ETHIOPIAN FOOD AND DRUG AUTHORITY

Medicine Evaluation and Marketing Authorization Led Executive officeGuideline on Variation Applications to Registered Vaccines

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Document History

Version No.	Reason for Amendment	Effective Date
001	Newly issued guideline	August 2022
002	The previous version was meant both for the vaccine and bio-therapeutics. Thus guideline revised to make it specific only for vaccine and develop a separate guideline for Bio-therapeutics as per the recommendation of the WHO-GBT audit for ML3	01/02/ 2024

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Table of Contents

ABBREVIATION

AN	Annual Notifiable
BSE	Bovine Spongiform Encephalopathy
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DRA	Drug Regulatory Authority
EFDA	Ethiopian Food and Drug Authority
eRIS	Electronic Regulatory Information System
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
HVAC	Heating Ventilating and Air conditioning
ICH	International Council for Harmonization
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MCB	Master Cell Bank
MSL	Master seed Lot
NRA	National Regulatory Authority
QA	Quality Assurance
QC	Quality control
SOP	Standard Operating Procedure
RRA	Reference Regulatory Authority
SRA	Stringent regulatory Authority
TSE	Transmissible Spongiform Encephalopathy
V_{maj}	Major Variation
V_{minAN}	Minor Variation with Annual Notification
V_{minIN}	Minor Variation with Immediate Notification

VminPA	Minor Variation with Prior Approval
WCB	Working Cell Bank
WFI	Water for Injection
WHO	World Health Organization
WSL	Working Seed Lot

1. INTRODUCTION

Ethiopian Food and Drug Authority (EFDA) of Ethiopia is responsible to protect the public health from unsafe, inefficacious and poor quality medicines by insuring effective and efficient pre and post-marketing authorization of medicines systems in the country.

Variations to particulars of a vaccine may be made to alter or to improve the vaccines, to introduce an additional safeguard due to new scientific knowledge or to meet market demands. The conditions of registration of a vaccine are therefore; considered dynamic taking into account that variation to the original registered dossier may become necessary during the lifetime of the vaccine. Throughout the life of a vaccine product, the marketing authorization holder or the manufacturer is responsible for the product that is placed in the market, and also required to take in to account technical and scientific progress, and to make any changes that may be required to enable the vaccines to be manufactured and checked by means of generally accepted scientific method. Once a vaccine is registered by the EFDA for use in Ethiopia, an applicant must notify and got approval from the Authority for changes that affect to vaccine's quality, safety and efficacy; on product labeling information changes; and other regulatory requirements" changes in accordance with article 21(1) of Food and Medicines Administration Proclamation No. 1112/2019. However, for variations having minimum potential on its performance may marketed once the manufacturer or person who register the product notify the authority of such variations in accordance with article 21(2) of this proclamation.

Technical requirements for the different types of variations are set out in this guideline in order to facilitate the submission of appropriate documentation by applicants and their assessment by the Authority and to ensure that variations to the Vaccines do not result in health concerns.

The license holder and/or manufacturer is responsible to follow-up and notify the Authority of post approval changes made to registered vaccines before being implemented except those changes that are annual notifiable (AN).

Therefore, this guideline is developed to facilitate applicants/manufacturers with information concerning documentation to be submitted for approval of variations to the registered vaccines and facilitate the evaluation process of dossier applications submitted by the applicant/manufacturers

2. OBJECTIVE

This guideline is intended to: assist applicants with the classification of changes made to the registered Vaccine; Guide applicants on the data package required to support changes that may potentially impact on the quality, safety and efficacy attributes; product and labeling information and other regulatory requirements of the registered vaccine.

3. SCOPE

This guideline is applicable to applications intending to make changes to registered vaccines. It also applies to all variations initiated by the applicant or requested by the Authority.

4. DEFINATION

Applicants

The person or entity who submits a registration application of product to the Authority and responsible for the product information

Adjuvant:

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

Antigen:

The following definitions apply in this document:

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

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

Authority

Authority means the Ethiopian Food and Drug Authority.

Comparability study:

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

Major Variations

Major variations mean changes that could have major effects on the overall safety, efficacy and quality of the vaccine. They are variations to the documentation that can be deemed neither to be minor variations nor to be variations for which the submission of a new dossier would be necessary.

Master cell bank (MCB):

an aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions

Minor Variation

Minor variations mean variation to the registered pharmaceutical finished product in terms of administrative data and/or changes that could have minimal or no adverse effects on the overall safety, efficacy and the quality of vaccine.

Notification:

Notifications means changes that could have minimal or no adverse effects on the overall safety, efficacy and quality of the vaccine. Such notifications do not require prior acceptance, but must be notified to the Authority before implementation of the change. e.g Periodic Safety Update Reports.

Prior approval:

A variation requiring approval from the EFDA prior to implementation of the variation

Quality attributes:

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

Reference Regulatory Authority:-

Is a national, regional or international body whose decisions or public information are considered by EFDA for its decision-making process with respect to the marketing authorization of medicinal products. WHO, WHO listed authorities and other national and regional bodies recognized as such by EFDA by defined selection criteria will be listed as reference authority as may be updated from time to time.

Seed lot:

A preparation of live cells (prokaryotic or eukaryotic) or viruses constituting the starting material for the vaccine antigen. A seed lot is of uniform composition (although not necessarily clonal), is derived from a single culture process and is aliquoted into appropriate storage containers, from which all future vaccine production will be derived either directly or via a seed lot system.

Source material/starting material:

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

Specification:

A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described. Specifications are critical quality

standards that are proposed and justified by the manufacturer and approved by the regulatory authorities.

Starting material:

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

Variation:

Variation means a post approval change to any aspect of a vaccine, including but not limited to a change to formulation, method and site of manufacture, specifications for the vaccine product, ingredients, container and container labelling, and product information.

Vaccine:

Preparations containing antigens capable of inducing a specific and active immunity in humans against an infectious agent or toxin

Working cell bank (WCB):

The working cell bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the master cell bank under defined culture conditions.

