FOOD AND DRUGS AUTHORITY

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GUIDELINES FOR REPORTING VARIATIONS TO A REGISTERED BIOLOGICAL PRODUCT

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1st July 2015	01	Initial Issue
8th January 2024	02	General review of the Guideline in line with the current structure.

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Executive Summary

The guidelines on variations to biological products provide a framework for managing changes to authorized biological medicinal products. These variations can impact the safety, efficacy, and quality of the product. The guidelines classify changes into major and minor variations, each requiring different levels of documentation and regulatory review.

The major changes involve significant changes that affect the quality, safety or efficacy of the biological product such as modifications to the manufacturing process or formulation, necessitating comprehensive data whiles minor variations, has a low potential in affecting the quality, safety or efficacy such as notifications on change of address or company logo.

The guidelines emphasize the importance of robust risk management and thorough documentation to ensure that changes do not compromise product quality. Overall, the guidelines aim to maintain high standards of patient safety while allowing for necessary innovations and improvements in biological products.

1.0 Introduction

The specifications of biological products are defined for the issuance of the FDA product marketing authorization, which is valid up to five years. To accommodate production, safety, and efficacy parameters which evolve with time, the product marketing authorization must be updated to reflect the product as it currently exists. Manufacturers are responsible for assessing the impact of planned and proposed changes on their product, and regulatory approval of the changes is needed to maintain the validity of the product marketing authorization. However, it is recognized that not all changes affect the product to the same extent. Some, like a change in the active ingredient, are so significant that the altered product is considered to be a new product, requiring a complete re-assessment and licensing procedure. Others, like the replacement of one equipment by another of similar technical characteristics and functioning principles, are considered as occurrences and are unlikely to affect product's quality.

In correspondence with good practices, usually the updating of a manufacturing process is well planned in advance, in such a way that allows an early evaluation of the improvement feasibility and potential impact in the process and product. After the marketing authorization of a biological product, it may happen that manufacturers introduce or plan to introduce changes in the manufacture of the product. Changes may be introduced to improve the quality of the biological product, the efficiency of the manufacturing process, or they could be made for marketing reasons. In addition, there may be changes to the labelling system of a biological product because of a new schedule, improving the management of a potential risk for a product by adding warnings, limiting or expanding the target population, etc.

This would include an emphasis on applying a science-based and risk-based approach to the quality, safety and efficacy assessment of the biological products. As such, the guidance documents were needed to outline the information needed to support quality, safety and efficacy changes to biological products which apply a modernized, science-based, and risk-based approach to this area.

Due to the implications and impact that these changes may have on the quality, safety and efficacy of the biological products, as well as to avoid additional regulatory burden,

this guideline serves as a general scheme to classify post registration variations. Changes are currently categorized in two groups according to their significance or impact on the attributes of the biological product.
These groups are as follows:

- Major changes (M) with a high potential to affect the quality, safety or efficacy of the biological product.
- Minor changes (N) with a low potential to affect quality, safety, or efficacy.

Using this scheme provided in this guidance, each change is classified according to how it is to be reported, and the amount of supporting information the Marketing Authorization Holder must submit.

1.1 Legal Basis

This guideline applies to variation to marketing authorisation for vaccines and biological products in accordance with Section 118 of the Public Health Act 851, of 2012.

1.2 Scope

This guidance document applies to MA holders intending to make changes to biological products that have received an approval to market the products.

This Guideline provides guidance for marketing authorization holders on the regulation of changes to the original marketing authorization for an approved biological product in terms of: (a) the procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable the FDA to evaluate the potential impact of the change on the quality, safety, and efficacy of the product.

2.0 Definitions and Abbreviations

Adjuvant :Component that potentiates the immune responses to an antigen/drug substance and/or modulates it towards the desired immune responses. Adjuvant may be of pharmaceutical origin (chemical/synthetic adjuvant) or of biological origin (biological adjuvant).

Batch: A quantity of drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, produced according to a single production order and

as attested by the signatories to the order. In the case of continuous manufacture, a batch corresponds to a defined fraction of the production that is characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Biological auxiliary material: Raw material from a biological source which is intended to be used as a processing aid in the fabrication of the drug. It may be absent from the drug or may remain as an impurity in the drug at the end of the manufacturing process (e.g., biological additives used to supplement cell culture medium in production fermenter, human antithrombin III used to complex and remove human thrombin).

Biological starting material: Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (e.g., plasma derivatives, ascetic fluid, bovine lung, etc.) or indirectly (e.g., cell substrate, host/vector production cells, eggs, viral strains, etc.)

Biosimilars: "Biosimilars" means a biological product which is similar in terms of quality, safety and efficacy to reference biological product licensed or approved in Ghana, or any innovator product approved in International Council of Harmonisation (ICH) member countries.

Biotherapeutic product: A biological medicinal product with the indication of treating human disease include all biologically active protein products (including plasma-fractionated products) which are used in the treatment of human diseases, and those intentionally modified by, for example, fusion proteins, PEGylation, conjugation with a cytotoxic drug or modification of rDNA sequences. They also include protein products used for in vivo diagnosis (for example, monoclonal antibody products used for imaging).

Certificate of suitability (CEP): A certificate of compliance of a substance with the relevant requirements of the European Pharmacopoeia monographs for use in medicinal products issued by the European Directorate for the Quality of Medicine of the Council of Europe (EDQM).

Change/ Variation: Refers to a change that includes, but is not limited to; the product composition, manufacturing process, quality controls, equipment, facilities or product labelling information made to an approved marketing authorization or license by the marketing authorization holder. Also referred to as variation.

Change-over procedure: A logical series of validated steps that ensures the proper cleaning of suites and equipment before the processing of a different product begins.

Closed process/closed system: Process equipment or process step in which the product is not exposed to the external environment. A closed system requires that the quality of materials entering or leaving the system and the manner in which these materials are added/removed from the system is carefully controlled.

Comparability study: The activities, including study design, conduct of studies and evaluation of data 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/drug substance 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, non-clinical or clinical data might contribute to the conclusion.

Comparability protocol: Establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of a negative effect for specific manufacturing changes on the safety or efficacy of the product. A comparability protocol is a highly specific, well-defined plan for the future implementation of a quality (i.e. manufacturing) change. Also referred to as post-approval change management protocol.

Container closure system refers to the following components: A primary container closure system is a packaging component that is in, or may come into, direct contact with the drug product dosage form (for example, vial or pre-filled syringe) or components that contribute to the container/closure integrity of the primary packaging material for a sterile product.

A secondary container closure system is a packaging component that is not, and will not be, in direct contact with the dosage form (for example, carton or tray).A functional secondary container closure system is a packaging material that is not in direct contact with the product and that provides additional protection or serves to deliver the product.

Control Strategy: A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Critical manufacturing step: A manufacturing process/step that may results in a potential change in the purity/impurity profile or due to the nature of the starting materials or resulting product/intermediate, requires containment within a specially designed manufacturing area or production facility, for example, the development and preparation of cell banks and seed lots, initial propagation, scale-up, blood and plasma pooling and fractionation, fermentation, harvesting, inactivation, purification, addition of adjuvants or preservatives, the conjugation and pooling of bulk concentrates and the final preparation of drug product including concentration/ diafiltration, formulation, sterile filtration, filling and lyophilization.

Critical process parameter: A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Quality Attribute: A physical, chemical, biological or microbiological property or characteristic that is selected for its ability to indicate the consistent quality of the product within an appropriate limit, range or distribution to ensure the desired product quality.

Design space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change.

Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Different host/media-type: Mammalian cells or any micro-organisms involved in the manufacture of a drug substance which are different from the existing hosts in the facility or use a cell culture or fermentation medium with significantly differing composition.

Dosage form: A drug product that has been processed to the point where it is now in a form in which it may be administered in individual doses.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The active pharmaceutical ingredient and associated molecules that may be subsequently formulated to produce the drug product.

Equivalent equipment: Equipment with the same technical parameters and fabricated with product- contact material of same or higher-grade quality. Equivalent equipment should give a product of same quality as the one processed by the previous equipment.

Excipient: Any component of the drug product, other than the active component/drug substance and the packaging material, generally added during formulation. Also referred to as “inactive ingredient” in other documents.

Facility/ Suite/Building: A Facility/ Suite / building in which a specific manufacturing operation or multiple operations take place, and for the purposes of this guidance only, the product-contact equipment housed within the aforementioned Facility/ Suite / building.
Fermentation train:
Equipment and conditions involved in the stepwise expansion of the cell culture process.

Final batch: A collection of sealed final containers that is homogeneous with respect to the composition of the product. A final batch must have been filled in one continuous working session.

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

HVAC (Heating, Ventilation, and Air Conditioning): Industry term for the systems and technology responsible for the heating, ventilation, and air conditioning in buildings. HVAC systems regulate comfort (temperature and humidity), energy efficiency, and air quality.

In-process control: Check performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as part of in-process control.

Intermediate: A material produced during steps in the manufacture of a biotherapeutic product that undergoes further processing before it becomes the drug product.

Manufacturer: Any person or legal entity engaged in the manufacture of a product subject to marketing authorization or licensure.

