretariat may request documented evidence.			

N. Container closure system

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
N1. Modification of a primary container closure system (e.g., new coating, adhesive, stopper, type of glass).	None	1 - 7	**A**
	1 - 3	1, 3	**R**
N2. Change from approved single-dose container to multi-dose container.	None	1 - 7	**A**
N3. Deletion of a container closure system.	None	1	**R**
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 quality of the container and does not modify the product contact material (e.g., increase thickness of the glass vial without changing interior dimension).

Supporting data

1. Product monograph, dosage forms, composition, packaging, inner and outer labels, as appropriate.
2. Process validation and / or evaluation studies, or provide equivalency rationale.
3. Information on the proposed container closure system (e.g., description, materials, specifications).
4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity tests.
5. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
6. Long-term stability studies; results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) finished product batches, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the NRA and WHO PQ Secretariat any failures in the ongoing long term stability studies. Bracketing and matrixing may be acceptable if scientifically justified.
7. Information demonstrating suitability of the proposed container / closure system (e.g., last media fill's results, transportation and / or interaction studies demonstrating preservation of protein integrity and maintenance of the sterility, the sterility in multi-dose container).

Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation and stability protocols / reports, and other studies). However, the WHO prequalification secretariat may request documented evidence.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
N4. Change in the supplier for a primary container closure component, involving:			
a) Replacement or addition of a supplier.	None	1 - 2	**R**
	1 - 2	None	**R**
b) Deletion of a supplier.	None	None	**R**

Conditions

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

Supporting data

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

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
N5. Change in the specifications used to release a primary* or functional secondary container closure component, involving:			
a) Deletion of a test.	1 - 2	1 - 2	**R**
b) Addition of a test.	3	1 - 2	**R**
c) Replacement of an analytical procedure.	6 - 7	1 - 3	**R**
d) Minor changes to an analytical procedure.	4 - 7	1 - 3	**R**
e) Widening of an acceptance criterion..	None	1 - 2	**R**
f) Tightening of an acceptance criterion.	8	1	**R**

Conditions

1. Deleted test has been demonstrated to be redundant or is no longer a pharmacopoeial requirement.
2. The change to the specifications does not affect the functional properties of the container closure component nor

result in a potential impact on the performance of the final product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. No change in the acceptance criteria outside of the approved ranges.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. New / modified analytical procedure maintains / 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, QC approved copy of the proposed specifications for the primary or functional secondary container closure component (or where applicable, the final version of the specifications to be signed by QC after NRA approval).
2. Rationale for the change in specifications for a primary container closure component.
3. Description of the analytical procedure and, if applicable, validation data.

Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation and stability protocols / reports, and other studies). However, the WHO Prequalification Secretariat may request documented evidence.

*Primary container closure: a packaging component that is or may be in direct contact with the dosage forms (e.g.: vials, pre-filled syringes). Secondary packaging component is a packaging component that is not and will not be in direct contact with the dosage from (e.g. carton, tray).

O. Stability of the finished product

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
O1. Change in the shelf life for the final product, involving:			
a) An extension.	None	1 – 4, 6	**A**
	1 - 5	1 - 2, 5	**A**
b) A reduction.	None	1 - 5	**A**
	6	2 - 4	**A**
Conditions			
1. No changes to the container closure system in direct contact with the final product with the potential impact on the final product; or to the recommended storage conditions. 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 (i.e. problems arising during manufacturing or stability concerns should be reported for evaluation).			
Supporting data			
1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained). 2. Proposed storage conditions and shelf life, as appropriate. 3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after NRA approval) and stability commitment. 4. Justification of the change to the post-approval stability protocol or stability commitment. 5. Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches). 6. Interim stability testing results and a commitment to notify the NRA and WHO prequalification programme of any failures in the ongoing long term stability studies. Extrapolation of shelf life should be justified and based on valid and current regulatory documents. Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation and stability protocols / reports, and other studies). However, the WHO Prequalification Secretariat may request documented evidence.			
O2. 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, change in storage temperature.	None	3 - 6	**N**
	1 - 2	1 - 2, 4 - 5	**N**
b) Addition of time point(s) into the post-approval stability protocol.	None	4 - 5	**N**
c) Addition of test(s) into the post-approval stability protocol.	3	4 - 5	**R**
d) Deletion of time point(s) from the post-approval stability protocol beyond the approved shelf life.	None	4 - 5	**R**
e) Deletion of time point(s) from the post-approval stability protocol within the approved shelf life.	4	4 - 5	**R**

Conditions

1. For the replacement of an analytical procedure, the results of method validation demonstrate that the new analytical procedure is at least equivalent to the approved analytical procedure.
2. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
4. The approved final product shelf life is at least 24 months.