5. REPORTING CATEGORIES AND PROCEDURE FOR SUBMISSION

To explain what is needed for the reporting of variations introduced in the production and control of EFDA registered vaccines, this guideline 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

5.1. Reporting Categories:

Based on the potential effect of the variations on the quality attributes (i.e. identity, strength, quality controls, purity, potency) of the vaccines and on their potential impact on the quality, safety or efficacy, changes are categorized into major and minor changes.

The reporting of variations registered vaccines covers the following categories:

5.1.1. Minor variations:

a. Minor variation that requires prior approval (Vmin PA)

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

If the proposed change affect the content of marketing authorization certificate issued by the Authority, the Authority will issued amended certificate. However; if the change does not result in the change of the content of marketing authorization certificate issued by the Authority, acceptance letter shall be issued as evidence of approval.

b. Immediate Notification (Vmin IN):

These are changes that must be notified immediately to the authority before being implemented by the manufacturer. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes can be considered accepted if an objection is not issued by the Authority within 30 calendar days of the date of acknowledgement of receipt of the application.

c. Annual Notifications (Vmin AN):

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted. The documentation indicated for annual notifications should be available

on request or at the time of inspection.

Annual notifications should be submitted to the Authority within 12 months of implementation of the changes. For convenience applicants may group several annual notification changes as a single submission.

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

5.1.2. Major variations (Vmaj):

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the Vaccine. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by the Authority is required before the changes can be implemented.

If the proposed change affect the content of marketing authorization certificate issued by the Authority, the Authority will issued the amended certificate. However; if the change does not result in the change of the content of marketing authorization certificate issued by the Authority, acceptance letter shall be issued as evidence of approval.

5.1.3. Procedure for submission

All variation applications should be submitted online through EFDA electronic Regulatory Information System (eRIS) portal at https://www.eris.efda.gov.et/). An applicant required to submit individual changes as a separate variation application. However, grouping of variations is acceptable only under the following circumstances:

- When variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new analytical procedure;
- when the same change affects multiple vaccines products, e.g. addition of a new antigen manufacturing site;
- When all the changes are annual notification.

5.1.4. Conditions to be fulfilled

For each variation, attempts have been made to identify particular circumstances where lower

reporting requirements (VminIN, VminAN or VminPA) are possible. A change that does not meet all of the conditions stipulated for these specific circumstances is considered to be a Vmaj.

5.1.5. Documentation required

For each variation, certain documents have been identified as supporting data. This has been done to indicate to applicants what documents should be provided. For all changes it remains the responsibility of the applicant to provide all necessary documents to demonstrate that the change does not have a negative effect on the safety, efficacy or quality of the vaccine. Regardless of the documents specified, applicants should ensure that they have provided all relevant information to support the variation. However, the authority may request documentation as required.

6. DOSSIER REQUIREMENTS FOR VARIATIONS TO REGISTERED PRODUCTS

This section includes the list of types of variations. These variations are numbered, the conditions and the require documentation are identified and the reporting type indicated below.

6.1. Administrative Changes

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
1.	Change and addition of local agent (s) and/orconsultant.	a-b	a-b	Vmin PA
Conditions to be fulfilled a. Must hold a valid medicine import license and/or consultant certificate. b. The importer has no pending disciplinary case with the EFDA.				
Documentation required a. Agency agreement made between the local agent or consultant and the manufacturer/marketing authorization holder as described in the guideline for registration of medicines b. A copy of import license for local agent or license for consultant.				
S.N.	**Description of change**	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
2.	Change in the name of the final vaccine product	a-c		Vmin PA
Conditions to be fulfilled a. The NRA has authorized a new name. b. There is no change to the product (formulation, release & shelf-life specifications,manufacturing source & process) except for the product name change				

c. The first and the last three letters of trade name is not identical with a registered finishedpharmaceutical product in Ethiopia

Documentation required

a) Copy of the NRA letter of acceptance of the new name or updated CPP from thenational drug regulatory authority (DRA) in which the new name is approved.

b) A declaration from the marketing authorization holder that there is no other changes to the product/label except for the drug product name change.

c) Revised product information including samples of actual package inserts and labeling incorporating the proposed variation.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3.	Change in the name and/or a corporate address of the supplier of the vaccine product	a	a	Vmin IN

Conditions to be fulfilled

a. Confirmation that the supplier of the product remains the same legal entity

Documentation required

a. A formal document from a relevant official body (e.g. the national regulatory authority(NRA))in which the new name and/or address is mentioned.

S.N.	Description of change	Conditions tobe fulfilled	Documentationon required	Reporting type
4.	Change in the name and/or address naming of the marketing authorization holder of the registeredVaccine product	a	a-b	**Vmin IN**

Conditions to be fulfilled

a. The marketing authorization holder of the registered vaccine product shall remain the same legalentity.

Documentation required

a. Sample of actual packaging insert and labels incorporating the proposed variation,where applicable
b. Approval for change of name and address MAH as per statutory requirements.

S.N.	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
5.	Other minor variations such as (Change logo of applicant/ manufacturer, change in the design or layout of packaging, Change in the colour of design of the package.	a-c	a-c	**Vmin IN**

Conditions to be fulfilled

a. There is no change in the content of finished pharmaceutical product.
b. The change in colour design of the package is not affect the legibility of the label.
c. There is no change in the indication and safety of the product.

Documentation required

a. The summary of the change made in comparison with the previous approved packagelabeling.
b. Reason for making such changes.
c. Actual sample and/or colour print out of the new and the present package labelling.