Marketing authorization: A formal authorization for a medicine to be marketed. Once an NRA approves a marketing authorization application for a new medicine, the medicine may be marketed and may be available to be prescribed by physicians.

Marketing authorization application: A formal application to the NRA for approval to market a new medicine. The purpose of the marketing authorization application is to determine whether the medicine meets the statutory standards for safety, efficacy, product labelling information and manufacturing.

Marketing Authorization holder (MA holder): Any person or legal entity or sponsor, or manufacturer or importer / license manufacturer to manufacture / market a medicinal product that has received marketing authorization or licensure to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change

to the marketing authorization or license and is referred to as the manufacturer or applicant in this or other documents.

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.

Mock-Up (i.e. Label, Carton, PI): A full colour, actual size copy of the labels and a colour representation of the packages intended to be used for the sale of the drug, including all presentation/design elements, proposed graphics, fonts, colours and text

Multi-product facility/Suite: A facility where more than one product of the same type or products from different classes are fabricated (e.g., pharmaceutical and biological products).

Non-critical area: Area that does not encompass process steps.

Non-critical excipient: Excipient with no active function, e.g., solution used to adjust pH.

Non-critical manufacturing step: A manufacturing process/step that has no impact upon purity and impurity profile or requires no specific facility considerations, for example, buffer and media preparation, storage of intermediates, and packaging (note that some biological products may require critical temperature and/or light control during packaging).

Open system: Any steps in a manufacturing process where in-process materials or components are exposed to the external environment.

Pilot scale: A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Presentation: Container that contains the drug product. The container may be used directly or indirectly in the administration of the drug (e.g., vials, pre-filled syringes, pre-filled pens).

Primary container closure component: Packaging material in direct contact with the product.

Primary packaging site: Site involved in the activity of putting a drug in its primary container which is, or may be, in direct contact with the dosage form.

Process validation: Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

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

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

Quality change: A change in the manufacturing process, product composition, quality control testing, equipment or facility. Also referred to as “chemistry manufacturing and control (CMC) change” in other documents.

Raw materials: A general term used to denote the culture media components, reagents or solvents intended for use in the production of starting material, drug substance, intermediates or drug products.

Real-time release testing: Testing that provides the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

Reference standards/materials: Well-characterized materials used as references against which batches of biological products are assessed. These materials remain fundamental to ensuring the quality of biological products as well as the consistency of production and are essential for the establishment of appropriate clinical dosing.

Reprocessing: Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications.

r-DNA products: Recombinant DNA (rDNA) molecules are DNA molecules formed by laboratory methods of genetic recombination (such as molecular cloning) that bring together genetic material from multiple sources, creating sequences.

Re-test period: For biologics, also sometimes known as shelf life.

Safety and efficacy change: A change that has an impact on the clinical use of the biotherapeutic product in relation to safety, efficacy, dosage and administration, and that requires data from clinical or post-marketing studies, and in some instances clinically relevant nonclinical studies, to support the change

Secondary packaging facility: Site involved in packaging activities using a packaging component that is not, and will not be, in direct contact with the dosage form (for example, putting the primary container in the outer container or affixing labels).

Shelf life (also referred to as expiration period): The period of time during which a drug substance or drug product, if stored under the conditions defined on the container label, is expected to comply with the specification, as determined by stability studies on a

number of batches of the product. The expiry date is assigned to each batch by adding the shelf-life period to the date of manufacture.

Site/Premises: The land occupied legally by company, which contains one or more manufacturing facilities/suites/buildings cumulatively shall be called as premises, which will have its own manufacturing license number issued by licensing authority.

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 materials: Materials that mark the beginning of the manufacturing process, as described in a marketing authorization or product license. Generally, starting material refers to a substance of defined chemical properties and structure that contributes an important and/or significant structural element(s) to the active substance (examples for 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 the 1) cells; 2) microorganisms; 3) plants, plant parts, macroscopic fungi or algae; or 4) animal tissues, organs or body fluid from which the antigen (drug substance) is derived.

Strength: Quantity of medicinal ingredient in a particular dosage form. For solution, concentration of the active pharmaceutical ingredient multiplied by the fill volume.

Vaccine: A biological preparation that is used to stimulate the body’s immune response against diseases.

Validation: The demonstration, with documentary evidence, shows that any procedure, process, equipment, material, activity or system will consistently produce a result meeting predetermined acceptance criterion.

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.

3.0 Requirements

3.1 Reporting Categories and Procedure for submissions

To better explain what is needed for the reporting of variations introduced in the production and control of biological products as well, this guideline lists a number of changes likely to occur over the lifespan of a biological product, the timing for reporting to the FDA, and required supporting evidence to justify the change. The reporting of variation on quality, safety, efficacy/effectiveness covers the following categories: Minor (N) and Major (M) Variations some of which may require the Authority's approval before implementation. Minor variations are the same as Notifications.

The Authority will process minor and major variation applications within 3 months and 6 months respectively from receipt of the application and will update its records accordingly. The FDA will communicate deficiencies in submitted variation applications to Marketing Authorization Holder(s).

The following should be submitted to the Authority where applicable, with the relevant part of the dossier:

- A cover letter.
- A completed FDA variation application form published on FDA website
- Requisite variation application fees as per the FDA's fee schedule
- Representative product samples as applicable

Minor variations pertaining to the administrative section to keep the product information up-to-date and to facilitate documentation management should be reported, as described in this document.

Any minor changes that have been implemented should be clearly identified in the affected documents (e.g., dossier (CTD, labels, package inserts, etc.) with the filing of any subsequent submission to the Authority.

The conditions to be fulfilled for a given change to be classified as either a minor variation or major variation change. If any of the conditions outlined for a minor change are not fulfilled, the change is automatically considered as a major variation.

The supporting data for a given change to be submitted to FDA by the applicant. Where applicable, the corresponding modules of the dossier for the supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided; and The Authority reserves the right to request additional information, or conditions not specifically described in this document, as deemed appropriate.

Reporting Categories for Safety, Efficacy Changes

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

- Major variation/M (Safety and Efficacy)
- Minor variation/N (Safety and Efficacy)

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

The type and scope of the required supporting non-clinical and/or clinical safety and efficacy data are determined case-by-case on the basis of risk-benefit considerations related to the impact of the changes. Additionally, non-clinical and/or clinical data generated in other countries may be used for such risk benefit consideration.

Other considerations which may be applicable for vaccines only are; robustness of the immune response elicited by the vaccine and availability of a correlate of protection (i.e. data establishing a threshold level of antibody needed to protect against the development of disease following exposure)

- Availability of animal models
- Vaccine attributes (e.g. live vaccines as opposed to inactivated ones).

MA holders are encouraged to consult the FDA on the adequacy of the clinical data needed to support a safety and efficacy change if deemed necessary. Additionally, some changes such as dosage form, content of excipients or residual components, or delivery device may require clinical data as well as revision of the product labelling information.

The FDA may also be consulted on the data required to support such changes.
If the conditions / supporting data outlined for a given change are not fulfilled, then appropriate scientific justification shall be provided by the MA holders.

Major variation (Safety and Efficacy)

A major variation is defined as a change to the label of a drug that has the potential to change the exposure levels of the drug, either by expanding the population that is exposed (i.e. related to market expansion), or by increasing individual exposure. Label changes that can result in increased exposure levels of the drug include:

- Addition or expansion of a safety claim or efficacy claim, whether explicit or implied
- Change in the strength, route of administration, recommended dose/dosing range, dosage form, dosing schedule, including the addition of a booster dose.
- Co-administration with other vaccines or biological products
- Deletion or reduction of existing risk management measures (e.g. contraindications, adverse events, warnings or cautionary text/statements, in the product labelling information).

The changes included in this reporting category shall not be implemented for commercial purposes without prior approval from the FDA.
Examples of major variations include but are not limited to the following:

- The addition of a new contraindication, a change in an existing contraindication, the addition of a serious warning or precaution or the tightening of clinical monitoring requiring a change to the labels of sections of the Package Insert.
- Changes to the existing text of the label that refers to any potential benefits of the drug (implied or explicit), including claims regarding the safety profile or efficacy. This includes changes in text with reference to sub-populations and any reference to possible claims regarding side effects.
- Addition of a new indication or the revision to existing text of a current indication.
- Addition of a new route of administration, dosage form, or strength.
- A change regarding the mechanism of action of the product as detailed in the Action and Clinical Pharmacology section of the Product labelling that results in an explicit or implicit claim.
- A change to the Clinical Trial section of the Product labelling which results in a new

claim, explicit or implied (e.g., listing of additional outcome measures, or revision to the description of study design such that a new benefit is implied for a specific subpopulation).

