FOREWORD

The Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India had published Post Approval Changes in Biological Products: Quality Safety and Efficacy Documents (Document No.-PAC/1108 Version – 1.1) in the year 2008. It was prepared in line with the international guidelines and in accordance with Drugs and Cosmetics Rules, 1945 and Drugs Cosmetics Act, 1940. Now, the Post Approval Changes in Biological Products: Quality Safety and Efficacy Documents (Document No-PAC/2024 Version – 1.2) is updated to align with updated international guidelines, New Drugs and Clinical Trials Rules, 2019 and SUGAM application process after consultation with the stakeholders and it is published after considering the public suggestions / comments / objections.

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Abbreviations

AEFI	:	Adverse Event Following Immunization
BAN	:	British Approved Names
BSE	:	Bovine Spongiform Encephalopathy
CDSCO	:	Central Drugs Standard Control Organization
CMC	:	Chemistry, Manufacturing and Control
CQA	:	Critical Quality Attribute
CTD	:	Common Technical Document
EDQM	:	European Directorate for the Quality of Medicines & HealthCare
GMP	:	Good Manufacturing Practices
HA	:	Haemagglutinin
HVAC	:	Heating, Ventilation, Air Conditioning
ICH	:	International Council for Harmonization
INN	:	International Non-proprietary Name
MA	:	Marketing Authorization
MCB	:	Master Cell Bank
NA	:	Neuraminidase
NC	:	Notifiable Change
NCL	:	National Control Laboratory
NIBSC	:	National Institute for Biological Standards and Control
NRA	:	National Regulatory Authority
PAC	:	Post Approval Change
PACMP	:	Post-approval change management protocol
PI	:	Package Insert
PK/PD	:	Pharmacokinetic/pharmacodynamic
PPD	:	Product Permission Document
PSUR	:	Periodic Safety Update Report
QC	:	Quality Control
SBP	:	Similar Biotherapeutic Products
SPC	:	Summary of Product Characteristics
TAG	:	Technical Advisory Group

TSE	:	Transmissible Spongiform Encephalopathy
USAN	:	United States Adopted Name
WCB	:	Working Cell Bank
WFI	:	Water for Injection
WHO	:	World Health Organization

1. INTRODUCTION

This document is intended to provide guidance to manufacturers on regulating changes to already licensed biological products in order to assure their continued quality, safety and efficacy, as well as continuity in supply and access.

Changes are essential for the continual improvement of the manufacturing process and for maintaining state-of-the-art control of biological products, and often need to be implemented after the product has been approved (that is, when it has been licensed or when marketing authorization has been received). Changes may be made for a variety of reasons, including: (a) to maintain routine production (for example, replenishment of reference standards, or change of raw materials); (b) to improve product quality, or the efficiency and consistency of manufacture (for example, changes in the manufacturing process, equipment or facility, or adding a new manufacturing site); (c) to make safety or efficacy changes (for example, adding a new indication, changing the dosage regimen, or adding information on co-administration with other medicines); (d) to update product labelling information (for example, improvement of the management of risk by addition of a warning statement for a particular target population, or limiting the target population); or (e) to address administrative changes (for example, change in the proper/nonproprietary or trade name of a biological product).

Marketing authorization holders should recognize that:

- any change to a biological product has a potential impact on the quality, safety and/or efficacy of that product;
- any change to the information associated with the product (that is, product labelling information) may have an impact on its safe and effective use.

The regulation of changes to approved biological products is key to ensuring that products of consistent quality, safety and efficacy are marketed after they receive authorization or licensure. An attempt has been made to cover a range of possible changes in manufacture, quality control, safety, efficacy and product labelling information and to provide guidance on the data needed to support changes to

approved biological products in order to ensure comparability of the pre-change and post-change products with respect to quality, safety and efficacy.

This document is intended to serve as a guide for post-approval changes to biological products. The categories of changes and reporting procedures are provided in the main body of the document and the data requirements to support the proposed changes are provided in the subsequent sections.

Purpose and scope

This Guideline provides guidance for marketing authorization holders on the regulation of changes to the original marketing authorization dossier or product license 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 NRAs to evaluate the potential impact of the change on the quality, safety and efficacy of the product.

1.1 Objectives

a) To assist with the classification of changes made to biological products approved by CDSCO for import / manufacturing and marketing in India.

b) To provide Marketing Authorization Holders (MA holders) with recommendations on the data to support a change which would be considered sufficient to allow a determination of the impact of the change on the quality of the approved products as it relates to safety, efficacy and/or effective use of the products.

1.2 Scope and Application

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

1.3 Background

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.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Reporting Categories for Quality Changes

The following criteria are meant to provide guidance with respect to the classification of a change. Specific change examples based on the application of these criteria are provided in this guidance. For assistance in classifying a change, MA holders are advised to contact CDSCO.

2.1.1 Level I – Supplements (Major Quality Changes)

Level I - Supplements (Major Quality Changes) are changes that have a *substantial potential* to have an adverse effect on the identity, strength, quality, purity, or potency of a biological product as these factors may relate to the safety and/or efficacy of the product.

In general, a change that is supported by extensive documentation and/or requiring extensive assessment of the supporting documentation would be considered a Level I - Supplement (Major Quality Change) (e.g., a change supported by *in-vivo* studies). This is to allow CDSCO the opportunity to apply the principles of risk management by having the necessary time for an appropriate assessment of the documentation. This assessment will take into consideration any potential impact upon market availability as well as the adverse effects on the identity, strength, quality, purity, or potency of the biological product.

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

The changes included in this reporting category shall be submitted along with the recommended supporting data, to CDSCO. Appropriate fee, as applicable and in accordance with rules shall be paid along with submission.

2.1.2 Level II – Notifiable Changes (Moderate Quality Changes)

Level II - Notifiable Changes (Moderate Quality Changes) are changes that have a *moderate potential* to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety and/or efficacy of the product.

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

The changes included in this reporting category should be submitted along with the recommended supporting data, to CDSCO as a Notifiable Change (NC).