6.2. Manufacturing and Quality Control changes

6.2.1. Cell banks and seed lots

S. N.	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Categories
6.	**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	a	a, b, e, g-i	**Vmaj**
	b. Generation of a new Working CellBank (WCB)	None	a, b	**Vmaj**
		b-d	a, b	**Vmin IN**
	c. Change in cell bank storage site	g	J	**Vmin IN**
7.	**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)	a	a, e-i, k	V**maj**
	b. Generation of a new WSL	b, c	e-j, k	**Vmin IN**
		b-d	e-f, k	**Vmin AN**
	c. Generation of a new Working Seed Lot (WSL) by extending the passage level of an existing WSL beyond an approved level.	None	e-j, k	V**maj**
	d. Change in seed lot storage site	g	j	**Vmin IN**
8.	**Change in cell bank /seed lot testing site**			
	Change in cell bank /seed lot testing site	e, g	j	**Vmin AN**
9.	**Change in cell bank /seed lot qualification protocol**			
	Change in cell bank /seed lot qualification protocol	None	c, d	V**maj**
		f	d	**Vmin AN**

Conditions to be fulfilled

a. The new MCB is related and generated from a pre-approved MCB or WCB or the new MSL is generated from a pre-approved MSL or WSL.

b. The new cell bank/seed lot is generated from a pre-approved MCB/MSL.

c. The new cell bank/seed lot is at the pre-approved passage level.

d. The new cell bank/seed lot is released according to a pre-approved protocol/process or as described in the original license.

e. No changes have been made to the tests/acceptance criteria used for the release of the cell bank/seed lot.

f. The protocol is considered more stringent (i.e. addition of new tests or narrowing of acceptance criteria).

g. No changes have been made to the storage conditions used for the cell

h. bank/seed lot and the transport conditions of the cell bank/seed lot has been validated

Documentation required

a. Qualification of the cell bank or seed lot according to guidelines considered acceptable bythe NRA.

b. Information on the characterization and testing of the MCB /WCB, and cells from the end-of production passage or post-production passage.

c. Justification of the change to the cell bank/seed lot qualification protocol.

d. Updated cell bank/seed lot qualification protocol and describe the numbers of passages.

e. 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

f. Quality control test results as quantitative data in tabular format for the new seed lot.

g. 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.

h. 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.

i. Updated post-approval stability protocol.

j. Evidence that the new company/facility is GMP-compliant.

k. Revised information on the quality and controls of critical starting materials (for example specific pathogen free eggs and chickens) used in the generation of the new WSL where applicable.

6.2.2. Manufacture of bulk

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
10.	**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	a - g, i–m, o	**Vmaj**
		a – e	c, g, i-l	**Vmin AN**
	b. Introduction of microbial hosts into a multi-product mammalian cell culture suite or vice versa.	None	m-n	**Vmaj**
	c. Conversion of production and related area(s) from campaign to concurrent for a multi-product facility.	f	p-q	**Vmaj**
	d. Conversion of a bulk manufacturing facility from single product to multi- product.	e	l-m, o	**Vmaj**
	e. Addition of product(s) to an approved multi-product manufacturing facility.	d-e, g	m, p	**Vmaj**
	f. Introduction of a different host/media-type into an approved multi-product facility.	g	h, o	**Vmin AN**
	g. Deletion of a manufacturing facility or manufacturer for a bulk intermediate, or bulk.	None	None	**Vmin AN**

Conditions to be fulfilled

a. This is an addition of a manufacturing facility/suite to an approved manufacturing site.
b. The process is an equivalent of the approved process and controls.
c. The new facility/suite is under the same Quality Assurance (QA)/Quality Control (QC) oversight.
d. No changes have been made to the approved and validated cleaning and change-over procedures.
e. The proposed change does not involve additional containment requirements.
f. The manufacturing process is a closed process for shared areas.
g. 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)

Documentation required

a. Confirmation that the proposed manufacturing site has been inspected and is licensed by the Authority and/or has been audited by the reference regulatory authority recognized as SRA or WHO and valid GMP certificate from NRA of the country of origin)
b. Updated module 3 or new dossier (CTD).
c. Name, address, and responsibility of the proposed production facility or facility involved in manufacturing and testing.
d. 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
e. Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed bulk.
f. 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.

g. 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).

h. Information on the in-process control testing to demonstrate lack of carry-over or cross-contamination.

i. 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).

j. 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.

k. 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.

l. 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.

m. 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.

n. Results of the environmental monitoring studies in critical classified areas.

o. 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.

p. Data demonstrating lack of carry-over or cross-contamination.
q. Description of the segregation procedures to avoid cross-contamination. Manufacturer should consider quoting the procedures or SOPs in place

S.N.	Description of the change	Conditions To be fulfilled	Documentation required	Reporting category
11.	**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	a-b, e	**Vmin IN**
	b. Relocation of equipment to another room in the same facility, qualification of a new room or change in classification of an existing room.	a-c	c-e	**Vmin AN**
	c. Modification to a manufacturing area or to an existing service/system (e.g., change to WFI systems or HVAC systems, moving a wall).	a-b	c-e	**Vmin AN**
	d. Change in the location of steps in the production process within the same facility.	a	d-e	**Vmin AN**

Conditions to be fulfilled

a. The change has no impact on the risk of contamination or cross-contamination.

b. The modification has no product impact.

c. Re-qualification of the equipment follows the original qualification protocol, if applicable

Documentation required

a. Information on the in-process control testing.

b. Process validation and/or evaluation studies (e.g., equipment qualification). The proposed validation protocol is acceptable, but data could be requested.

c. Information demonstrating re-qualification of the equipment or re-qualification of the change (e.g., operational qualification, performance qualification), as appropriate.

d. 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).

e. Results of the environmental monitoring studies in critical classified areas.