- Data being added from an efficacy or safety (tolerability) study in a special population.
- A change in condition of use from prescription to non-prescription status.
- An existing contraindication, warning or cautionary text anywhere in the Product.
- Labelling, has been deleted in its entirety, has been modified to reflect a reduction or diminishment in risk/harm management measure. These may result from a range of supporting data (e.g., post-marketing data, safety studies, pharmacokinetic data etc.).
- Existing text regarding an adverse event or set of events that has been modified to reflect, in any way, an apparent reduction in risk/harm. This includes changes related only to animal data.
- Minor risk/harm management changes (Safety and Efficacy) change is defined as a change to the label that has the potential to improve the management of risk/harm to the population currently indicated for use of the drug, or in any other way exposed to the drug by:
    - The identification or characterization of any adverse event following immunization (AEFI) resulting in the addition or strengthening of risk management measures for an adverse event which was identified to be consistent with a causal association to immunization with the vaccine concerned.
    - The addition or strengthening of risk management measures, including instructions on dosing or any other conditions of use.
    - The identification of subgroups, or conditions of use, for which the benefit/risk profile of biological product has the potential to be less favorable.

The changes included in this reporting category shall not be implemented for commercial purpose without prior approval from the FDA.

Examples of Minor risk/harm management changes (Safety and Efficacy) include addition to, strengthening or clarification of text anywhere in these sections: Contraindications, Warnings and Precautions and Adverse Events.

- The instructions for use including dosage and administration, in the Product labelling have been reworded and/or otherwise altered with respect to risk/harm management to optimize the safe use of the drug.

- A new drug interaction has been added, or an existing drug interaction has been better characterized that identifies a risk/harm.
- A change to the toxicology data, explicitly or implied, stating an increase in risk/harm to the target population (other changes to the toxicology data, in general, are submitted as major variation (Safety and Efficacy) that are not risk/harm management changes.
- An existing indication has been withdrawn in its entirety or the indication has been modified for the purpose of risk/harm management including a reduction in scope.
- A change to improve the clarity of the message to patients in Part III of the Product labelling.
- Revisions to the existing text of the labels to add clarity to the safe use of the drug, but without expanding, explicitly or implied, the claims of the drug.

Minor non risk/harm management changes (Safety and Efficacy) are minor variations (Safety and Efficacy) that do not meet the criteria of a major variation (Safety and Efficacy), but for which prior approval by the FDA is required. Examples include but are not limited to the following:

- Changes to the text related to the Overdose section (e.g., additional overdose symptoms or treatments).
- Changes made to the text of the Pharmacology, Microbiology, Toxicology sections of the Package Insert, except where criteria for minor variation risk/harm management changes (Safety and Efficacy) are met.
- A new drug interaction or pharmacokinetic study has been added or has been better characterized with no risk/harm identified and does not expand the claim of the drug, explicitly or implied.
- The addition of data or modification of text, other major variation, minor variation risk/harm management changes (Safety and Efficacy) that are risk/harm management changes or minor notification, that does not result in any other changes to the information provided to the Health Care Professional or

patient/consumer. For these changes, the applicant is not seeking a statement that may be interpreted as a new claim.

Minor notification (Safety and Efficacy)

A minor variation is defined as any change to the label that is not expected to impact the safety, efficacy, and/or effective use of the drug. The changes included in this reporting category may be implemented by the applicant without prior review of the data supporting such a change by the FDA.

Examples of minor variation include but are not limited to the following:

- The existing text of the labels have been revised to add clarity and maintain consistency with common label phrase standards (e.g., change from "Product labelling information available on request" to "Product labelling information available to health care professional on request".
- Change from "Not recommended for children" to "Not for use in children".
- Revisions to Product labelling to standardize text in each of the following sections: Overdose, Missed Dose, How to Store It or Reporting Suspected Side Effects.
- Any change in spelling of the text of the label (e.g.,"addition" is replaced by "addition"
- Updating bar codes and technical codes.
- Removing graphics.
- Removing non-regulatory label information.
- Changing colour of graphics where there is no text overlay or changing colour of company logo.
- Updating contact information (e.g., customer service number, website addresses, etc.).

Documentation – Safety and Efficacy Changes

For a change under these categories (Safety and Efficacy), the MA holder should submit an application to the FDA that may include but is not limited to;

- a detailed description and rationale of the proposed change
- a summary of the methods used, and studies performed to evaluate the effect of the change on the biological products safety or efficacy.
- amended product labelling information.

- clinical studies (protocol, statistical analysis plan, clinical study report and Periodic Benefit Risk Evaluation Report (PBRER) data or bioequivalence trials, pharmacokinetic studies, pharmacodynamic studies, epidemiological data, pharmacovigilance studies, review reports/analysis of specific safety concerns, if applicable)
- the risk management plan/pharmacovigilance plan or patient registry data.
- Other data that may be relevant to the submission. Real world information regarding drug use, declarations/attestations, opinion papers, conference presentations, publications in peer-reviewed scientific journals and drug utilization information.
- Pre-submission meeting minutes or other written feedback, if applicable.

Product labeling information changes

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

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

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

b. Change in the frequency of occurrence of a given adverse reaction.

c. Addition of contraindication or warning (such as identification of a specific subpopulation as being at greater risk, such as individuals with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (for example, required testing prior to vaccination, specific monitoring following vaccination and ensuring patient awareness of certain risks).

d. Strengthening or clarification of product labelling information text relating to contraindications, warnings, precautions and adverse reactions.

e. Revisions to the instructions for use, including dosage, administration and preparation for administration to optimize the safe use of the vaccine.

Examples of changes that make a new application necessary.

These include the following:

a. Change to add new route of administration.

b. Change to add a new dosage form (such as replacement of a suspension for injection with a lyophilized form.)

c. Change to add a new strength.

d. Change to add a new delivery device (such as adding a needle-free jet injector)

Special Considerations

Comparative Studies

The need for and extent of a comparability exercise depends upon the potential impact of the change(s) on the quality, safety and efficacy of the product. Comparability exercises can range from analytical testing alone (for example, where process changes have no impact on any quality attribute) to a comprehensive exercise requiring nonclinical and clinical bridging studies. For example, a change in the culture conditions or in the purification process may cause the alteration of the glycosylation profile of the product, including site directed glycosylation. Alteration of glycosylation profiles may cause a change in the pharmacokinetic /pharmacodynamic (PK/PD) profile of the product. If comparability can be demonstrated through analytical studies alone, then nonclinical or clinical studies with the post change product are not necessary. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and/ or differences are observed between some critical quality attributes of the pre-change and post-change product, it may be necessary to include a combination of quality, nonclinical and/or clinical studies in the comparability exercise.

Bridging Clinical Studies

A number of changes outlined in this guidance document include recommendations for supporting by bridging clinical studies.

Clinical bridging studies are trials in which a parameter of interest (e.g. manufacturing process, formulation, dosing schedule) is directly compared with a changed version of that

parameter with respect to the effect of the change on the product's clinical performance. Comparison of immune responses and safety outcomes (e.g. rates of common and serious AEFIs) are often the primary objectives. If the immune response and safety profiles are similar, the safety and efficacy of the vaccine can be inferred.

If the physicochemical properties, biological activity, purity and/or level of impurities of the pre-change and post change product are comparable, the safety and efficacy of the biotherapeutics product can be inferred. However, nonclinical and/or clinical bridging studies may be required when analytical data alone either do not establish comparability or are insufficient to do so. The comparison of efficacy responses and safety outcomes (for example, PK/PD profile, or rates of common adverse events and serious adverse events) is often the primary objective.

For ethical reasons, it is desirable to apply the 3R principles (Replacement, Reduction, Refinement) to the use of animals where scientifically appropriate.
The following are examples of changes that are likely to require nonclinical and/or clinical bridging studies: generation of a new MCB derived from a different host cell line;

a) a new dosage form.
b) a new formulation (for example, a new excipient)
c) a new presentation (for example, addition of pre-filled pens to vials)
d) a new route of administration; and
e) a new dosing schedule

For these and comparable changes, any proposed use of alternative approaches to a bridging study must be justified and discussed with the FDA
In some cases, safety and efficacy data comparing the approved vaccine to the vaccine produced with the change (bridging studies) may be required. The following are examples of manufacturing changes that may require clinical bridging studies:

- use of a new or re-derived antigen (i.e. re-derived virus seed or bacterial cell bank) or host cell line (i.e. re-derived master cell bank).
- new agents used for inactivation or splitting of the antigen.
- a new dosage form (e.g., lyophilized powder to liquid, Intramuscular to Subcutaneous, oral to injectable).

- a new formulation (e.g. amount of ingredients, adjuvants, preservatives, reactogenic residual components from the manufacturing process).

MA holders should consult the applicable “The New Drugs and Clinical Trials Rules, 2019”, ICH and WHO guidance documents when conducting clinical bridging studies.

Stability Testing

If stability studies are recommended to support a change, these studies should be conducted in accordance with applicable FDA, ICH and WHO guidance documents, including:

a. Stability Testing of New Drug Substances and Products (Q1A)
b. Stability Testing: Photostability Testing of New Drug Substances and Products (Q1B)
c. Stability Testing for New Dosage Forms (Q1C)
d. Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (Q1D)
e. Evaluation of Stability Data (Q1E)
f. Stability Testing of Biotechnological/Biological Products (Q5C)
g. Guidelines on stability evaluation of vaccines. In: WHO Expert Committee on Biological Standardization: Fifty-Seventh report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 962).