2.1.3 Level III – Annual Notification (Minor Quality Changes)

Level III -Annual Notification (Minor Quality Changes) are changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety and/or efficacy of the product. The changes included in this reporting category may be implemented by the MA holder without the prior review by CDSCO of the data supporting such a change (except for cases of change in shelf life of DS and DP).

2.1.4 Level IV – Changes (Record of Changes)

Level IV (Quality only) changes are changes to a biological product that are not Level I, Level II or Level III and are not expected to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety and/or efficacy of the drug product. The changes included in this reporting category may be implemented by the MA holders without prior review by CDSCO. The changes should be retained as part of the drug product's record at manufacturing site and should comply with the requirements of 'Good Manufacturing

Practices'. For importers, the said data to be submitted once in three years during re registration of RC.

A list of examples of Level IV changes is provided in Appendix 1.

2.2 Documentation – Quality Changes

2.2.1 General Information

The examples presented in Post Approval Changes (Biologics) are intended to assist with the classification of changes made to the Quality, Safety, Efficacy and Administrative information. The information summarized in the tables provides recommendations for:

a) The conditions to be fulfilled for a given change are classified as a Level I, II, III or IV change. If the conditions outlined for a given change are not fulfilled, the particular change is automatically considered the next higher level of change.; For example, if any of the conditions recommended for a Level II - Notifiable Change are not fulfilled, the change is considered a Level I - Supplement. Similarly, if any of the conditions recommended for a Level I - Supplement are not fulfilled, the change would warrant the filing of a New Drug.

b) The supporting data for a given change is either to be submitted to CDSCO and/or maintained by the MA holders. Wherever applicable, the corresponding sections of the application for the supporting data have been identified; if any supporting data is not provided / not applicable, then a justification should be provided.

c) The reporting categories (e.g., Supplement, Notifiable Change, Annual Notification and Record of Changes).

2.2.2 Supporting Data – Level I and Level II Changes:

All data recommended to support the change should be provided with the submission. Where applicable, these data should be provided in the format defined by CDSCO or in the format of Common Technical Documents (CTD).

Supporting Data Common to Level I and Level II Changes:

The following should be included, where applicable, in the submission package for Level I and Level II Quality changes:

a) a covering letter (including a list of changes describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used);
b) where relevant, a side-by-side comparison of the previously approved and the changed information;

In addition to the above common information, recommendations are included in Post Approval Change (Biologics) categories outlining the specific information to support the various changes of Quality, Safety, Efficacy and Administrative. It should be noted that the common information is not repeated for the various changes outlined in the sections.

When cross-references are made to previously submitted information, details on the cross-referenced information should be indicated in the covering letter (e.g., brand name / generic name of the drug product, MA holders name, submission type, File number, date approved).

2.2.3 Supporting Data – Level III Changes

Annual notifications shall be submitted to CDSCO by 1st quarter of every calendar year. Any data for calendar year (January to December) that may have been generated by the MA holders in support of a Level III change should not be submitted with annual notification, however, should be available to CDSCO within thirty (30) calendar days, if requested. For submission of each minor change, Appendix 2: Annual Report Form (Minor Changes) of this guidance shall be referred by MA holder.

Note: For extension of shelf life that is categorized as Level III as per this guidance, MA holder should submit the PAC application along with applicable supporting documents and should implement the change only after approval from CDSCO.

2.2.4 Supporting Data – Level IV Changes

The Quality changes included in this category should be retained as part of the drug product's record by MA holder and comply with the requirements of 'Good Manufacturing Practices'. These changes should be annotated / updated in the affected documents (e.g., Package Insert, SPC or PPD) with the filing of the next submission to CDSCO.

2.3 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:

- Level I – Supplements (Safety and Efficacy);
- Level II – Notifiable Changes (Safety and Efficacy) i.e. risk/harm management change
- Level II – Notifiable Changes (Safety and Efficacy) that are not risk/harm management changes
- Level III – Annual Notifications (Safety and Efficacy)

Further information on each category is provided below.

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:

- 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; and
- vaccine attributes (e.g. live vaccines as opposed to inactivated ones).

MA holders are encouraged to consult CDSCO 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. CDSCO 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.

2.3.1 Level I – Supplements (Safety and Efficacy)

A Level I change 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; or
- 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 purpose without prior approval from CDSCO.

Examples: Examples of Level I changes 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 has been 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 has been modified to reflect, in any way, an apparent reduction in risk/harm. This includes changes related only to animal data.

Note: The changes that are considered as "New Drugs" as per "The New Drugs and Clinical Trials Rules, 2019, MA holder should submit the MA application in Form CT-21/Form CT-18 in SUGAM with applicable fee along with supporting documentation as described for the respective post approval change category, followed by amendment / endorsement of current Form 28 D license, as applicable .

Note: A declaration to state that no change to other remaining section/s of the MA dossier, including impact on safety/efficacy, shall be submitted, as applicable.

2.3.2 Level II – Notifiable Change (Safety and Efficacy) that are risk/harm management changes

A Level II - Notifiable (Safety and Efficacy) change (i.e. risk/harm management 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; and

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

Examples:

Examples of Level II – Notifiable (Safety and Efficacy) that are risk/harm management changes include but are not limited to the following:

- An addition to, strengthening or clarification of text anywhere in these sections: Contraindications, Warnings and Precautions and Adverse Events. These

changes may include the provision of recommended risk/harm management actions (e.g., required testing prior to initiation of the drug, specific monitoring during product use, ensuring patient awareness of certain risks, etc.), or the identification of a specific sub-population as being at greater risk such as those with a concomitant condition, those taking concomitant medicine, or a specific age group.

- 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 Level II - Supplements (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.

2.3.3 Level II – Notifiable Change (Safety and Efficacy) that are not risk/harm management changes

There are some Level II - Notifiable (Safety and Efficacy) changes that do not meet the criteria of a Level I - Supplement or a risk/harm management change of a Level II - Notifiable (Safety and Efficacy), but for which prior approval by CDSCO 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 Level II – Notifiable (Safety and Efficacy) risk/harm management changes 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 than Level I - Supplements, Level II – Notifiable (Safety and Efficacy) that are risk/harm management changes or Level III changes, 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.