Supporting data

1. Copies or summaries of analytical procedures, if new analytical procedures are used.
2. Copies or summaries of validation reports, if new analytical procedures are used.
3. Proposed storage conditions and or shelf life, as appropriate.
4. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after approval by the NRA) and stability commitment.
5. Justification of the change to the post-approval stability protocol or stability commitment.
6. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).

Manufacturer could make reference to relevant documents (SOP, approved specifications analytical procedures, validation and stability protocols / reports, and other studies). However, the WHO Prequalification Secretariat may request documented evidence.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
O3. Change in the labeled storage conditions for the final product or the diluted or reconstituted product, involving:			
a) Addition or change of storage condition for the final product (e.g., widening or tightening of a temperature criterion).	None	1 - 5	**A**
b) Addition of a cautionary statement.	1	1 - 2, 4 - 5	**N**
c) Deletion of a cautionary statement.	None	1 - 2, 4, 6	**N**

Conditions

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

Supporting data

1. Revised product monograph (e.g., title page, composition and packaging and pharmaceutical information and inner and outer labels, as applicable.
2. Proposed storage conditions and shelf life.
3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after approval by the NRA) and stability commitment.
4. Justification of the change in the labeled storage conditions/cautionary statement.
5. Results of stability testing (e.g., full real time/real temperature stability data covering the proposed shelf life generated on one (1) commercial scale batch).
6. Results of stability testing (e.g., full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches).

Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation and stability protocols / reports, and other studies). However, the WHO Prequalification Secretariat may request documented evidence.

Appendix 3
Safety, Efficacy and Product Label Information changes

Introduction

Clinical data required as evidence of safety and efficacy in populations where vaccines are supplied through UN agencies, thus subject to the prequalification by WHO, may differ from the set of clinical data that an NRA considers sufficient to issue a Marketing Authorization. WHO takes into consideration the characteristics of the intended population for UN supply purposes, therefore the package of information must be looked at on a case-by-case basis for the initial submission for prequalification and the same applies to some variations. There may be cases where prequalification may be granted based on limited clinical data for certain regions / populations, with a clear statement that reflects the limitations of the prequalification status until, further clinical data is submitted and deemed sufficient to extend the scope of the prequalification as the basis for a global recommendation. The specific requirements in terms of subgroups, population size, comparators, co-administration with other Expanded Programme of Immunization (EPI) vaccines, etc., must be discussed with the Prequalification Secretariat on a case-by-case basis.

Variations Type A – Requires WHO approval before implementation.

Criteria

Variations Type **A** are defined as those changes to the labeling of a prequalified vaccine that has the potential to increase the exposure levels of the product, either by expanding the population that is exposed, or by increasing individual exposure. The label changes that can result in increased exposure levels of the drug include:

a) The addition or expansion of a safety claim, indication or efficacy claim, whether explicit or implicit;
b) The addition of a new route of administration, new strength (potency), or increase in recommended dose / dosing range;
c) The identification or characterization of any adverse events;
d) The identification of subgroups, or conditions of use, for which the benefit to risk profile of the vaccine has the potential to be less favorable; and

Changes that exceed the criteria for this category thus falling under the category of new application are also included in this reporting category.

e) An existing indication has been withdrawn in its entirety.
f) An existing route of administration, dosage form and/or strength has been deleted due to safety reasons.

In these cases, a well-planned consultation with the WHO Prequalification Secretariat is highly recommended.