Pharmaceutical Development and Quality by Design

The International Council for Harmonization (ICH) has developed two guidelines, Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) and Q8: Pharmaceutical Development and Q8 Annex which describe respectively the suggested contents for the 3.2.S.2.2 to 3.2.S.2.6 sections and for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the Common Technical Document (CTD) format.

The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors.

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and

manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls.

Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change that would require prior approval but should be documented with the requisite Change Controls where necessary.
Movement outside of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

Multiple Changes

Multiple related changes, involving various combinations of individual changes, may be submitted in the same application. For example, a manufacturing site change may also involve changes to the equipment and manufacturing process. For submissions that include multiple changes, the marketing authorization holder should clearly specify which data support each change. Multiple major or moderate quality changes for the same product may be filed in a single submission provided that the changes are related and/or supported by the same information. Minor quality changes that were implemented previously and that are related and/or consequential to a moderate or major quality change should be described in the major variation for the moderate or major quality change. If the proposed changes are related, the marketing authorization holder should indicate the association between them. The marketing authorization holder should also clearly specify which supporting data support which change. Such changes could affect both the drug substance and the drug product. If too many changes are filed within the same submission, or if major issues are identified with a change and extensive time would be required to review them, the FDA may ask the marketing authorization holder to divide the changes into separate submissions and to resubmit the applications. If the recommended reporting categories for the individual changes differ, the submission should be in accordance with the most restrictive of the categories recommended for the individual changes. In the case of numerous changes of the same category, the FDA may reclassify the submission to the next higher level on the basis of the potential impact of the totality of the changes on the quality, safety and efficacy of the product. This reclassification should be communicated to the marketing authorization holder at the start

of the assessment.

In case where an identical change is applicable to multiple drugs, a single submission may be submitted capturing the impacted products in the cover letter and supported with appropriate data.

Similar Biotherapeutic Products (SBP) / Similar Biologics

Following approval, an SBP is considered to be independent from the reference product and has its own life cycle. The manufacturer is not required to re-establish similarity to the reference product when comparability exercises are conducted.

A major change in clinical use for an SBP that relies on the previously demonstrated similarity provided in the original approval of the SBP may be considered by the FDA on a case-by-case basis. For example, a new indication given to the reference product after approval of an SBP should not automatically be given to the SBP. However, when new safety information on the reference product is added after the original approval of the SBP, the labelling information changes of the SBP should follow the changes made for the reference product unless it can be demonstrated that the new information on the reference product is not relevant to the SBP.

The following tables provides description, conditions to be fulfilled, supporting data and reporting category on quality, safety and efficacy changes that may be made by MA Holders.

	Description of the change	**Conditions to be fulfilled**	**Supporting data**	**Reporting category**
1.	**Change in the name and/or address of the marketing authorization holder that was granted the license of the biological product.**	1	1,2	N

Conditions

1.The marketing authorization holder shall remain the same legal entity

Supporting data

1. Approval for change of name as per statutory requirements.
2. Notification of new name if the manufacturer is sold or merged with another company. Note that if address changes due to site change, then PSF needs to be resubmitted with fresh quality; safety and efficacy data.

	Description of the Change	Conditions to be fulfilled	Supporting Data	Reporting Category
2.	**Company sale, purchase, merger.**	1	1, 2,3	N

Conditions

1. The marketing authorization holder shall remain the same legal entity.

Supporting data

1. Approval for sale/purchase as per statutory requirements.
2. Notification of new name if the manufacturer is sold or merged with another company.
3. Revised labeling.

3.	**Change in the (invented) name of the product.**	1	1,2	N

Conditions

1. The NRA has authorized a new name.

Supporting data

1. Copy of the NRA letter of acceptance of the new (invented) name.
2. Revised product information.

4.	**Changes to cell banks:**

	a) Generation of a new Master Cell Bank (MCB) from the same expression construct with same or closely related cell line; or generation of a new MCB from a different expression construct with the same coding sequence and the same cell line; or adaptation of a MCB into a new fermentation medium.	None	1-3, 5-8	M
	b) Generation of a new MCB	1	1-3, 5-7	M
	c) Generation of a new Working Cell Bank (WCB).	1	2– 4,1-2	M
5.	**Changes to the seed lots:**			
	a) New Master Seed lot (MSL); or Working Seed Lot (WSL) extended beyond an approved passage level.	None	3-7,9	M
	b) Generation of a new (WSB).	2-4	3-7	M

Conditions

1. The new MCB is generated from a pre-approved Master or Working Cell Bank.
2. The new cell bank/seed lot is generated from a pre-approved MCB/MSL.
3. The new cell bank/seed lot is at the pre-approved passage level.
4. The new cell bank/seed lot is released according to a pre-approved protocol.

Supporting data

1. Qualification of the cell bank.
2. Information on the characterization and testing of the post-production cell bank forrecombinant product /non-recombinant product.
3. Comparability of the approved and proposed product with respect to physico- chemical characterization, biological activity, and impurity profile (notice that occasionally, the manufacturer may be required to undertake bridging non-clinical orclinical studies, to support the quality data).
4. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for the new seed lot (certificate of analysis to be provided).
5. 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 bulk derived from the new cell/seed lot (certificates of analysis to be provided).
6. 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 FDA of any failures in the ongoing long term stability studies.
7. Updated, Quality Control (QC) approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and commitment to place the first commercial scale batch of the final product manufactured using the proposed bulk into the long-term stability programme (quoting the corresponding procedure or SOP).
8. Supporting non-clinical and clinical data or a request for a waiver of in-vivo

	studies. 9. Supporting clinical data.			
6.	**Changes to a bulk manufacturing facility, involving**:			
	a) Replacement or addition of a manufacturing facility for the bulk,or any intermediate of the bulk.	1-5,	1-7, 9-13,15	M
	b) Introduction of microbial hosts in to a multi–product mammalian cell culture suite or vice versa.	None	13 -14	M
	c) Conversion of production and related area (s) from campaign to concurrent for a multi -product facility.	6	16 -17	M
	d) Conversion of a bulk manufacturing facility from single-product to multi-product.	5	12 -13,15	M
	e) Addition of product (s) to an approved multi-product manufacturing facility.	4-5, 7	13,16	M
	f) Introduction of a different host/media-type into an approved multi-product facility.	7	8,15	M
	g) Deletion of a manufacturing facility or manufacturer for a bulk intermediate, or bulk.	None	None	M
Conditions 1. This is an addition of a manufacturing facility/suite to an approved manufacturing site. 2. The process is an exact replicate of the approved process and controls. 3. The new facility/suite is under the same Quality Assurance (QA)/Quality Control (QC) oversight. 4. No changes have been made to the approved and validated cleaning and change-over procedures.				

5. The proposed change does not involve additional containment requirements.

6. The manufacturing process is a closed process for shared areas.

7. No changes to the cleaning protocol are necessary to support the introduction of new products (no changes in acceptance criteria, and no new materials have been introduced that need to be evaluated for clearance in a cleaning step).

Supporting data

1. Confirmation that the proposed manufacturing site has been inspected and is licensed by FDA and/or has been audited by WHO.

2. Updated Chapter 3or new dossier (CTD).

3. Name, address, and responsibility of the proposed production facility or facility involved in manufacturing and testing.

4. For antigenic substances obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathies (TSEs) agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance). ATSE Certificate of Suitability from a qualified laboratory, if available, is acceptable for raw materials, auxiliary materials, and reagents only. This is also applicable for substances used in conjugation or linkages processes.

5. Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed bulk.

6. Summary of the process validation and/or evaluation studies. Reference to the protocols and validation reports. The complete report with all raw data could be requested during review and/or during a site audit.

7. Comparability of the approved and proposed bulk with respect to physico- chemical characterization, biological activity, and impurity profile (notice that occasionally, the manufacturer may be required to undertake bridging non- clinical or clinical studies, to support the quality data).

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

9.Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches

	of the approved and proposed bulk (certificates of analysis to be provided). 10. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed bulk, or longer if less than three (3) time points are available (including the zero-time point), as well as commitment to notify FDA of any failures in the on- going long term stability studies. Manufacturer should consider quoting the corresponding procedures or SOPs for on-going studies. 11.Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after NRA) and commitment to place the first commercial scale batch of the final product manufactured using the proposed bulk into the stability programme. Manufacturer should consider quoting the corresponding procedures or SOPs for on-going studies. 12. Information on the proposed production facility involved in the manufacture of the bulk, including the complete set of floor plans and flowcharts (drawings, room classification, water systems, HVAC systems), as well as the cleaning and shipping validation, as appropriate. 13. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If this is not the case, a signed attestation from the manufacturer that no changes were made to the change- over procedures. 14. Results of the environmental monitoring studies in critical classified areas. 15. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination. 16. Data demonstrating lack of carry-over or cross-contamination. Description of the segregation procedures to avoid cross-contamination. Manufacturer should consider quoting the procedures or SOPs in place.			
7.	**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	None	1-2, 5	M

	environmental risk to the product.			
	b) Relocation of equipment to another room in the same facility, qualification of a new room or change in classification of an existing room.	1-3	3-5	M
	c) Modification to a manufacturing area or to an existing service/system (e.g., change to WFI systems or HVAC systems, moving a wall).	1-2	3-5	M
	d) Change in the location of steps in the production process within the same facility.	1	4-5	M

Conditions

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

Supporting data

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

Results of the environmental monitoring studies in critical classified areas.