2.3.4 Level III (Safety and Efficacy) Changes – Annual Notification

A Level III change 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 by CDSCO of the data supporting such a change. Any data that may have been generated by the MA holder in support of a Level III change should be submitted to DCGI within 30 calendar days, upon request.

Examples of Level III related changes 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.,"adition" 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.).

2.3.5 Documentation – Safety and Efficacy Changes:

For a change under these categories (Safety and Efficacy), the MA holder should submit an application to CDSCO 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 Safety Update Report (PSUR) 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.

2.4 Administrative Product Labelling Information Changes

Administrative product labelling information changes are changes that are not expected to affect the safe and efficacious use of the biological product. In some cases, these changes may require reporting to the CDSCO and receipt of approval

prior to implementation, while in other cases reporting may not be required, as follows:

- Examples of product labelling information changes that require approval by the CDSCO prior to implementation are changes in the name of the MA holder that are due to a merger or changes in the proper name or trade name of the biological product. The changes in this category are considered important for reasons of liability and monitoring.
    - *Product labelling changes submitted along with the MA transfer or license amendment application, to the CDSCO, may not require separate reporting.*
- Examples of product labelling information changes that do not require approval by the CDSCO prior to implementation are changes to a distributor's address or minor changes in format. These changes should be reported to the CDSCO as part of subsequent safety and efficacy changes or product labelling information changes when updated product labelling information is included.

For an administrative product labelling information change that requires approval prior to implementation, the MA holder should submit an application containing background information on the change and annotated and clean drafts of the product labelling information. The review and approval timeline for an administrative product labelling information change shall be around 30 days from the date of submission.

3. SPECIAL CONSIDERATIONS

3.1 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 (see also section 3.2 on Bridging Clinical Studies). 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.

3.2 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.

a) 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;

b) a new dosage form;
c) a new formulation (for example, a new excipient);
d) a new presentation (for example, addition of pre-filled pens to vials); (e) 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 CDSCO

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.

3.3 Stability Testing

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

a. The New Drugs and Clinical Trials Rules, 2019
b. Stability Testing of New Drug Substances and Products (Q1A)
c. Stability Testing: Photostability Testing of New Drug Substances and Products (Q1B)
d. Stability Testing for New Dosage Forms (Q1C)
e. Bracketing and Matrixing Designs for Stability Testing of New Drug

Substances and Products (Q1D)

f. Evaluation of Stability Data (Q1E)
g. Stability Testing of Biotechnological/Biological Products (Q5C)
h. 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).

3.4 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.

For example, some of the Post Approval Changes that are listed in Post-Approval Changes (Biologics) of this guidance document as Level I - Supplements (Major

Quality Changes) or Level II - Notifiable Changes (Moderate Quality Changes) may not require approval prior to implementation if they are within the approved design space.

If desired, a MA holder may also establish a new design space for an existing product. This would provide the advantage, once approved, of limiting the necessity to file future submissions for changes within the ranges of the design space.

If proposed and approved, the details of the design space should be recorded in the PPD. MA holders are encouraged to discuss with CDSCO when considering the establishment of a design space.

3.5 Multiple Changes

Multiple related changes, involving various combinations of individual changes, may be submitted in the same supplement. 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 Supplement change 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 CDSCO may ask the marketing authorization holder to divide the changes into separate submissions and to resubmit the file. If the recommended reporting categories for the individual changes differ, the submission should be in accordance with the most restrictive of the categories recommended for the individual changes. In the case of numerous changes of the same category, the

CDSCO 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.

3.6 Post-Approval Change Management Protocol-PACMP

Post-approval change management protocol (PACMP) establishes a framework for a well-defined plan for the future implementation of a quality change, including the tests to be done and acceptable limits to be achieved to demonstrate the lack of negative effect of specific manufacturing changes on the quality, safety or efficacy of a biological product. A comparability protocol is a highly specific plan for the future implementation of a quality change.

For some changes, the routine quality tests performed to release the drug substance or drug product are not considered adequate for assessing the impact of the change, and additional in-process tests and characterization tests may be needed (e.g. addition of bioburden and endotoxin tests to support the removal of preservatives from the manufacturing process). Comparability protocols are often used for routine replenishment of WCBs and reference standards used in quality control tests when the remaining aliquots of reference standards expire or diminish.

Comparability can be demonstrated for a particular step/stage of manufacture (eg. Upstream manufacturing change could be evaluated within the drug substance manufacturing stage). For such approach of comparability scientific justification should be provided without generating drug product data for comparability.

The purpose of a comparability protocol is to allow for a more expedient distribution of a product by permitting the MA holder to submit a protocol for a change which, if approved, may justify a reduced reporting category for the change when the comparability data are obtained and the change is implemented.

3.7 Production Documents

Production documents (i.e. executed lot records) or topics related to GMP are in general not required to support changes to the MA dossier or product license. However, such documents may be requested and should be available during site GMP inspections.

3.8 Expedited Review Procedure (Reliance Pathway)

Expedited review/Reliance pathway can be considered in Biological products for priority diseases to treat serious or life-threatening illness with unmet medical needs, in public health emergencies or during shortages, and also for orphan products.

The CDSCO office could recognize the decision of recognized regulatory authorities (Reference NRA) and may expedite the review of the change submission on case by case basis, once the change is submitted through expedited review / reliance pathway procedure.

The CDSCO office performs an assessment of the decision of the recognized regulatory authority to determine if recognition of that recognized regulatory authority decision is appropriate. The submission consists of:

- the cover letter from the MA holder informing the procuring NRA about the change;
- a copy of the approval letter and assessment report issued by recognized reference country;
- a detailed description of the change along with supporting data.

If accepted, the review and approval timeline shall be expedited.

3.9 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 CDSCO

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.

4. POST APPROVAL CHANGES (BIOLOGICALS)

The change examples presented below are intended to assist with the classification of changes made to the Quality, Safety, Efficacy and administrative information of biological products. The information summarized in the tables provides recommendations for:

a. The conditions to be fulfilled for a given change to be classified under reporting category as a either a Level I - Supplement, a Level II - Notifiable Change, or a Level III - Annual Notification.
b. The supporting data for a given change, either to be submitted to the CDSCO and/or retained as part of the drug product's record by MA holder. If any of the supporting data outlined for a given change are not provided, are different or are not considered applicable, adequate scientific justification should be provided.