S N.	Description of the change	Conditions To be fulfilled	Documentation required	Reporting category
12.	**Change to the antigen fermentation, viral propagation or cellular propagation process**			
	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	a-f, i, k	**Vmaj**
	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)	b, d	a-f, h, j	**Vmin IN**
	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)	a-f, i-k	a-d	**Vmin AN**
13.	**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	a, b, e-g, i, k, l	**Vmaj**
	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)	b, d	a, b, f-g, j, k	**VminAN**

	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)	a-e	a, b	**VminIN**
14.	**Scale-up of the manufacturing process**			
	a. At the fermentation stage.	c-f, k-m	c, f, g, i, k	**Vmaj**
	b. At the purification stage.	a, c, e, g	f, g, i, k	**Vmaj**
15. .	Change in supplier of raw materials/reagents of biological origin (e.g., fetal calf serum, insulin, human serum albumin)	None	d, h, l, m	**VminAN**
		h	d, h	**VminAN**
16.	Change in source of raw materials/reagents of biological origin	None	d, g, l, m	**Vmin AN**
		h	d, g	**Vmin AN**
17.	Introduction of reprocessing steps	n	h, j, k, n	**VminIN**

Conditions to be fulfilled

a. No change in the principle of the sterilization procedures of the antigen.

b. The change does not impact the viral clearance data or the chemical nature of an in activating agent.

c. No change in the antigen specification outside of the approved limits.

d. No change in the impurity profile of the antigen outside of the approved limits.

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

f. The change does not affect the purification process.

g. The change in scale is linear.

h. The change is for compendial raw materials of biological origin (excluding human plasma-derived materials).

i. The new fermentation train is identical to the approved fermentation train(s).

j. No change in the approved in vitro cell age.

k. The change is not expected to have an impact on the quality, safety or efficacy of the final product.

l. No change in the proportionality of the raw materials (i.e., the change in scale is linear).

m. The change in scale involves the use of the same bioreactor (i.e., does not involve the use of a larger bioreactor).

n. The need for reprocessing is not due to recurrent deviations from the validated process and theroot cause triggering reprocessing is identified.

Documentation required

a. 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.

b. 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).

c. If the change results in an increase in the number of population doublings or sub-cultivations, information on the characterization and testing of the post-production cell bank for recombinant product, or of the antigen for non- recombinant product.

d. 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).

e. Process validation study reports.

f. 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.

g. 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.

h. 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.

i. 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.

j. 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.

k. 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.

l. Information assessing the risk with respect to potential contamination with adventitious agents

(e.g., impact on the viral clearance studies, BSE/TSE risk).

m. Information demonstrating comparability of the raw materials/reagents of both sources.

n. 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

S. N.	Description of Change	Conditions tobe fulfilled	Documentation required	Reporting Categories
18.	**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	a-f	**Vmin IN**
	b. introduction of new equipment with the same operating principles but different product contact material	None	a, c-f	**VminAN**
	c. introduction of new equipment with different operating principles but the same product contact material	None	a-c, e, f	**Vmin AN**
	d. Replacement of equipment with equivalent equipment (including filter)	None	a, e-g	**Vmin AN**
Conditions to be fulfilled **None**				

Documentation required

a. Information on the in-process control testing.
b. Process validation study reports.
c. 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).
d. Information on leachables and extractables.
e. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
f. Information demonstrating requalification of the equipment or requalification of the change.
g. Rationale for regarding the equipment as similar/comparable, as applicable

S.N.	Description of Change	Conditions to be Fulfilled	Documentation required	Reporting Categories
19.	**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 thecell banks or seed lots	None	a, c-f, h, k	**VminAN**
	b. raw materials/ intermediates: narrowing of the approved specification limits for starting materials / intermediates	a-d	a, c-g	**VminAN**
20.	**Change to in-process tests or limits applied during manufacture of the antigen, involving:**			

	a. Narrowing of in-processlimits	c, f, h, i	b, f	**Vmin AN**
	b. Addition of new in-process test and limits	d, e, j, k	b-f,h, j	**Vmin AN**
	c. Deletion of a non-significant in-process test	d-f	b,f, i	**Vmin AN**
	d. Widening of the approved in-process limits, which may have a significant effect on the overall quality of the antigen	None	b-f, h, j,k	**Vmin IN**
		c-e	b, f, h, j,k	V**min AN**
	e. deletion of an in-process test which may have a significant effect on the overall quality of the antigen	None	b,f,h, j	**Vmin AN**
	f. addition or replacement of an in-process test as a result of a safety or quality issue	None	b-f,h, j	**Vmin AN**

Conditions to be fulfilled

a. The change in specification for the materials is within the approved limits.

b. The grade of the materials is the same or is of higher quality, where appropriate.

c. No change in the final antigen specification outside the approved limits.

d. No change in the impurity profile of the final antigen outside the approved limits.

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

f. The test does not concern a critical attribute (e.g. content, impurity, any critical physical characteristics or microbial purity).

g. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.

h. No change in the in-process controls outside the approved limits.

i. The test procedure remains the same, or changes in the test procedure are minor.

j. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

k. 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).

Documentation required

a. 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.

b. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed antigen.

c. Updated antigen specification, if changed.

d. Copies or summaries of analytical procedures, if new analytical procedures are used.

e. Validation study reports, if new analytical procedures are used.

f. Comparative table or description, where applicable, of pre- and post-change in-process tests/limits.

g. 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.

h. 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.

i. Justification/risk assessment showing that the attribute is non-significant.

j. Justification for the new in-process test and limits.

k. 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

6.2.3. Control of the bulk

S. N.	Description of the change	Conditions tobe fulfilled	Documentation required	Reporting category
21.	**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 tests to a new company not approved in the current market authorization or license.	a-c	a, b	**Vmin AN**
	b. transfer of the QC testing activities for a pharmacopoeial tests to a new company not	a	a, b	**Vmin AN**

	approved in the current market authorization or license			

Conditions to be fulfilled

a. 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).

b. No changes to the test method.

c. Transfer within a site approved in the current market authorization for the performance of other tests

Documentation required

a. Information demonstrating technology transfer qualification

b. Evidence that the new company / facility is GMP compliant.