8.	**Change to the bulk fermentation process involving:**			
	a) Critical change (e.g., incorporation of disposable bioreactor technology).	None	1-3, 6-7, 9,11	M
	b) A change with moderate potential to adversely impact quality of the product (e.g., extension of the *in-vitro* cell age beyond validatedparameters).	2, 4	2-3, 6,8, 10	M

	c) A non-critical change, such as: change in harvesting and/or pooling procedures which doesnot affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale; or duplication of a fermentation train; or addition of identical or similar/comparable bioreactors.	1-6, 9-10	2-3, 6,8	M
9.	**Change to the bulk purification process involving**			
	a) A critical change (e.g., change that impact the viral clearance capacity of the process or the impurity profile of the bulk negatively).	None	1-2, 5-7,9, 11-12	M
	b) A change with moderate potential to adversely impact quality of the product (e.g., change in the chemical separation method, for example ion-exchange HPLC to reverse phase HPLC).	2, 4	1-2, 6,7, 10 - 11	M
		1-5	1-2, 6,8	M
10.	**Scale-up of the manufacturing process**			
	a) At the fermentation stage.	11 -12	3, 6-7,9,11,14	M
	b) At the purification stage.	1, 3,5, 7	6-7, 9,11	M
11.		None	4, 8,12-13	M

	Change in supplier of auxiliary materials/reagents of biological origin (e.g., foetal calf serum, insulin, human serum albumin)	8	4,8	M
12.	**Change in source of auxiliary materials/ reagents of biological origin**	None	4, 7,12 -13	M
		8	4,7	M
13.	**Introduction of reprocessing steps**	None	5, 8,10-11	M

Conditions

1. No change in the principle of the sterilization procedures of the bulk.
2. The change does not impact the viral clearance data or the chemical nature of an in activating agent for a vaccine.
3. No change in the specifications of the bulk outside of the approved ranges.
4. No change in the impurity profile of the bulk outside of the approved limits.
5. The change is not needed by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The scale-up is linear.
8. The change is for a compendia auxiliary materials/reagent of biological origin (excluding human plasma-derived materials).
9. The new fermentation strain is identical to the approved fermentation strain(s), if applicable.
10. No change in the approved in-vitro cell age.
11. No change in the proportionality of the raw materials (i.e. the scale-up is linear).
12. The scale-up involves the use of the same bioreactor (i.e. does not involve the use of a larger bioreactor).

Supporting data

1. Flow diagram (including process and in-process controls) of the proposed manufacturing process (es) and a brief narrative description of the proposed

manufacturing process (es).

2. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed bulk.

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

4. For bulks 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). ATSE Certificate of Suitability, if available, is acceptable for raw materials, auxiliary materials, and reagents only.

5. Process validation and/or evaluation studies (e.g., for aseptic processing and sterilization).

6. Comparability of the approved and proposed product with respect to physico-chemical characterization, biological activity, and impurity profile.

7. 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).

8. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the approved and proposed bulk (certificate of analysis can be provided).

9. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed bulk, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the FDA of any failures in the ongoing long term stability studies.

10. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on one (1) commercial scale batch 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 FDA of any failures in the ongoing long term stability studies.

11. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the Protocol to be signed by QC) and stability commitment to place the first commercial scale batch of the final product manufactured using the proposed bulk into the stability programme.

12. Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk), orates Certificate of Suitability, if available.

13. Information demonstrating comparability of the auxiliary materials/reagents of both sources.

14. Rationale for regarding the bioreactors as similar/comparable, if applicable.

14.	**Change in product-contact equipment used in the bulk manufacturing process, such as:**			
	a) Equipment having different operating principles/properties from those originally approved.	1-3	1-3	M
	b) Introduction of new product-contact equipment used in a critical step (e.g., change in equipment model for a continuous centrifuge, water bath for viral in activation).	1-3	1-3	M
	c) Replacement of equipment with an equivalent.	None	3	M

Conditions

1. The change does not affect equipment used in the fermentation process.

2. The manufacturing process is not impacted by the change in product-contact equipment.

3. The change has no product impact on the product

Supporting data

1. Information on the in-process control testing.

2. Process validation and/or evaluation studies, including equipment qualification, as appropriate. The proposed validation protocol is acceptable, but data could be requested.

3. Information demonstrating re-qualification of the equipment (e.g., operational qualification, performance qualification).

15.	**Change in specifications for the materials, involving:**	None	1-2	M
16.	a) Raw materials, starting materials.	1, 3-4	1, 3-6	M
	b) Solvents, reagents, catalysts.	2-4	1, 3-6	M
	Change in the in-process controls performed at critical steps used in the manufacture of the bulk.	3-8	2-6	M

Conditions

1. The change in specifications for the materials is/should be within the approved ranges.
2. The grade of the materials is the same or is of higher quality.
3. No change in specifications of the bulk outside of the approved ranges.
4. No change in the impurity profile of the bulk outside of the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
7. No change in the principle of the sterilization procedures of the bulk.
8. No change in the in-process control limits outside of the approved ranges.

Supporting data

1. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed bulk.

2. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed bulk. 3. Updated, QC approved copy of the proposed bulk specifications (or where applicable, the final version of the specifications to be signed by QC), if changed. 4. Copies or summaries of analytical procedures, if new analytical procedures are used. 5. Copies or summaries of validation reports, if new analytical procedures are used. 6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the approved and proposed bulk.				
17.	**Major change to the following process validation protocols used during the manufacture of the bulk: protocol for the manufacture of cell bank/seed bank, protocol for the introduction of product into an approved multi product facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process.**	None	1-2	M
Conditions None. **Supporting data** 1. Proposed validation protocol. Proper identification of the protocols. Status of the approval. Process validation and/or evaluation studies could be requested by the FDA. 2. Rationale for the change in the validation protocol.				
18.	**Changes affecting the quality control (QC) testing of the bulk, involving:**			

	a) Transfer of the QC testing activities for a non-pharmacopoeia assay (in- house) to a new company or to a different facility within the same company	None	1-2	M
	b) Transfer of the QC testing activities for a Pharmacopoeia assay (in-house) to a new company not listed on the Establishment License of the manufacturer/ sponsor	1	1-2	M
Conditions 1. The transferred QC test is not a potency assay or a bioassay. **Supporting data** 1. Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant.				
19.	**Change in the specifications used to release the bulk, involving:**			
	a) Deletion of a test.	None	1,6	M
	b) Addition of a test.	1-2	1-3, 6	M
	c) Replacement of an analytical procedure.	None	1-3, 5-6	M
	d)Minor changes to an approvedanalytical procedure.	3-7	1, 5-6	M
	e) Change from an in-house analytical procedure to a pharmacopeia analytical procedure or change from an approved compendium. Analytical procedure to a harmonized compendia procedure.	3, 7	1-3	M

	f) Widening of an acceptance criterion.	None	1,6	M
	g) Tightening of an acceptance criterion.	8-9	1	M

Conditions

1. No change in the limits/acceptance criteria outside of approved ranges for approved assays.
2. The addition of a test is not to monitor new impurity species.
3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same 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.
5. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
6. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
7. The change does not concern potency testing.
8. The change is within the range of approved acceptance criteria.
9. Acceptance criterion for any Class 3 residual solvent is within the limits (e.g., as harmonized in
ICH).

Supporting data

1. Updated, QC approved copy of the proposed bulk specifications (or where applicable, the final version of the specifications to be signed by QC).
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used. 4. Where an in-house analytical procedure is used and it is claimed to be identical to other standards, results of an equivalency study between the in-house/professed method/compendia methods should be performed.
5. Comparative results demonstrating that the approved and proposed analytical procedure are equivalent.
6. Justification of the proposed bulk specifications (e.g., test parameters, acceptance

criteria, or analytical procedures).				
20.	**Reference Standards or Material:**			
	a) Change the reference standards from Pharmacopoeia to in- house.	None	1-2	M
	b) Change the reference standards from in- house/professed to pharmacopoeia.	1-2	1-2	M
	c) Qualification of a new lot of reference standard against the approved reference standard.	1-2	2	M
	d) Extension of reference standard shelf life.	2	3	M

Conditions

1. Qualification of the reference standard is performed according to the approved protocol (i.e.no deviation from the approved protocol; details of the protocol can be provided- dates, code, identification, status, level of approval).
2. The reference standard is not for a bacterial or a viral vaccine.

Supporting data

1. Revised Product monograph to reflect the change in reference standard.
2. Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis).
3. Summary of stability testing and results to support the extension of reference standard shelf life.

21.	**Container closure system (for bulk)**			
	a) Change in the primary container closure system (s) for the storage and shipment of the bulk.	None	1-2	M
		1-2	1,3	M

Conditions

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.
2. The change does not concern a sterile bulk.