The supporting data should be provided in the appropriate sections of the CTD modules and in the separate documents, wherever required.

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Change in the name of the drug substance, (e.g, change in name of drug substance for seasonal influenza vaccine, Covid-19 vaccine, change in compendial name of drug substance, or change from in-house to compendial name of the drug substance)	1	1-3	Annual Notification

Conditions

1. Confirmation that information on the drug substance has not changed as a result of the submission (e.g., cross reference(s) should be provided to the previously approved drug submission, quoting the date approved and approval number(s)).

Supporting Data

1. Product Monograph [e.g. Title Page, Storage and Stability (Part I), Dosage Forms, Composition, Packaging] and Revised product labelling information (Inner and Outer Labels), as applicable.
2. Information on the changed nomenclature of the drug substance (e.g., Recommended INN, compendial name, chemical name(s)) (3.2.S.1.1).
3. Evidence that the changed name for the drug substance is recognized (e.g., proof of acceptance by WHO, a copy of recommended INN, USAN, BAN).

3.2.S.2 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. Change to a drug substance manufacturing facility / suite or site / premises including DS testing sites (release, stability, etc.) involving:			
a. Replacement or addition of manufacturing facility / suite in a new geographical site / premises and / or manufacturer of the drug substance, or any intermediate of the drug substance	11	1-6, 8-12, 15, 16	Supplement
Note: MA holder shall submit MA application in Form CT-21/Form CT-18 in SUGAM with applicable fees along with supporting documentation as described for the post approval change category, for addition of manufacturer or for addition of manufacturing facility/suite, for a drug substance, in a new geographical site/ premises. CDSCO will issue a No Objection Certificate for obtaining an amendment / endorsement of the current Form 28 D license, as applicable. A declaration to state that no change to other remaining section/s of the MA dossier, including impact on safety/efficacy, shall be submitted, as applicable.			
b. replacement or addition of manufacturing facility / suite to manufacture drug substance or any intermediate of the drug substance in existing manufacturing site / premises	1-6	1-6, 8-12, 15, 16	Notifiable Change
c. conversion of a drug substance manufacturing facility / suite from single-product to multi-product	4, 5	11, 12, 15	Notifiable Change
d. Conversion of production and	5, 7	13, 15	Notifiable

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
related area(s) from campaign to concurrent for a multiproduct facility / suite			Change
e. introduction of yeasts/bacterial cell culture into a multi-product microbial fermentation facility / suite	3-5	11-13, 15	Notifiable Change
f. Introduction of microbial hosts into a multi-product mammalian cell culture facility / suite or vice versa	None	12, 14	Supplement
g. introduction of a different host/media-type into an approved multi-product facility / suite.	8	7, 15	Annual Notification
h. addition of product(s) to an approved multi - product manufacturing suite / facility.	4, 5, 8	12, 13	Annual Notification
i. deletion of a manufacturing facility / suite or manufacturer for a starting material, bulk intermediate, or drug substance.	9, 10	None	Annual Notification

Conditions

1. The proposed manufacturing facility/suite is a CDSCO approved drug substance manufacturing site / premises for the same MA holder.
2. No changes have been made to the validated manufacturing process and controls, and identical or equivalent equipment are used.
3. The production process and controls are the same as those used by the. MA holder within the existing approved facility.
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 facility / suite or site / premises is under same Quality system oversight
7. The manufacturing process is a closed process for shared areas.
8. 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
9. There should remain at least one site/manufacturer, as previously authorized, performing the same function as the one(s) to be deleted.
10. The deletion should not be due to critical deficiencies in manufacturing (for example, recurrent out-of-specification events, environmental monitoring failures, etc.).
11. No changes have been made to the starting material and the expression system

Supporting Data

1. Updated or relevant DMF (CMC Module 3 Quality) data of drug substance. (3.2.S)
2. Name, address, and responsibility of the changed production facility or facility involved in manufacturing and testing. (3.2.S.2.1)
3. For drug substances obtained from or drug substances 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). A TSE Certificate of Suitability (CEP) 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. (3.2.S.2.3)
4. Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the changed drug substance, if revised (3.2.S.2.4).
5. Process validation and/or evaluation studies (e.g., for aseptic processing and

sterilization). (3.2.S.2.5).

6. Comparability of the approved and changed product with respect to physico–chemical characterization, biological activity, impurity profile, comparability of the equipment and operating principles for the manufacturing processes including technology transfer documentation as applicable for the product at the existing vs the proposed new facility/suite (3.2.S.2.6). (Occasionally, the manufacturer may be required to undertake bridging non-clinical or clinical studies, to support the quality data, when quality data is insufficient to establish comparability)
7. Information on the in-process control testing to demonstrate lack of carry-over or cross-contamination (3.2.S.2.2).
8. Description of the batches, certificates of analyses, summary of in-process control results and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the approved and changed drug substance Matrixing, bracketing, use of smaller-scale batches, use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified (refer ICH Q1D) (3.2.S.2.5 & 3.2.S.4.4)
9. Results of a) accelerated stability testing (usually a minimum of three (3) months) and b) a minimum of three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed changed drug substance, as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.S.7.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug substance may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO.
10. Updated post-approval stability protocol and stability commitment to place the first production scale batch of the drug product manufactured using the changed drug substance into the stability programme, as applicable (3.2.S.7.2).
11. Information on the changed production facility involved in manufacturer of Drug substance, 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. (3.2.A.1)

12. Information describing the change-over procedures for shared product contact equipment's and the segregation procedures, as applicable. If no revisions, a statement from the manufacturer that no changes were made to the change-over procedures.
13. Data demonstrating lack of carry-over or cross-contamination
14. Results of the environmental monitoring studies in critical classified areas.
15. Information on the cleaning procedures (including data in a summary validation report and the master cleaning protocol for the introduction of new products, as applicable) demonstrating lack of carry over or cross contamination
16. Evidence of GMP compliance of the facility