Examples of **Type A** changes include but are not limited to the following:

1) Any change to the existing text of the labels (including changes to the package inserts that refer to any potential benefits of the vaccine, implicit or explicit, including claims regarding the safety profile or efficacy (i.e., changes in text with reference to sub-populations and possible claims regarding side effects).
2) A new indication has been added, including reintroduction of an indication that was approved and was subsequently withdrawn, or the existing text of an indication has been revised.
3) Any change to the clinical sections and/or parts of the dossier and package insert which results in a new claim, explicit or implicit (e.g., listing of additional outcome measures, or revision to the description of study design resulting in a new benefit for a specific sub-population).
4) A new route of administration has been added.
5) A new strength has been added.
6) An existing contraindication, warning or cautionary text anywhere in the product monograph / package insert, has been deleted in its entirety, has been altered so as to reflect a reduction in risk, and/or in a risk management measure. These may result from a range of supporting data (e.g., post-marketing data, safety studies, etc.).
7) Existing text regarding an adverse event or set of events has been altered to reflect an apparent reduction in risk.
8) An existing text in the labeling of the vaccine has been deleted, reworded and/or otherwise altered. This would include any change as a result of new immunological data related to a special population or sub-population.
9) Addition with the purpose of strengthening or clarifying text anywhere in the sections: CONTRAINDICATIONS, WARNINGS, PRECAUTIONS and/or ADVERSE EVENTS of the package insert, or relevant section of the Product Information, including changes as a result of recommendations of an advisory committee. These changes may include the provision of recommended risk-management actions (e.g., required testing prior to introduction of the vaccine, specific monitoring after introduction, ensuring vaccinee awareness of certain risks, etc.), or the identification of a specific sub-population as being at greater risk, such as those with a concomitant condition, or a specific age group.
10) The instructions for use including dosage and administration, anywhere in the package insert, have been reworded and/or otherwise altered with respect to optimizing the safe use of the vaccine.
11) An existing indication has been altered for risk management purposes including reduction in scope.
12) A new interaction with co-administered vaccines or medicines has been added, or an existing interaction has been better characterized, that alters the conditions of use in terms of risk management (e.g., a precautionary statement is added as the result of the new data).
13) The existing text of the labels (e.g., product monograph, package insert, inner and outer labels) that have has been revised to add clarity as it relates to the safe use of the vaccine, but without expanding, explicitly or implicitly, the claims of the product.
14) A change made only to the text dedicated to the section of information of the patient of the package insert (e.g., to improve the clarity of the message to consumers).

Submission Filing

The changes included in this reporting category should be filed, along with the recommended supporting data, to the WHO PQ Secretariat.

Supporting Data – Type A changes

a) Clinical trial/study data relevant to the submission.

This may include but is not limited to: clinical trials (whether focused on efficacy or safety), epidemiological data/study results, pharmacovigilance studies, Periodic Safety Update Report (PSUR) data, review reports/analysis of specific safety concerns, pharmacovigilance plans or patient registry data.

(b) Other data which may be relevant to the submission.

This may include, but is not limited to: rationale, declarations/attestations, opinion papers, conference presentations, publications in peer-reviewed scientific journals and product utilization information.

Variations Type R – Annual Reporting

Criteria

A Type R change is defined as any change to the label that is not expected to impact the safety, efficacy, and/or effective use of the vaccine. The changes included in this reporting category may be implemented without the prior review by the WHO PQ Secretariat of the supporting data. Type R changes should be reported to WHO in the Prequalified Vaccine Annual Report (PQVAR).

Results of confirmatory clinical trials (either intermediate or final) that were part of a commitment by the manufacturer at the time of prequalification, that does not imply any change in the labeling of the prequalified vaccine is included in this category and reported annually, as appropriate.

Examples:

Examples of Type **R** changes include but are not limited to the following:

1) Any change to the layout of the label that does not represent a change to the labelling requirement for artwork, font, position or the terms of the market authorization.
2) Changing a publication in the reference section of the product monograph/package insert listed as “in press” to a published listing.
3) The existing text of the labels has been revised to add clarity as it relates to maintaining consistency with common label phrase.