Supporting data

1. Information on the proposed container closure system (e.g., description, specifications).
2. Demonstration of compatibility with the bulk.
3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (e.g., results of transportation or interaction studies, extractable/leachable studies).
4. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed bulk or longer if less than three (3) time points are available (including the zero-time point), as well as commitment to notify the FDA of any failures in the ongoing long term stability studies. Results from one (1) batch may be sufficient based on rationale.

22.	**Change in the shelf life for the bulk or for a stored intermediate of the bulk, involving:**			
	a) Extension.	None	1-4, 6	M
		1-5	1-2, 5	M
	b) Reduction.	None	1-5	M
		6	2-4	M

Conditions

1. No changes to the container closure system in direct contact with the bulk with the potential of impact on the bulk; or to the recommended storage conditions of the bulk.
2. The approved shelf life is at least 24months.
3. Full long-term stability data are available covering the proposed shelf life and are based on stability data generated on at least three (3) commercial scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes were not observed in the stability data.

6. The reduction in the shelf life is not necessitated by recurring events arising during manufacture or because of stability concerns (i.e.: problems arising during manufacturing or stability concerns should be reported for evaluation).

Supporting data

1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. Proposed storage conditions and shelf life, as appropriate.
3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches). For intermediates, data to show that the extension of shelf life has no negative impact on the production of the bulk.
6. Interim stability testing results and a commitment to notify FDA 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.

23.	**Change in the post-approval stability protocol of the bulk, involving:**			
	a) Major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature.	None	3-6	M
	b) Addition of time point (s) into the post-approval stability protocol.	1-2	1-2, 4-5	M
	c) Addition of test(s) into the post-approval stability protocol.	None	4-5	M
	d) Deletion of time point (s) from the post approval stability protocol beyond the approved shelf life.	3	4-5	M

	e) Deletion of time point (s) from the post-approval stability protocol within the approved shelf life.	None	4-5	M

Conditions

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

Supporting data

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

24.	**Change in the labeled storage conditions for the bulk, involving:**			
	a) Addition or change storage condition for the bulk (e.g., widening or tightening of a temperature criterion.	None	1–5	M
		1-2	1-4	M

Conditions

1. Change is not necessitated by recurring events arising during manufacture or

because of stability concerns. 2. The change consists in the tightening of a temperature criterion within the approved ranges. **Supporting data** 1. Revised product monograph (e.g., where applicable, title page, composition and packaging and Pharmaceutical information section) and inner and outer labels, as applicable. 2. Proposed storage conditions and shelf life. 3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment. 4. Justification of the change in the labeled storage conditions/cautionary statement. 5. Results of stability testing (i.e.: full real time/real temperature stability data covering the proposed shelf life generated on one (1) commercial scale batch).				
25.	**Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:**			
	a) Deletion of an in-process test.	4-5	4	M
	b) Replacement or addition of an in-process test.	1, 4-6	1-3, 5	M
	c) Widening of an acceptance criterion.	None	1, 4-5	M
	d) Tightening of an acceptance criterion.	None	1, 4-5	M
		2	1	M

Conditions 1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns. 2. The change is within the range of approved acceptance criteria. 3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. 4. No change in the principle of the sterilization procedures of the finished product. 5. The deleted test has been demonstrated to be redundant with respect to the remaining tests. 6. Replaced or added analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. **Supporting data** 1. Description of the proposed process controls or acceptance criteria. 2. Method validation for any new analytical procedures (reference to the protocols / validation reports, procedures used). The FDA, at any time, may ask for documented evidence. 3. Copies or summaries of analytical procedures, if new analytical procedures are used. 4. Data to show that the relaxation has not a negative impact on the quality of the batch. Results for at least one (1) commercial scale batch are required. 5.Rationale for the change supported by data.				
26.	**Major change to the following process validation protocols used during the manufacture of the final product: introduction of product into an approved multiproduct facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process)**	None	1-2	M

Conditions

None.

Supporting data

1. Proposed validation protocol (code, date of approval, plan, etc.). Process validation and/or evaluation studies

could be requested. The FDA at any time may ask for documented evidence.

2. Rationale for the change in the validation protocol.

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

Conditions

1. No major changes in the manufacturing process to accommodate the new fill volume.

2. The new concentration is bracketed by existing approved concentrations.

3. No change in the dose recommended.

Supporting data

1. Chapters of the dossier (CTD) should be updated accordingly

2. Confirmation that information on the bulk has not changed as a result of the submission (e.g., cross reference(s) should be provided to the previously approved

dossier (CTD) or revised information on the bulk, if any of the attributes have changed.
3. Description and composition of the finished form.
4. Discussion of the components of the finished product, as appropriate (e.g., choice of excipients, compatibility of bulk and excipients, the leachates, compatibility with new container closure system (as appropriate)).
5. Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation and/or evaluation studies. Manufacturer may refer to these documents in the variation submission. FDA may request to review one or more of these documents if deemed necessary.
6. Control of excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited).
7. Specification(s), analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three (3) consecutive commercial scale batches. Bracketing for multiple strength products, container sizes and/or fills maybe acceptable if scientifically justified.
8. Information on the container closure system, if any of the components have changed (e.g., description, materials of construction, summary of specifications).
9. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed final product, or longer if less than three (3) time points are available (including the zero-time point), as well as commitment to notify the FDA of any failures in the ongoing long term stability studies.
10. Supporting clinical data or a request for a waiver of in-vivo studies.

28.	**Change involving a chemical / synthetic adjuvant:**			
	a) Change in supplier/manufacturer of a chemical/synthetic adjuvant.	None	4-6, 10	M
		1-2	5	M
	b) Change in manufacture process of a chemical/synthetic adjuvant.	None	4-6, 10	M
		1-2	5	M
	c) Change in release specifications of a chemical/synthetic adjuvant (including the tests and/or the	None	6-7, 10	M
		1, 3	7-9	M

	analytical procedures).			

Conditions

None.

Supporting data

1. Proposed validation protocol (code, date of approval, plan, etc.). Process validation and/or evaluation studies could be requested. The FDA at any time, may ask for documented evidences.

2. Rationale for the change in the validation protocol.

29.	**Change involving a biological adjuvant:**			
	a) Change in supplier of a biological adjuvant.	None	1-7, 10 -11	M
	b) Change in manufacture of a biological adjuvant.	None	1-7, 10	M
		3	1-5, 7	M
	c) Change in release specifications of a biological adjuvant (the tests and/or the analytical procedures).	None	6-10	M
		1, 2	7-9	M

Conditions

1. No change in the release specifications of the adjuvant outside of the approved ranges.

2. Change in specifications consists in the addition of a new test or a minor change to an analytical procedure.

3. No change in the supplier of the adjuvant.

Supporting data.

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

2. Information on the quality and controls of the materials (e.g., raw materials, starting materials) used in the manufacture of the proposed adjuvant.

3. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.

4. Process validation and/or evaluation studies (e.g., for manufacturing of the adjuvant).

5. Description of the general properties, characteristic features and characterization

data of the adjuvant.

6. 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 adjuvant, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failure in the ongoing long term stability studies.

7. Updated, QC approval of the proposed specifications for the adjuvant (or final version of the specifications).

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

9. Copies or summaries of validation reports, if new analytical procedures are used.

10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the final product with the approved and proposed adjuvant, as applicable. Certificates of analysis to be provided.

11. Supporting non-clinical and clinical data, if applicable.

30.	**Change to diluents, involving:**			
	a) Replacement of or addition tothe source of a diluents.	None	1-7	M
		1-3	1	M
	b) Change in manufacture of a chemical/synthetic adjuvant.	None	4-6, 10	M
	c) Change in facility used to manufacture a diluent (same company).	1-2	3-4, 6-7	M
	d) Addition of a diluents filling line.	1-2, 4	1-4, 6	M

Conditions

1. The diluents are water for injection (WFI) or a salt solution.

2. After reconstitution, there will be no change in the final product specifications outside of the approved ranges.

3. The proposed diluents is commercially available in the country of manufacture of the

vaccine.

4. The addition of the diluents filling line in a filling facility approved by FDA

Supporting data

1. Flow diagram (including process and in-process controls) of the proposed manufacturing process (es) and a brief narrative description of the proposed manufacturing process (es).

2. Updated, QC approved copy of the proposed specifications for the diluents (or where applicable, the final version of the specifications to be signed by QC).

3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed diluents (certificates of analysis to be provided as applicable).

4. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed diluent, or longer if less than three (3) time points are available (including the zero-time point).

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

6. Cleaning procedures (including data in a summary validation report) demonstrating lack of carry-over or cross-contamination

7. Information on the proposed production facility involved in manufacturing of the diluent, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems).