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
3. Change/Modification in a facility/ premises involved in the manufacture of a drug substance, such as:			
a. for an active ingredient manufactured in an open system, any changes which affect the trends or action limits of the environmental monitoring program	None	1, 2, 5	Notifiable Change
b. relocation of equipment to another room in the same facility/suite/ premises or another approved facility / suite/ premises, Qualification of a new room or change in classification of an existing room	1-3	3-5	Annual Notification
c. Modification to a manufacturing area or to an existing service /	1, 2	3-5	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
system (e.g., change to WFI systems or HVAC systems, moving a wall).			
d. change in the location of steps in the production process within the same facility	1	1, 4, 5	Annual Notification

Conditions

1. The change in the location of steps has no impact on the risk of contamination or cross-contamination and is supported by validated cleaning procedures.
2. The modification has no direct product impact.
3. Re-qualification of the equipment follows the original qualification protocol, if applicable.

Supporting Data

1. Information on the in-process control testing (3.2.S.2.2).
2. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug substance, including technology transfer validation, equipment qualification, as appropriate (3.2.S.2.5).
3. Information demonstrating re-qualification of the equipment or re- qualification of the change (operational qualification, performance qualification), as appropriate. (3.2.A.1)
4. Information on the modified production facility/area involved in manufacturing, including the floor plans and flow charts (drawings, room classification, water systems, HVAC systems). (3.2.A.1)
5. Results of the environmental monitoring studies in critical classified areas.

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
4. Change to the drug substance fermentation, viral propagation or			

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
cellular propagation process, involving:			
a. a critical change with high potential to have an impact on the quality of the antigen / drug substance or final product (e.g. incorporation of disposable bioreactor technology)	None	1-5, 7-11	Supplement
b. a change with moderate potential to have an impact on the quality of the drug substance or final product (e.g. extension of the *in-vitro* cell age beyond validated parameters)	2, 4	1-5, 7, 8, 12, 13	Notifiable Change
c. a non-critical change with minimal potential to have an impact on the quality of the drug substance or drug product, such as (e.g., change in harvesting and/or pooling procedures which does not 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).	1-5, 7-10, 12	1-6, 8, 12	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
5. Change to the drug substance purification process involving:			
a. a critical change (a change with high potential to have an impact on the quality of the drug substance or final product) (e.g. a change that could potentially have an impact on the viral clearance capacity of the process or the impurity profile of the drug substance)	None	1-3, 5, 7-11	Supplement
b. a change with moderate potential to have an impact on the quality of the drug substance or final product (e.g. a change in the chemical separation method, such as ion-exchange HPLC to reverse-phase HPLC)	2, 4	1-3, 5, 7-9, 11, 13	Notifiable Change
c. a noncritical change with minimal potential to have an impact on the quality of the drug substance or final product (e.g. addition of an in-line filtration step equivalent to the approved filtration step)	1-5	1-3, 6, 8, 12	Annual Notification
6. Change in scale of the manufacturing process:			
a. at the fermentation, viral propagation or cellular propagation stage	3-5, 8, 9, 11, 12	2, 4, 7-10	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
b. at the purification stage	1-3, 5, 9	2, 7-10	Notifiable Change
7. Change in the parameters of an approved holding step or addition of a new holding step	none	7, 14	Notifiable Change

Conditions

1. The change does not concern the method of sterilization of a sterile drug substance.
2. The change does not impact the viral clearance data or the source of a chemical nature of an inactivating agent.
3. No change in the drug substance specifications outside of the approved limits.
4. No change in the impurity profile of the drug substance outside of the approved limits.
5. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6. The change does not result in a change to the drug substance specification.
7. The scale-up consists in the addition of identical bioreactors/fermenter or new fermentation train is identical to the to the approved fermentation train(s)
8. The change does not affect the purification process.
9. The scale-up is linear with respect to proportionality of production parameters and raw materials.
10. No change in the approved in-vitro cell age
11. The change is not expected to have an impact on the quality, safety or efficacy of the final product
12. The change in scale involves the use of the same bioreactor (i.e., does not involve the use of a larger bioreactor)

Supporting Data

1. Justification for the classification of the change(s) as critical, moderate or non-critical as it relates to the impact on the quality of the antigen/drug substance.
2. Flow diagram (including process and in-process controls) of the changed manufacturing process(es) and a brief narrative description of the changed manufacturing process(es) (3.2.S.2.2).
3. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the changed drug substance when there is change in the raw material (3.2.S.2.3)

4. If the change results in an increase in the number of population doublings or subcultivations, information on the characterization and testing of the post-production cell bank for recombinant product, or of the drug substance for non-recombinant product. (3.2.S.2.3)
5. For drug substances obtained from or manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information assessing the risk with respect to potential contamination with adventitious agents and evidence that the material does not pose a potential BSE/TSE risk, and there is no impact on the viral clearance studies(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) (3.2.S.2.3).
6. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed drug substance (3.2.S.2.4).
7. Process validation and/or evaluation studies (e.g., for aseptic processing and sterilization, new reprocessing step, new or revised holding step) (3.2.S.2.5).
8. Comparability of the approved and changed product with respect to physico-chemical characterization, biological activity, and impurity profile. Occasionally, bridging non-clinical and/or clinical studies may be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and/or clinical studies should be determined on a case-by-case basis taking into consideration the quality comparability findings, the nature and level of the knowledge of the biological, existing relevant nonclinical and clinical data, and aspects of biological use (3.2.S.2.6).
9. Description of the batches, certificates of analyses, and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the approved and changed drug substance (3.2.S.2.5 & 3.2.S.4.4). Matrixing, bracketing, the use of smaller scale batches, and/or the use of less than 3 batches may be acceptable where justified (refer ICH Q1D)