22.	**Change in the specifications used to release the bulk, involving**			
	a. deletion of a test	None	a, e, h	V**maj**
	b. addition of a test	a-c	a-c, e	V**minAN**
	c. replacement of an analytical procedure	None	a-e	V**maj**
	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	f, g	**Vmaj**
	e. minor changes to an approved analytical procedure	d-g	a, d, e	**Vmin AN**
	f. a change from an in-house analytical procedure to a recognized compendial/pharmacopoeial analytical procedure	d, g	a-c	**Vmin AN**
	g. widening of an acceptance criterion	None	a, e, h	V**minIN**
	h. narrowing of an acceptance criterion	a, h, i	a	V**minAN**

Conditions to be fulfilled

a. The change does not result from unexpected events arising during manufacture (e.g., new unqualified impurity, change in total impurity limits).

b. No change in the limits/acceptance criteria outside of the approved limits for theapproved assays.

c. The addition of test is not to monitor new impurity species.

d. No change in the acceptance criteria outside of the approved limits.

e. 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.

f. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

g. The change does not concern potency testing.

h. 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.

i. The analytical procedure remains the same, or changes to the analytical procedure are minor.

Documentation required

a. Updated antigen specification.

b. Copies or summaries of analytical procedures, if new analytical procedures are used.

c. Validation reports, if new analytical procedures are used.

d. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent

e. Justification for deletion of the test or for the proposed antigen specification (e.g., tests, acceptance criteria, or analytical procedures).

f. Data demonstrating that the change in animals/strains give comparable results with those obtainedusing the approved animals/strains.

g. Copies of relevant certificate of fitness for use (e.g., veterinary certificate).

h. Declaration/evidences that consistency of quality and of the production process is maintained.

6.2.4. Container closure system (for bulk)

S. N.	Descriptionof thechange	Conditions to be fulfilled	Documentation required	Reporting category
23.	**Change of container closure system (for bulk) in the following condition:**			
	Change in the primary container closure system(s) for the storage and shipment of the bulk.	None	a–b, d	V**maj**
		a	a, c	V**min AN**

Conditions to be fulfilled

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

Documentation required

a. Information on the proposed container closure system (e.g., description, specifications).
b. Demonstration of compatibility with the bulk.
c. 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).
d. 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 maybe sufficient based on rationale

6.3. Stability of the bulk

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
24.	**Change in the shelf life or the bulk or for as to red intermediate of the bulk, involving:**			
	Extension.	None	a-d, f	**Vmaj**
		a-e	a-b, e	**VminAN**
	Reduction.	None	a-e	**VminAN**
		f	b-d	**VminAN**

Conditions to be fulfilled

a. 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.

b. The approved shelf life is at least 24 months.

c. 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.

d. Stability data were generated in accordance with the approved stability protocol.

e. Significant changes were not observed in the stability data.

f. 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 reportedfor evaluation).

Documentation required

a. Summary of stability testing and results (e.g., studies conducted, protocols used, resultsobtained).

b. Proposed storage conditions and shelf life, as appropriate.

c. Updated, QC approved post-approval stability protocol (or where applicable, the finalversion of the protocol to be signed by QC) and stability commitment.

d. Justification of the change to the post-approval stability protocol or stability commitment.

e. 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. f. 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				
25.	**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	e -f	**Vmaj**
		a-b	a-b, d-e	**VminAN**
	b. Addition of time point(s) into the post-approval stability protocol.	None	d-f	**VminAN**
	c. Addition of test(s) into the post-approval stability protocol.	c	d-e	**VminAN**
	d. Deletion of time point(s) from the post approval stability protocol beyondthe approved shelf life.	None	d-e	**VminAN**
	e. Deletion of time point(s) from the post approval stability protocol with inthe approved shelf life.	d	d-e	**VminAN**

Conditions to be fulfilled a. For the replacement of an analytical procedure, the results of method validation demonstrate that thenew analytical procedure is at least equivalent to the approved analytical procedure. b. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. c. The addition of test(s) is not due to stability concerns or to the identification of new impurities. d. The approved bulk shelf life is at least 24 months.
Documentation required a. Copies or summaries of analytical procedures, if new analytical procedures are used. b. Copies or summaries of validation reports, if new analytical procedures are used. c. Proposed storage conditions and or shelf life, as appropriate. d. 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) e. Justification of the change to the post-approval stability protocol or stability commitment. 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).

6.4. Storage of the bulk

S. N.	Description of the change	Conditions to Be fulfilled	Documentation required	Reporting category
26.	**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	a–b	**VminAN**
		a-b	a-d	**VminAN**
	Conditions to be fulfilled a. Change is not necessitated by recurring events arising during manufacture orbecause of stability concerns.			

	b. The change consists in the tightening of a temperature criterion within the approved ranges.
	Documentation required a. Revised product monograph (e.g., where applicable, title page, composition and packaging and pharmaceutical information section) and inner and outer labels, as applicable. b. Proposed storage conditions and shelf life. c. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment. d. Justification of the change in the labeled storage conditions /cautionary statement. e. 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

6.4.1. In process control and process validation

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
27.	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	a-b	**Vmin AN**
Conditions to be fulfilled None.				

Documentation required

a) 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.
b) Rationale for the change in the validation protocol.

6.4.2. Final product characteristics

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
28.	**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	a - j	**Vmaj**
	b) Change in fill volume (same concentration, different volume).	None	a- c, e, g-i	**Vmaj**
		a, c	b - d, f, i	**Vmaj**
	c) Change in the concentration of the active ingredient (e.g., 20 unit/mL .vs.10 unit/mL).	None	b - d, f, h- j	**Vmaj**
		b-c	b -d, f, h	**Vmaj**
	d) Addition of a new presentation(e.g., addition of syringes to vials).	None	b - c, f, h-j	**Vmaj**

Conditions to be fulfilled

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

Documentation required

a. Section of the dossier (CTD, hybrid format) should be updated according to what is recommended by WHO (dossier content, format. See also document WHO TRS 978, ANNEX 6).

b. 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 (CTD) or revised information

on the bulk, if any of the attributes have changed.

c. Description and composition of the finished form.

d. 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)).

e. 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 the Authority‟s documents in the variation submission. The Authority may request to review one or more of these documents if deemed necessary.

f. 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).

g. 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.

h. Information on the container closure system, if any of the components have changed (e.g., description, materials of construction, summary of specifications).

i. 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.

j. Supporting clinical data or a request for a waiver of in vivo studies.