31.	**Change involving a final product manufacturer/manufacturing facility, such as:**			
	a) Replacement or addition of a manufacturing building for the final product (includes primarypackaging facility).	None	1-8, 10 -13	M
		1-4	1-4, 6-8, 10	M
	b) Replacement of a formulation/filling suite or addition of an equivalent formulation/ filling suite.	1	3-4, 6-7, 9,11,13 – 14	M

	c) Replacement or addition of a secondary packaging facility; a labeling/storage facility; or a distribution facility.	2-3	1-2, 4	M
	d) Deletion of a final product manufacturing facility.	None	None	M

Conditions

1. The formulation/filling facility is approved by FDA
2. No change in the composition, manufacturing process and final product specifications.
3. No change in the container/closure system.
4. The same validated manufacturing process is used.

Supporting data

1. Confirmation that the proposed manufacturing site is a GMP compliance facility.
2. Updated or new Drug Master File
3. Confirmation that information on the final product has not changed as a result of the submission (e.g., other than change in facility) or revised information on the final product, if any of the attributes have changed.
4. Name, address, and responsibility of the proposed production facility involved in manufacturing and testing.
5. 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.
6. Process validation and /or evaluation studies (e.g., equipment qualification, media fills, as appropriate).
7. 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 final product (certificates of analysis to be provided.

Bracketing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.

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

9. Commitment to place the first commercial scale batch of the finished product manufactured using the proposed formulation/filling suite into the stability programme, and to notify FDA of any failure in the ongoing long term stability studies. 10. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the finished product manufactured using the proposed manufacturing facility, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failure in the ongoing long term stability studies. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified. 11. Information on the proposed production facility involved in the manufacture of the finished product, 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. 12. Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as applicable. If no revisions, a signed attestation that no changes were made to the change–over procedures. 13. Results of the environmental monitoring studies in classified areas. 14. Rationale for considering the proposed formulation/filling suite as equivalent.				
32.	**Effect on the existing finished products in a finished product manufacturing facility involving introduction of a new product or change in concurrence:**			
	a) Conversion of a finished product manufacturing facility from single- product to multi-product).	None	1-3	M
	b) Conversion of formulation and filling area(s) from campaign to concurrent for multiple product manufacturing areas.	1	1-2	M

	c) Introduction of new product intoan approved multi-product formulation/filling suite.	2-4	1-3	M
Conditions 1. The manufacturing process is a closed process for shared areas. 2. The newly introduced product does not introduce significantly different risk issues. 3. The newly introduced product is not of significantly different strength (i.e., mg .vs .µg). 4. The maximum allowable carry-over is not affected by the introduction of the new product. **Supporting data** 1. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the Introduction of new products) demonstrating lack of carry-over or cross-contamination. 2. Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as appropriate. If no revisions, a signed attestation that no changes were made to the changeover procedures. 3. Information on the product (s) which shares the same equipment (e.g., therapeutic classification).				
33.	**Change in the final product manufacturing process, such as:**			
	a) Scale-up of the manufacturing process at the formulation/filling stage.	1-4	1, 3,5-6, 8, 10	M
	b) Addition or replacement of equipment (e.g., Formulation tank, filter housing, filling line and head, and lyophilizer).	None	1-4, 7,9	M
		5	3-4	M
	c) Product-contact equipment change from dedicated to shared (e.g., formulation tank, filter housing, filling line and head, lyophilizer).	None	9	M

	d) Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process.	1–4	1-3, 5,5, 10	M
	e) Change in process flow or procedures.	None	1-3, 5-6, 8	M
Conditions 1. The proposed scale uses similar/comparable equipment to that approved (N.B. change in equipment size is not considered as using similar/comparable equipment). 2. Any changes to the manufacturing process sand/or to the in-process controls are only those necessitated by the change in batch size (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized). 3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns. 4. No change in the principle of the sterilization procedures of the final product. 5. For product-contact equipment, the change is considered „like for like" (i.e., in term of product-contact material/equipment size).				
34.	**Change in the standard/monograph (i.e. specifications) claimed for the excipient:**			
	a) Change in the standard/monograph (i.e. specification) claimed for the excipient.	None	1- 4	M
		1-5	1-4	M
	b) Change in the specification for an excipient to comply with an updated pharmacopoeia standard/monograph.	2-3	1, 2-4	M
Conditions 1. The change is from a house/professed standard to a pharmacopoeia standard/monograph. 2. The change is made exclusively to comply with a pharmacopoeia				

standard/monograph.

3. No change to the specifications for the functional properties of the excipient outside of neither the approved ranges nor that result in a potential impact on the performance of the finished product.

4. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeia standard/monograph.

5. No deletion/change to analytical procedures, except to comply with a pharmacopoeia standard/Monograph.

Supporting data

1. Updated excipient specifications.

2. Where a house analytical procedure is used and a standard/monograph is claimed, results of an equivalency. Study between the house and compendia methods.

3. Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the finished final product).

4. Declaration that consistency of quality and of the production process of the excipient is maintained.

Supporting data

1. Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.

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

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

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

5. Description of the batches and summary of result, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed product (certificates of analysis to be provided). Bracketing for multiple strength products, container sizes and/or fills may be acceptable if justified.

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

7. Commitment to place the first commercial scale batch of the final product manufactured using the proposed formulation/filling suite into the stability programme, and to notify the FDA of any failure in the ongoing stability studies.
8. Stability test results from a minimum of three (3) months of accelerated and three (3) months of realtime/ 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 FDA of any failure in the ongoing long term stability studies. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.
9. Cleaning procedures (summary validation report) demonstrating lack of carry-over or cross-contamination.
10. Rationale for regarding the equipment as similar/comparable, as applicable.

35.	**Change in the specifications used to release the excipient, involving:**			
	a) Deletion of a test.	5	1, 3-4	M
	b) Addition of a test.	4	1-4	M
	c) Replacement of an analytical procedure.	1-3	1-2	M
	d) Minor changes to an approved analytical procedure.	None	1-2	M
	e) A change from a house/professed analytical procedure to a Schedule analytical procedure.	None	1-2	M
	f) To reflect a pharmacopoeia monograph update	None	1	M
	g) Widening of an acceptance criterion	4, 6	1, 3-4	M

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is

at least equivalent to the Approved analytical procedure. 2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity. 3. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeia monograph specifications for the excipient. 4. Acceptance criterion for Class 3 residual solvent is within the accepted international limits (e.g., as per recognized by ICH). 5. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeia requirement. 6. The change to the specifications does not affect the functional properties of the excipient nor result in a potential impact on the performance of the final product. **Supporting data** 1. Updated excipient specifications. 2. Where a house analytical procedure is used and a compendia standard is claimed, results of an equivalency study between the house and compendia methods. 3. Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the finished product). 4. Declaration that consistency of quality and of the production process of the excipient is maintained.				
36.	**Change in the source of an excipient. From a vegetable or synthetic source to a TSE risk (e.g., animal) source**.	None	2-8	M
37.	**Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source.**	2	1, 3,5-7	M
38.	**Change in manufacture of a biological excipient.**	None	3-8	M
		2	3, 5-8	M
		1-2	3, 5	M

39.	**Change in supplier for a human plasma-derived excipient (e.g., human serum albumin).**	None	4-9	M
		3-4	5-7, 10	M
40.	**Change in supplier of an excipient of non-biological origin or of biological origin (exclude human plasma derived excipient).**	1	3	M

Conditions

1. No change in the specifications of the excipient or final product outside of the approved ranges.
2. The change does not concern a human plasma-derived excipient.
3. The excipient from the new supplier is a FDA approved excipient.
4. No chemistry and manufacturing changes were made by the supplier of the new excipient since its last approval by FDA.

Supporting data

1.Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Details of the source or the excipient (e.g., animal species, country of origin) and the steps undertaken in processing to minimize the risk of TSE exposure.
3. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the proposed excipient with the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed excipient.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the proposed excipient (certificates of analysis to be provided).
6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) batches of the final product with the proposed excipient (certificates of analysis to be provided.
7. 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) batches of the final product with the proposed excipient, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failures in the ongoing long term stability studies. 8. Information assessing the risk with respect to potential contamination with adventitious sagents (e.g., impact on the viral clearance studies, BSE/TSE risk). 9. Complete manufacturing and clinical safety data to support the use of the proposed human plasma derived excipient. 10. Letter from the supplier certifying that no changes were made to the excipient since its last approval by stringent regulatory authority.				
41.	**Change affecting the quality control (QC) testing of the finished product, involving:**			
	a) Transfer of the QC testing activities for a non-pharmacopoeia assay (in- house) to a new company or to a different facility within the same company.	None	1-2	M
Conditions 1. The transferred QC test is not a potency assay or a bioassay. **Supporting data** 1.Information demonstrating technology transfer qualification. 2. Evidence that the new company/facility is GMP compliant.				
42.	**Change in the specifications used to release the finished product, involving:**			
	a) For sterile products, replacing the sterility test with process parametric release.	None	1-2, 6,8-9	M
	b) Deletion of a test.	None	2, 8-9	M
	c) Addition of a test.	1-2	2-4, 8	M

	d) Change in animal species/strains for a test (e.g., new species/strains, animals of different age, new supplier where genotype of the animal cannot be confirmed).	None	5, 10	M
	e) Replacement of an analytical procedure.	None	2-4, 7	M
	f) Minor changes to an approved analytical procedure.	3-6	3-4, 7	M
	g) Widening of an acceptance criterion.	None	2, 8-9	M
	h) Tightening of an acceptance criterion.	7-8	2	M

Conditions

1. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The addition of test is not to monitor new impurity species.
3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
6. The change does not concern potency testing.
7. The change is within the range of approved acceptance criteria.
8. Acceptance criterion for any residual solvent is within the international recommended specification (e.g., based on harmonized ICH limits).