10. Results of accelerated (usually a minimum of three (3) months) and a minimum of three (3) months of real time/real temperature testing on three (3) commercial scale batches of the changed drug substance as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.S.7.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug substance may be acceptable if scientifically justified (refer ICH Q1D).
11. Updated post-approval stability protocol and stability commitment to place the first production scale batch of the drug product manufactured using the changed drug substance into the stability programme, as applicable (3.2.S.7.2).
12. Description of the batches and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for one (1) commercial batch of the approved and proposed drug substance (3.2.S.2.5 & 3.2.S.4.4)
13. Comparative pre and post-change test results for the manufacturer's characterised key stability indicating attributes with at least one (1) commercial scale batch produced with the proposed changes under real time/real temperature testing conditions. Comparative pre-change test results do not need to be generated concurrently; relevant historical results for lots on the stability programme are acceptable. The data should cover a minimum of 3 months testing unless otherwise justified (3.2.S.7.3)
14. Demonstration that the new or revised holding step has no negative impact on the quality of the drug substance (data from one scientifically justified representative drug substance batch should be provided). (3.2.S.2.5)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
8. Changes to the cell bank:			
a. generation of new Master Cell Bank (MCB) from the same expression construct with same or closely related cell line; or	1	1, 5-8	Notifiable Change
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	1-8	Supplement
b. generation of a new MCB for a recombinant product or a viral vaccine	1	1-3, 5-7	Notifiable Change
c. generation of a new Working Cell Bank (WCB)	2-4	1, 2	Annual Notification
d. Extension of Shelf-life of the MCB or WCB	7	1, 2	Annual Notification
9. Changes to the Seed Bank/Lot:			
a. new Master Seed Bank/Lot (MSB/MSL).	None	1, 3-8	Supplement
b. Working Seed Bank/Lot (WSB/WSL) extended beyond an approved passage level.	None	3-8	Notifiable Change
c. Generation of a new WSB/WSL.	2-4	3, 4	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
10. Change in cell bank / seed bank/lot manufacturing site	None	1, 2, 9	Notifiable Change
11. Changes in cell bank / seed bank/lot testing / Storage site	5, 6	9	Annual Notification
12. Change in cell bank / seed bank/lot qualification protocol	None	10, 11	Notifiable Change
	6, 8	11	Annual Notification

Conditions

1. The new MCB is generated from the original clone or a pre-approved Master or Working Cell Bank or the new MSL is generated from a pre-approved MSL or WSL.
2. The new cell/seed bank is generated from a pre-approved MCB/MSB/pre-master bank/parent strain.
3. The new cell/seed bank is at the pre-approved passage level.
4. The new cell/seed bank is released according to a pre-approved protocol.
5. No changes have been made to the test or acceptance criteria used for the release of cell bank/ seed lot.
6. No changes have been made to the storage conditions used for the cell bank/seed lot and transport conditions of the cell bank/ seed lot has been validated.
7. The testing to support the extension of shelf-life is performed according to the pre-approved protocol.
8. The protocol is considered more stringent (that is, addition of new tests or narrowing of acceptance criteria).

Supporting Data

1. Qualification of the cell bank or seed lot. (3.2.S.2.3)

2. Information on the characterization and testing of the post-production cell bank for recombinant product, or of the product for non-recombinant product. (3.2.S.2.3)
3. Comparability of the approved and changed product with respect to physico-chemical characterization, biological activity, and impurity profile
4. Description of the batches, certificates of analyses, and summary of results as quantitative data, in a comparative tabular format, for the new seed lot (3.2.S.2.3).
5. Description of the batches, certificates of analyses, and summary of in-process and release testing results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the drug substance derived from the new cell/seed bank (. Matrixing, bracketing, the use of smaller-scale batches, and/or the use of fewer than 3 batches may be acceptable where justified (refer ICH Q1D) (3.2.S.2.5 & 3.2.S.4.4).
6. Results of accelerated (usually a minimum of three (3) months) and a minimum of three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed changed drug substance as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.S.7.3). Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than 3 batches and/or use of accelerated temperature conditions for stability testing may be acceptable where justified (refer ICH Q1D).
7. Updated post-approval stability protocol and stability commitment to place the first production scale batch of the drug product using the changed drug substance into the real time/real temperature stability programme (3.2.S.7.2).
8. Supporting non-clinical and clinical data or a request for a waiver of *in-vivo* studies.
9. Evidence that the new company or facility is GMP compliant.
10. Justification of the change to the cell bank/seed lot qualification protocol (3.2.S.2.3)
11. Updated cell bank/seed lot qualification protocol (3.2.S.2.3)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
13. Change in product-contact equipment / material used in drug substance manufacturing process, such as:			
a. Introduction of equipment having different operating principles / properties and different product contact material	None	1-3, 5-7	Notifiable Change
	1-3	1-3, 7	Annual Notification
b. Introduction of new equipment having same operating principles / properties but different product contact material	None	1, 5-7	Notifiable Change
	1-3	1, 3, 6, 7	Annual Notification
c. Introduction of new equipment having different operating principles/ properties but same product contact material	None	1, 2, 5, 7	Notifiable Change
	3	1-3, 5, 7	Annual Notification
d. Replacement of product contact equipment for an identical/ equivalent equipment.	6	1, 3, 5, 7, 8	Annual Notification
e. product-contact equipment change from dedicated to shared	4, 5	1, 4	Annual Notification
Conditions			

1. The change does not affect equipment used in the Fermentation process.
2. The manufacturing process is not impacted by the change in the product contact equipment.
3. The change has no impact on product quality.
4. The site is approved as multi-product facility by CDSCO.
5. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.
6. The change is considered “like for like” (e.g., change in supplier of the same filter).