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
29.	**Change involving a chemical / synthetic adjuvant:**			
	a) Change in supplier/manufacturer of a chemical / synthetic adjuvant.	None	d, e, i, j	**Vmin AN**
		a, b	e	**Vmin AN**
	b) Change in manufacture process of a chemical/ synthetic adjuvant.	None	c-e, i, j	**Vmin AN**
		None	f-j	**Vmin AN**
	c) Change in release specifications of a chemical/ synthetic adjuvant (including the tests and / or the analytical procedures).	a, c	f-h	**Vmin AN**
		None	d, e, i, j	**Vmin AN**
30.	**Change involving a biological adjuvant**			
	a) Change in supplier of a biological adjuvant.	None	a-f, j-l	**Vmin IN**
	b) Change in manufacture of a biological adjuvant.	None	a-f, i-k	**Vmaj**
		d	a-f, i-k	**Vmaj**
	c) Change in release specifications of a biological adjuvant (the tests and/or the analytical procedures).	None	f-j	**VminAN**
		a, c	f-h	**VminAN**

Conditions to be fulfilled

a. Any change in specification of the adjuvant is within the approved limits (i.e., narrowing of acceptance criterion).
b. The adjuvant is an aluminum salt.
c. The change in specification consists in the addition of a new test or in a minor change to an analytical procedure.
d. No change in the manufacturer and/or supplier of the adjuvant.

Documentation required

a. Information assessing the risk with respect to potential contamination with adventitious agents (e.g.,impact on the viral clearance studies, BSE/TSE risk).

b. Information on the quality and controls of the materials (e.g., raw materials, starting materials) used in the manufacture of the proposed adjuvant.
c. 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.
d. Process validation study reports (e.g., for manufacturing of the adjuvant) unless justified.
e. Description of the general properties including stability, characteristic features and characterization data of the adjuvant, as appropriate.
f. Updated copy of the proposed specification for the adjuvant (and updated analytical procedures if applicable).
g. Copies or summaries of analytical procedures, if new analytical procedures are used.
h. Validation study reports, if new analytical procedures are used.
i. 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.
j. 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.
k. Supporting non-clinical and clinical data, if in vitro tests are insufficient to prove comparability
l. Evidence of facility GMP compliance.

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
31.	**Change to diluent, involving:**			
	a. change in manufacturing process	None	a - e	Vmaj
		a	a-e	VminAN
	b. replacement of or addition to the source of a diluent	None	a-c	VminAN
		a-c	a-c, e	VminAN
	c. change in facility used to manufacture a diluent (same company)	a, b	a, c, e	VminAN
	d. addition of a diluent filling line	a, b, d	a, c, e	VminAN
	e. addition of a diluent intoan approved filling line	a, b	a, c, e	**VminAN**

Conditions to be fulfilled

a. 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.

b. After reconstitution, there is no change in the final product specification outside of the approved limits.

c. The proposed diluent is commercially available in the NRA country/jurisdiction.

d. The addition of the diluent filling line is in an approved filling facility.

Documentation required

a. 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).

b. Updated, copy of the proposed specification for the diluent.

c. 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.

d. Updated stability data on the product reconstituted with the new diluent.

e. Evidence of facility GMP compliance by NRA at country of manufacture and EFDA GMP Certificate

6.4.3. Manufacture of the finished product

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
32.	**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	a-g	**Vmaj**
		a-e	a-c, e-h	**Vmaj**
	b. replacement or addition of a secondary packaging facility; a labeling/storage facility; or a distribution facility	b, c	a-c	**VminIN**
	c. deletion of a final product manufacturing facility	None	None	**VminAN**

Conditions to be fulfilled

a. The proposed facility is an approved formulation/filling facility (for the same company/MA holder).
b. No change in the composition, manufacturing process and final product specification.
c. No change in the container/closure system and storage conditions.
d. The same validated manufacturing process is used.
e. 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.

Documentation required

a. Name, address, and responsibility of the proposed production facility involved in manufacturing and testing.
b. Evidence of facility GMP compliance by NRA at country of manufacture and EFDA GMP Certificates.
c. 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.
d. 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.
e. Process validation study reports. The data should include transport between sites if relevant.
f. Study reports. The data should include transport between sites if relevant.
g. 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.
h. 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 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.

i. Rationale for considering the proposed formulation/filling suite as equivalent.

S. N.	Description of the change	Conditions tobe fulfilled	Documentation required	Reporting category
33.	**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	a- c	**Vmaj**
	b) Conversion of formulation and filling area(s) from campaign to concurrent for multiple product manufacturing areas.	a	a-b	**Vmin AN**
	c) Introduction of new product into an approved multi-productformulation/filling suite.	b-d	a-c	**Vmin AN**

Conditions to be fulfilled

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

Documentation required

a. Cleaning procedures (including data in a summary validation report and the cleaning protocol for theintroduction of new products) demonstrating lack of carry-over or cross-contamination.
b. 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.
c. Information on the product(s) which share the same equipment

*Manufacturer may refer to this data in the variation submission. The Authority 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.

S. N.	Description of the change	Conditions tobe fulfilled	Documentationrequired	Reporting Category
34.	**Change in the final product manufacturing process, such as:**			
	a) Scale-up of the manufacturing process at the formulation/filling stage.	a-d	a, c, e-f, h, j	**VminAN**
	b) Addition or replacement of equipment (e.g., formulation tank, filter housing, filling line and head, and lyophilizer).	None	a-d, g, i	**Vmin AN**
		e	c-d	**Vmin IN**
	c) Product-contact equipment change from dedicated to shared (e.g., formulation tank, filter housing, filling line and head, lyophilizer).	None	i	**Vmin AN**
	d) Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process.	a-d	a-c, e, g, j	**Vmin AN**
	e) Change in process flow or procedures.	None	a-c, e-f, h	**Vmin AN**

Conditions to be fulfilled

a. The proposed scale uses similar / comparable equipment to that approved (N.B. change in equipment size is not considered as using similar / comparable equipment).

b. 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).

c. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.

d. No change in the principle of the sterilization procedures of the final product.

e. For product-contact equipment, the change is considered „like for like" (i.e., in term of product-contact material/equipment size).