4) Any change in spelling of the text of the label (e.g., “addition” is replaced by “addition”).
5) Any changes made to the text of the Pharmacology, Microbiology, and Toxicology of the product insert that does not alter the conditions of use in any way.
6) A change to the clinical trial section which does not alter the conditions of use in any way.
7) A new interaction study has been added, or an existing interaction has been better characterized, that does not alter the conditions of use of the vaccine in any way. A change solely to a percentage (observed or reported) appearing in an adverse events table, where there is no associated change to cautionary text in the product monograph / package insert (e.g., no explicit conditions of use to be affected). This includes both decreases and increases to the value.
8) The addition of data or modification of text, other than Category **N** or **R** changes, which does not result in any other changes to the information provided to health care professionals or users.
9) Any addition to the reference section of the product monograph/package.
10) Insert that does not affect any other text in the label or that does not alter the conditions of use of the vaccine in any way.

Submission Filing

The changes included in this reporting category should be submitted, to the WHO PQ Secretariat as part of the PQVAR.

Supporting Data –Type R Changes

Any data that may have been generated by the sponsor in support of a Type R change should not be submitted but should be available to WHO/PQ Secretariat when requested.

Appendix 4
Model cover letter.

(< FROM MANUFACTURER > LOGO)

<Date, YY/MM/DD>

RE: <VACCINE PROPRIETARY / INVENTED NAME.> – Letter for the submission of variations

Dear <Name of the Coordinator PQ,

<Name of Manufacturer> hereby submit the variation(s) to a WHO prequalified vaccine(s) and supporting documentation (if applicable) corresponding to the Product Summary File (PSF) for < Vaccine Name>, in accordance with Chapter 5 of the Guidance on Variations to a Prequalified Vaccine.

The submission is also in compliance with the Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies, **WHO TRS 978, ANNEX 6**.

A short regulatory overview is provided, including discussions, agreements with local NRA and potential date for implementation of the variations.

<Name & signature (s)>

Appendix 5
Submission of variations to a WHO prequalified vaccine.

☐ **AUTHORIZED BY THE NRA**
☐ **AUTHORIZED BY THE NRA BUT NOT YET IMPLEMENTED BY THE MANUFACTURER**
☐ **NOT YET AUTHORIZED BY THE NRA**

REPORTING CATEGORY (tick all applicable options)

☐ **Type N** ☐ **Single variation**
☐ **Type A** ☐ **Multiple variations**

VARIATION(S) IMPACT ON:

☐ **Administrative Information (Appendix 1)**
☐ **Manufacturing (Appendix 2)**
☐ **Quality Control (Appendix 2)**
☐ **Safety (Appendix 3)**
☐ **Efficacy (Appendix 3)**

Name and address of the manufacturer:	**Name and address of contact person:** **Telephone number:** **Fax number (optional):** **E-mail:**

PRODUCTS CONCERNED BY THIS SUBMISSION

(Proprietary / Invented name(s))	Active component(s)	Presentation(s)	Strength(s)

If this list is very extensive (e.g.: more than one page) it may be added as an annex to the form.

PRECISE SCOPE AND BACKGROUND FOR THE VARIATIONS, AND JUSTIFICATION IN CASE OF MORE THAN ONE VARIATION IN THE SAME SUBMISSION FORM (e.g.: consecutive variations), if applicable.

(*Include a description and background of all the proposed variations. If a variation concerns an unforeseen change (e.g.: not included in the guidance document), provide a justification for its proposed reporting category).*

PRESENT CONDITION	PROPOSED CONDITION

Specify the precise present and proposed wording or specification, including dossier (WHO PSF; WHO CTD format) section number(s). For labelling and package leaflet variations, underline or highlight the changed words presented in the table above or provide as a separate Annex (including mock-up labels identifying the changes).

If this list is very extensive the table may be extended by adding pages as needed.

Declaration by the manufacturer (responsible or contact person**):**

I hereby submit a notification/application for the above variation(s) in accordance with the WHO Guidance document…….in the context of the Prequalification of Vaccines. I therefore declare that (*Please tick the appropriate declarations*):

- ☐ There are no other changes than those identified in this submission
- ☐ Where applicable, all conditions set for the variation(s) concerned are fulfilled;
- ☐ All the documentation supporting each variation is available upon WHO request;
- ☐ This notification/submission has been submitted / discussed with the NRA responsible for the regulatory oversight of the prequalified product*;*

Signature: _____

Name: _____

Status (Job title) _____

Date _____

Glossary

Note: This section is currently under construction and will be published for public consultation in the second draft of the document.