Supporting Data

1. Information on the in-process control testing. (3.2.S.2.2)
2. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug substance, including technology transfer validation, as appropriate. (3.2.S.2.5)
3. Information on qualification or demonstrating re-qualification of the equipment or re- qualification of the change
4. Information describing the change-over procedures for the shared product-contact equipment.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one commercial scale batch of the drug substance produced with the approved and proposed product contact equipment/material. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action). (3.2.S.4.4)
6. Information on leachables and extractables as applicable.
7. Information on the new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment
8. Demonstration that performance of the proposed equipment is equivalent to the approved equipment (i.e. data from one batch)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
14. Change in the specifications of materials, involving:			
a. Change in supplier of auxiliary materials / reagents of biological origin (e.g., fetal calf serum, insulin, human serum albumin, trypsin)	None	11, 12-15	Notifiable Change
	16	11, 12	Annual Notification
b. Change in source of auxiliary materials / reagents of biological origin (e.g., fetal calf serum, insulin, human serum albumin, trypsin)	None	6, 11, 13-15	Notifiable Change
	16	6, 11	Annual Notification
c. raw materials/intermediates: widening of the approved specifications limits for starting materials, which may have a significant effect on the overall quality of the drug substance and/or final product.	None	1, 3, 4, 6, 7	Notifiable Change
	1-3, 12, 13	1, 3-7, 11	Annual Notification
d. raw materials/intermediates: Narrowing of the approved specification limits for starting materials/ intermediates	1, 2, 6, 7	1, 3-5, 7, 12	Annual Notification
e. solvents, reagents, catalysts	1, 2, 7	1, 3-5	Annual Notification
f. Change in raw materials testing site	6	10	Annual Notification
15. Change to the in-process tests and/or acceptance criteria applied during the drug substance manufacturing process or on Intermediates, involving:			
a. narrowing of in-process limits	None	2, 12, 13	Notifiable

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
			Change
	1, 3, 8, 9	2, 7	Annual Notification
b. replacement or addition of new in-process test	2-5, 8-11	2-5, 7,8, 12, 13	Annual Notification
c. deletion of a non-significant in-process test	1-3, 5, 8, 12, 14, 15	2, 7, 9, 12	Annual Notification
d. widening of the approved in-process limits, which may have a significant effect on the overall quality of the drug substance	None	2-8, 12, 13	Notifiable Change
	1-3, 12	2, 6-8	Annual Notification
e. deletion of an in-process test which may have a significant effect on the overall quality of the antigen/drug substance	None	2, 6, 7, 8	Annual Notification
f. addition or replacement of an in-process test as a result of a safety or quality issue	None	2-7, 8	Notifiable Change
g. revision as per updated pharmacopoeia	1, 2	2	Annual Notification
16. Change in in-process control testing site Note: Transfer of in-process control testing to a different facility within a GMP-compliant site is not considered to be a reportable change but is treated as a minor GMP change (Level IV) and is reviewed during inspections	1-3, 8, 11	10	Annual Notification

Conditions

1. No change in the drug substance specifications outside of approved ranges, except for revision as per updated pharmacopoeia.
2. No change in the impurity profile of the drug substance outside the approved limits.
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
4. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
5. The change does not affect the principle of sterilization of a sterile drug substance.
6. The change in specification for the materials is within the approved limit except for revision as per updated pharmacopoeia.
7. The grade of the materials is same or is of higher quality, where appropriate.
8. No change in the in-process controls outside the approved limits.
9. The test procedure remains the same, or changes in the test procedure are minor.
10. The test method is not a biological/immunological/immunochemical or physicochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
11. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity, if applicable.
12. The test does not concern the critical attribute (e.g. content, impurity, any physical characteristics or microbial purity.)
13. The change has no significant effect on the overall quality of the drug substance and/or drug product and there are no changes to the cell banks
14. The deleted test has been demonstrated to be redundant with respect to the remaining tests
15. The deleted test is not for a viral clearance/removal step
16. The change is for compendial auxiliary materials/reagents of biological origin (excluding human plasma derived materials).

Supporting Data

1. Revised information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the changed drug substance (3.2.S.2.3).
2. Revised information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed drug substance (3.2.S.2.4).
3. Updated specifications of the drug substance, if affected by the change (3.2.S.4.1).
4. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.S.4.2).
5. Copies or summaries of validation reports, if new analytical procedures are used (3.2.S.4.3).
6. Description of the batches, certificates of analyses, and summary of in-process and release testing results (as quantitative data), in a comparative tabular format, for at least three (3) commercial scale batches of the approved and changed drug substance. (3.2.S.2.5 & 3.2.S.4.4). Matrixing, bracketing, the use of smaller-scale batches, the use of fewer than three batches and/or leveraging data from scientifically justified representative batches, or batches not necessarily manufactured consecutively, may be acceptable where justified (refer ICH Q1D)
7. Comparative table or description, where applicable, of pre- and post-change in-process tests/limits.

   Results of accelerated and a minimum of three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed changed drug substance are available as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.S.7.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug substance may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder and agreed by CDSCO.
8. Justification for the new in-process test and limits.

9. Justification/risk assessment showing that the attribute is non-significant.
10. Evidence that new company/facility is GMP-compliant.
11. For drug substance obtained from, or manufactured with, reagents obtained from sources that are at risk of transmitting bovine spongiform encephalopathy/ transmissible spongiform encephalopathy (BSE/TSE) agents (for example, ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (for example, name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, use and previous acceptance of the material) (3.2.S.2.3)
12. Description of the batches, certificates of analyses, and summary of in-process and release testing results (as quantitative data), in a comparative tabular format, for at least one (1) commercial batch of the approved and changed drug substance. Batch data on the next two full-production batches should be made available on request and reported by the MA holder if outside specification (with proposed action). The use of a smaller-scale batch may be acceptable where justified. (3.2.S.2.5 & 3.2.S.4.4)
13. Rationale for the change supported by data.
14. Information demonstrating comparability of the auxiliary materials/reagents or starting materials of both sources
15. Information assessing the risk with respect to potential contamination with adventitious agents (eg. Impact on the viral clearance studies, BSE/TSE risks)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
17. Change in the approved design space, involving:			
a. establishment of a new design space	None	1	Supplement
b. expansion of the approved design space	None	1	Supplement

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
c. reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space	1	1	Annual Notification
Conditions			
1. The reduction in design space is not necessitated by recurring problems having arisen during manufacture.			
Supporting Data			
1. Manufacturing development data to support the establishment or changes to the design space (including changes to process parametric release for sterile products) (3.2.S.2.6)			

3.2.S.3 Characterization

There are not any quality change examples for this section at the present time that have not
been addressed in other sections.