Documentation required

a. 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.

b. Information on the in-process control testing, as applicable.

c. 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.

d. Information demonstrating qualification of the equipment (operational qualification, performance, qualification), or qualification of the change, as applicable.

e. 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.

f. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).

g. 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 the Authority of any failure in the ongoing stability studies.

h. 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/orfills may be acceptable if scientifically justified.

i. Cleaning procedures (summary validation report) demonstrating lack of carry-over or cross-contamination.

j. Rationale for regarding the equipment as similar / comparable, as applicable.

6.5. Control of excipients

S. N.	Description of the change	Conditions to be fulfilled	Documentationn required	Reporting category
35.	**Change in the specifications used to release the excipient, involving:** Note: This change not include adjuvant			
	a) Deletion of a test.	e, h	a, c	Vmin IN
	b) Addition of a test.	d	a- c	Vmin AN
	c) Replacement of an analytical procedure.	a-c	a, b	Vmin AN
	d) Minor changes to an approved analytical procedure.	None	a, b	Vmin AN
	e) A change from a house/professed analytical procedure to recognized compendial analytical procedure.	None	a, b	Vmin AN
	f) Widening of an acceptance criterion	None	a, c	Vmin AN
	g) Narrowing of an acceptance criterion	c, d, f, g	a	Vmin AN

Conditions to be fulfilled

a. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.

b. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

c. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeial monograph specifications for the excipient.

d. 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.

e. The deleted test has been demonstrated to be redundant with respect to the remaining tests or isno longer a pharmacopoeial requirement.

f. The analytical procedure remains the same, or changes in the test procedure are minor

g. The change does not result from unexpected events arising during manufacture, e.g., new unqualified impurity; change in total impurity limits

h. 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.

Documentation required

a. Updated excipient specifications.

b. 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.

c. 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).

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
36.	Change in the source of an excipient from a vegetable or synthetic sourceto a human or animal source that may pose a TSE or viral risk.	None	b-g	**Vmaj**
37.	Change in the source of an excipient froma TSE risk (e.g., animal) source to a vegetable or synthetic source	None	a, c, e, f	**VminIN**
38.	Replacement in the source of an excipient froma TSE risk source toa different TSE risk source	e, f	b-g	**VminAN**
39.	Change in manufacture of a biological excipient. *Note: excludes biological adjuvants, refer to adjuvant specific changes for details*	None	b-g	**Vmaj**
		b	b-g	**VminIN**
		a, b	b-g	**VminAN**
40.	Change in supplier for plasma - derived excipient(e.g., human serum albumin).	None	d- h	**Vmaj**
		c, d	e, f, i	**VminIN**

41.	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	c, e-g	**VminIN**
		a, e, f	c	**VminAN**
42.	Change in excipient testing site	a	j	**VminAN**

Conditions to be fulfilled

a. No change in the specifications of the excipient or final product outside of the approved limits.
b. The change does not concern a human plasma-derived excipient.
c. 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.
d. The excipient does not influence the structure/conformation of the active ingredient.
e. 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.
f. Any new excipient does not require the assessment of viral safety data.

Documentation required

a. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
b. 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.
c. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the proposed excipient with the approved excipient.
d. 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.
e. 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.
f. 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
g. 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.
h. Complete manufacturing and clinical safety data to support the use of the proposed human plasma- derived excipient.
i. Letter from the supplier certifying that no changes were made to the plasma derived excipient compared to the currently approved corresponding medicinal product.
j. Evidence that the new company/facility work under acceptable quality standards.

6.6. Control of the final product

S. N.	Description of the change	Conditions tobe fulfilled	Documentation required	Reporting category
43.	**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	a, b	**Vmaj**
	b. transfer of the QC testing activities for a pharmacopoeial assay to a new company	a	a, b	**Vmaj**
Conditions to be fulfilled a. The transferred QC test is not a potency assay or a bioassay				
Documentation required a. Information demonstrating technology transfer qualification. b. Evidence that the new company/facility is GMP compliant by NRA at country of manufacture andEFDA GMP Certificate.				

S.N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
44.	**Change in the specifications used to release the finished product, involving:**			
	a) For sterile products, replacing the sterility test with process parametric release.	None	a-b, f, h-i	**Vmin IN**
	b) Deletion of a test.	None	b, h, i	**Vmaj**
	c) Addition of a test.	a-b	b-d, h	**Vmin IN**
	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	e, j	**Vmin IN**
	e) Replacement of an analytical procedure.	f	b-d, g	**Vmin AN**
	f) Minor changes to an approved analytical procedure.	c-f	c-d, g	**Vmin AN**
	g) Widening of an acceptance criterion.	None	b, h, i	**Vmin IN**
	h) Tightening of an acceptance criterion.	g-h	b	**Vmin AN**

Conditions to be fulfilled

a. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
b. The addition of test is not to monitor new impurity species.
c. No change in the acceptance criteria outside of the approved ranges.
d. 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.

e. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

f. The change does not concern potency testing.

g. The change is within the range of approved acceptance criteria.

h. Acceptance criterion for any residual solvent is within the international recommended specification (e.g., based on harmonized ICH limits).

i. The change does not result from unexpected events arising in the manufacturing process (e.g.: with impact on the impurity profile of the product).

j. The analytical procedure remains the same or changes to the procedure are minor.

Documentation required

a. Process validation and / or evaluation studies or validation protocol of the proposed finished product.
b. Updated, QC approved finished product specifications (final version to be signed by QC).
c. Copies or summaries of analytical procedures, if new analytical procedures are used.
d. Copies or summaries of validation reports, if new analytical procedures are used.
e. Data showing that change in animals gives comparable results with those obtained using approved animals.
f. 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). There should be sufficient data to support sterility assurance system.
g. 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).
h. Justification of the proposed finished product specifications (e.g., demonstration of the suitability of the monograph to control the finished product, including degradation products). If deletion of test, the reason for deletion should be provided.
i. Declaration that consistency of quality and of the production process is maintained.
j. Copies of relevant certificate of fitness for use.