Supporting data

1. Process validation and/or evaluation studies or validation protocol of the proposed finished product.
2. Updated, QC approved finished product specifications (final version to be signed by QC).
3. Copies or summaries of analytical procedures, if new analytical

procedures are used.

4. Copies or summaries of validation reports, if new analytical procedures are used.

5. Data showing that change in animals gives comparable results with those obtained using approved animals.

6. 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).

7. Justification of the proposed finished product specifications (e.g., demonstration of the suitability of the monograph to control the finished product, including degradation products).

8. Declaration that consistency of quality and of the production process is maintained.

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

43.	**Change affecting the quality control (QC) testing of the finished product, involving:**			
	a) Change the reference standardsfrom Pharmacopoeia to house.	None	1-2	M
	b) Change the reference standardsfrom in-house / professed to pharmacopoeia.	1-2	1-2	M
	c) Qualification of a new lot of reference standard against the approved reference standard.	1-2	2	M
	d) Extension of reference standard shelf life.	2	3	M

Conditions

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

2. The reference standard is not for a bacterial or a viral vaccine.

Supporting data

1. Revised Product monograph to reflect the change in reference standard.

2. Information demonstrating qualification of the proposed reference standards or

materials (e.g., source, characterization, certificate of analysis).

3. Summary of stability testing and results to support the extension of reference standard shelf life.

44.	**Modification of a primary container Closure system, in contact with the medicinal product (e.g., new coating, adhesive, stopper, type of glass).**	None	1-7	M
		1-3	1, 3	M
45.	**Change from approved single-dose container to multi-dose container.**	None	1-7	M
46.	**Deletion of a container closure system.**	None	1	M

Conditions

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

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

3. The change is made only to improve quality of the container and does not modify the product contact material (e.g., increase thickness of the glass vial without changing interior dimension).

Supporting data

1. Product monograph, dosage forms, composition, packaging, inner and outer labels, as appropriate.

2. Process validation and /or evaluation studies, or provide equivalency rationale.

3. Information on the proposed container closure system (e.g., description, materials, specifications).

4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity tests.

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

6. Long-term stability studies; results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) finished product batches, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failures in the ongoing long term stability studies. Bracketing and matrixing may be acceptable if scientifically justified.

7. Information demonstrating suitability of the proposed container/closure system (e.g., last media fill‟s results, transportation and /or interaction studies demonstrating preservation of protein integrity and maintenance of the sterility, the sterility in multi-dose container).

47.	**Change in the supplier for a primary container closure component, involving:**			
	a) Replacement or addition of a supplier.	None	1-2	M
		1-2	None	M
	b) Deletion of a supplier.	None	None	M

Conditions

1. No change in the type of container closure, materials of construction, shape, dimensions or in the

sterilization process for a sterile container closure component.

2. No change in the specification of the container closure component outside of the approved ranges.

Supporting data

1. Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing).

2. Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications).

48.	**Change in the specifications used to release a primary or functional secondary container closure component, involving:**			
	a) Deletion of a supplier.	1-2	1-2	M

	b) Addition of a test.	3	1-2	M
	c) Replacement of an analytical procedure.	6-7	1-3	M
	d) Minor changes to an analytical procedure.	4-7	1-3	M
	e) Widening of an acceptance criterion.	None	1-2	M
	f) Tightening of an acceptance criterion.	8	1	M

Conditions

1. Deleted test has been demonstrated to be redundant or is no longer a pharmacopoeia requirement.
2. The change to the specifications does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the final product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
4. No change in the acceptance criteria outside of the approved ranges.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. New/modified analytical procedure maintains/tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeia monograph specifications for the container closure component.

Supporting data

1. Updated, QC approved copy of the proposed specifications for the primary or functional secondary container closure component (or where applicable, the final version of the specifications to be signed by)
2. Rationale for the change in specifications for a primary container closure component.

3. Description of the analytical procedure and, if applicable, validation data.				
49.	**Change in the shelf life for the final product, involving:**			
	a) An extension.	None	1– 4,6	M
		1-5	1-2, 5	M
	b) A reduction.	None	1-5	M
		6	2-4	M

Conditions

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

Supporting data

1. Summary of stability testing and results (e.g., studies conducted, protocols used,results obtained).
2. Proposed storage conditions and shelf life, as appropriate.
3. Updated, QC approved post-approval stability protocol (or where applicable, the finalversion of the protocol to be signed by QC) and stability commitment.
4. Justification of the change to the post-approval stability protocol or stabilitycommitment.
5. Results of stability testing (i.e., full real time/real temperature stability data coveringthe proposed shelf life generated on at least three (3) commercial scale batches).
6. Interim stability testing results and a commitment to notify FDA 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.

50.	**Change in the post-approval stability protocol of the final product, involving:**			
		None	3-6	M

	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.	1-2	1-2, 4-5	M
	b) Addition of time point (s) intothe post-approval stability protocol.	None	4-5	M
	c) Addition of test (s) into the post-approval stability protocol.	3	4-5	M
	d) Deletion of time point (s) from the post-approval stability protocol beyond the approvedshelf life.	None	4-5	M
	e) Deletion of time point (s) from the post-approval stability protocol within the approved shelf life.	4	4-5	M

Conditions

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

Supporting data

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

Copies or summaries of validation reports, if new analytical proceduresare used.

Proposed storage conditions and or shelf life, as appropriate.

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

Justification of the change to the post-approval stability protocol orstability 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 thealternate test).

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	1-5	M
		1-2	1-4	M
	b) Addition of a cautionary statement.	1	1-2, 4-5	M

	c) Deletion of a cautionary statement.	None	1-2, 4,6	M

Conditions

1. The change is not necessitated by recurring events arising during manufacture orbecause of stability concerns.
2. The change consists in the tightening of a temperature criterion within the approvedranges.

Supporting data

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

Efficacy and Safety Changes				
52.	**Change in the efficacy parameter**			
	a. Addition of a new therapeutic indication and/or modification of an approved one	1	1-5	Major Variation
	b. Deletion of a therapeutic indication	None	3	Minor Variation

	c. Modification of an approved safety claim, indication or efficacy claim whether explicit or implicit (e.g. expansion of the age of use or restriction of an indication based on clinical studies demonstrating lack of efficacy)	1	1-5	Major Variation

Conditions

1. No change in strength, dosage form and route of administration.

Supporting Data

1. Clinical data along with applicable preclinical data.
2. Copy of approval with new indication or any other regulatory certificate issued by other recognized NRA or NRA of country of origin with new indication.
3. Copy of current Summary of Product Characteristics with proposed change,
4. Published data or relevant literature supporting the proposed change, if any.
5. Duly signed FDA variation application, with applicable fees

	Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Category**
53.	**Change / modification in the approved claim**			
	a. new route of administration, new strength (potency), or increase in the recommended dose / dosage range	1	1-5	Major variation

Conditions

1. No change in dosage form and indication.

Supporting Data

1. Clinical data along with applicable preclinical data
2. Copy of approval with new route of administration or any other regulatory certificate issued by other recognized NRA or NRA of country of origin with new route of administration.

3. Copy of current SmPC with the proposed change. 4. Published data or relevant literature supporting the proposed change, if any. 5. Duly signed FDA variation application, with applicable fees				
	Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Category**
54.	**Other changes related to safety and efficacy, involving**			
	a. change to add information on shedding and transmission	1	1-4	Minor variation
	b. change in the recommended dose and/ or dosing schedule (addition or modification new vaccination regimen)	None	1-4	Major variation
	c. change to use in specific risk groups (e.g. use in pregnant women or immunocompromised patients)	1	1-4	Minor variation
	d. change to add information on co- administration with other vaccines or medicines	1	1-4	Minor variation
	e. change to add a new delivery device	1	1-4	Major variation

	f. Change in existing risk-management measures: (i) deletion of an existing route of administration, dosage form and/or strength due to safety reasons; (ii) deletion of a contraindication (for example, use in pregnant women); (iii) changing a contraindication to a precaution.	1	1-4	Minor variation
Conditions 1. No change in strength, dosage form and indication. Supporting Data 1. Clinical data along with applicable non-clinical data. 2. Copy of approval for proposed change or any other regulatory certificate issued by other recognized NRA or NRA of country of origin with proposed change 3. Copy of current SmPC with proposed change. 4. Published data or relevant literature supporting the proposed change, if any.				
	Description of Change	**Conditions to be Fulfilled**	**Supporting Data**	**Reporting Category**
	a. **Changes or replacement to the active substance of a seasonal, pre-pandemic or pandemic biological product**	None	1-3	Major variation
Conditions None **Supporting Data** 1. Revised CMC sections and labelling. 2. Pre-clinical data (Module 4) as applicable.				

3. Clinical data (Module 5) as applicable.