6.7. Container closure system

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
45.	Modification of a primary container closure system (e.g., new coating, adhesive,stopper, type of glass).	None	a-g	**Vmaj**
		a-c	a, c	**Vmin AN**
46.	Change from approved single-dose container to multi-dose container	None	a-g	**Vmaj**
47.	Deletion of a container closure system.	None	a	**Vmin AN**

Conditions to be fulfilled

a. No change in the type of container closure or materials of construction.

b. No change in the shape or dimensions of the container closure.

c. 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).

Documentation required

a. Product monograph, dosage forms, composition, packaging, inner and outer labels, as appropriate.
b. Process validation and / or evaluation studies, or provide equivalency rationale.
c. Information on the proposed container closure system (e.g., description, materials, specifications).
d. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity tests.
e. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
f. 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 the Authority any failures in the ongoing long term stability studies. Bracketing and matrixing may be acceptable if scientifically justified.
g. 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).

S. N.	Description of the change	Conditions to befulfilled	Documentation required	Reporting category
48.	**Change in the specifications used to release a primary* or functionalsecondary container closure component, involving:**			
	a. Deletion of a test.	a-b	a-b	**Vmin AN**
	b. Addition of a test.	c	a-c	**Vmin AN**
	c. Replacement of an analytical procedure.	f-g	a-c	**Vmin AN**
	d. Minor changes to an analytical procedure.	d-g	a-c	**Vmin AN**
	e. Widening of an acceptance criterion.	None	a-b	**Vmin AN**
	f. Tighteningof an acceptance criterion.	h	a	**Vmin AN**

Conditions to be fulfilled

a. Deleted test has been demonstrated to be redundant or is no longer a pharmacopoeial requirement.

b. 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.

c. The change is not necessitated by recurring events arising during manufactureor because of stability concerns.

d. No change in the acceptance criteria outside of the approved ranges.

e. The new analytical procedure is of the same type.

f. Results of method validation demonstrate that the new or modified analytical procedureis at least equivalent to the approved analytical procedure.

g. New / modified analytical procedure maintains / tightens precision, accuracy, specificity

And sensitivity. h. 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.
Documentation required a. 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). b. Rationale for the change in specifications for a primary container closure component. c. Description of the analytical procedure and, if applicable, validation data.

*****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).

6.8. Stability of the finished product

S. N.	Description of the change	Conditions to be fulfilled	Documentationon required	Reporting category
49.	**Change in the shelf life for the final product, involving:**			
	a) An extension.	None	a–d, f	**Vmaj**
		a-e	a-b, e	**Vmaj**
	b) A reduction.	None	a-e	**Vmaj**
		f	b-d	**Vmaj**

Conditions to be fulfilled

a. 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.

b. The approved shelf life is at least 24 months.

c. 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.

d. Stability data were generated in accordance with the approved stability protocol.

e. Significant changes were not observed in the stability data.

f. 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).

Documentation required

a. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).

b. Proposed storage conditions and shelf life, as appropriate.

c. 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.

d. Justification of the change to the post-approval stability protocol or stability commitment.

e. 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).

f. Interim stability testing results and a commitment to notify the NRA and the Authority 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

S. N.	Description of thechange	Conditionstobe fulfilled	Documentationrequired	Reporting category
50.	**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	c-f	**Vmin IN**
		a-b	a-b, d-e	**Vmin IN**
	b. Addition of time point(s) into the post-approval stability protocol.	None	d-e	**Vmin IN**
	c. Addition of test(s) into the post-approval stability protocol.	c	d-e	**Vmin AN**
	d. Deletion of time point(s) from the post- approval stability protocol beyond the approved shelf life.	None	d-e	**Vmin AN**
	e. Deletion of time point(s) from the post- approval stability protocol within the approved shelf life.	d	d-e	**Vmin AN**

Conditions to be fulfilled

a. For the replacement of an analytical procedure, the results of method validation demonstrate that the newanalytical procedure is at least equivalent to the approved analytical procedure.

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

c. The addition of test(s) is not due to stability concerns or to the identification of new impurities.

d. The approved final product shelf life is at least 24 months
Documentation required a. Copies or summaries of analytical procedures, if new analytical procedures are used. b. Copies or summaries of validation reports, if new analytical procedures are used. c. Proposed storage conditions and or shelf life, as appropriate. d. 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. e. Justification of the change to the post-approval stability protocol or stability commitment. f. 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).

S. N.	Description of the change	Conditions to be fulfilled	Documentation required	Reporting category
51.	**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	a-e	**Vmaj**
	b. Addition of a cautionary statement.	a	a-b, d-e	**Vmin IN**
	c. Deletion of a cautionary statement.	None	a-b, d, f	**Vmin IN**

Conditions to be fulfilled

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

Documentation required

a. Revised product monograph (e.g., title page, composition and packaging and pharmaceutical information and inner and outer labels, as applicable.
b. Proposed storage conditions and shelf life.
c. 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.
d. Justification of the change in the labeled storage conditions/cautionary statement.
e. 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).
f. 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).
g. Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation and stability protocols / reports, and other studies). However, the Authority may request documented evidence.

REFERENCE

1. Guidance on Variations to a Prequalified Vaccines, Version 7, Vaccine Assessment Group, Prequalification Team (PQT), Regulation of Medicines and other Health Technologies (RHT), Department of Essential Medicines and Health Products (EMP) World Health Organization (WHO), July 2015, Geneva, Switzerland.
2. Malaysian Variation Guideline for Biologics, first Edition, National Pharmaceutical Regulation Division (a.k.a. NPRA), Ministry of Health, January 2017, Malaysia.
3. Guidance on Variation Applications to Registered medicines, 2nd edition, Ethiopia Food and Drug Authority (EFDA), July 2015, Addis Ababa, Ethiopia.