3.2.S.4 Control of the Drug Substance

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
18. Change in the standard / monograph (i.e., specifications) claimed for the drug substance, involving:			
a. change from the Pharmacopoeial standard or a monograph to an in-house standard	None	1-3, 5, 7	Notifiable Change
b. change in the standard claimed for the drug substance (e.g., from in-	None	1-6	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
house to pharmacopoeial standard) or from one pharmacopoeial standard/monograph to a different/pharmacopoeial standard/monograph	1-3	1-3	Annual Notification
c. change in the specifications for the drug substance to comply with an updated pharmacopoeial monograph **Note:** Change in specifications and analytical procedures for the drug substance to comply with an updated pharmacopoeial monograph within 6 months of pharmacopoeia update should be captured under Level IV changes	1, 2	1-3	Annual Notification

Conditions

1. The change is made exclusively to comply with the (applicable) pharmacopoeia / standard.
2. No change to the specifications for functional properties of the drug substance, outside the approved ranges.
3. No deletion or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specifications except to comply with pharmacopoeial standard / monograph.

Supporting Data

1. Revised product labelling information (Package Insert, Inner and Outer Labels), as applicable.
2. Updated, copy of changed/proposed drug substance specifications (3.2.S.4.1).

3. Where an in-house analytical procedure is used and a standard is claimed, results of an equivalency study between the In-house and compendial methods.
4. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least three (3) commercial scale batches of the changed drug substance (3.2.S.4.4).
5. Justification of the changed drug substance specifications (e.g., demonstration of the suitability of the monograph to control the drug substance, including impurities) (3.2.S.4.5).
6. Demonstration that consistency of quality and of the production process is maintained.
7. Copies or summaries of validation reports, if new analytical procedures are used (3.2.S.4.3).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
19. Changes in the control strategy of the drug substance, involving:			
a. Change from end-product testing to upstream controls for some test(s) (e.g., Real-Time Release Testing, process analytical technology)	None	1-5	Supplement
b. Addition of a new Critical Quality Attribute (CQA) in the control strategy	None	1-5	Notifiable Change
c. Deletion of a Critical Quality Attribute (CQA) from the control strategy	None	1, 5	Notifiable Change

Conditions:

None

Supporting Data

1. Information on the controls performed at critical steps of the manufacturing

process and on intermediates of the proposed drug substance (3.2.S.2.4)

2. Updated, copy of the changed/proposed drug substance specifications (or where applicable, the final version of the specifications to be signed by QC after CDSCO approval), if changed (3.2.S.4.1)
3. Copies or summaries of analytical procedures, if new analytical procedures are used. (3.2.S.4.2)
4. Copies or summaries of validation reports, if new analytical procedures are used. (3.2.S.4.3)
5. Justification and supporting data for each proposed change to the control strategy.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
20. Changes affecting the quality control (QC) testing of the drug substance (release and stability), involving:			
a. transfer of the QC testing activities for a non-pharmacopoeial assay (in-house) to a new company/premises, to a different facility within the same company/premises or to a different laboratory within the same facility not approved in the current market authorization or license.	None	1, 2	Notifiable Change
	1-4	1, 2	Annual Notification
b. transfer of the QC testing activities for a pharmacopoeial assay to a new company/premises not approved	None	1, 2	Notifiable Change
	2	1, 2	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
in the current market authorization or license.			

Conditions

1. The transfer involves the relocation of the equipment and laboratory staff to the new laboratory or facility.
2. The transferred QC test is not a potency assay or a bioassay.
3. No changes are made to the test method.
4. The transfer is within a facility approved in the current marketing authorization for the performance of other tests

Supporting Data

1. Information demonstrating technology transfer qualification for the non-pharmacopoeial assays or verification for the pharmacopoeial assays (3.2.S.2.5).
2. Evidence that the new company/facility is GMP compliant.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
21. Change in the test for Drug Substance at Release / Shelf life involving:			
a. deletion of a test	None	1, 6, 7	Notifiable Change
	1, 7	1, 6	Annual Notification
b. replacement or addition of a test	None	1-6	Notifiable Change
	1, 2, 8	1-3, 6	Annual Notification
c. relaxation of an acceptance criterion	None	1, 6, 7	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
d. tightening of an acceptance criterion	1, 2, 4, 9	1	Annual Notification

Conditions

1. The change is not necessitated by unexpected 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. Acceptance criterion for residuals are within recognized or approved acceptance limits, e.g., within ICH limits for Class 3 residual solvent or pharmacopoeial requirements.
5. The deleted analytical procedure has been demonstrated to be redundant with respect to the remaining analytical procedures.
6. The change does not concern sterility testing.
7. The analytical procedure/test is deleted in-line with the updated pharmacopoeia / Standard; or there is no change in the compliance status of applicable pharmacopoeia / Standard (e.g. The deleted test is the Abnormal Toxicity Test/General Safety Test).
8. The addition of test is not to monitor new impurity species.
9. The analytical procedures remain the same or changes to analytical procedure are minor.

Supporting Data

1. Updated drug substance specifications (3.2.S.4.1).
2. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.S.4.2).
3. Copies or summaries of validation reports, if new analytical procedures are used (3.2.S.4.3).
4. Where an in -house analytical procedure is used and a Pharmacopoeial standard

is claimed, results of an equivalency study between the In-house and compendial methods.

5. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least three (3) commercial scale batches of the changed drug substance (3.2.S.4.4).
6. Justification of the changed drug substance specifications (e.g., test parameters, acceptance criteria, or analytical procedures) (3.2.S.4.5).
7. Documented evidence that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
22. Change in the analytical procedures for the drug substance, involving			
a. deletion of an analytical procedure.	1	1, 5	Notifiable Change
	1, 6	1, 5	Annual Notification
b. replacement or addition of an analytical procedure.	None	1-5	Notifiable Change
	5, 7, 8	1-5	Annual Notification
c. minor changes to an approved analytical procedure.	1-3, 5, 8	1, 4, 5	Annual Notification
d. a change from an in-house analytical procedure to a Pharmacopoeial analytical procedure.	1, 5	1-3	Annual Notification
e. change in animal species/strains for a test (e.g., new species/strains, animals of different	None	6, 7	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
age, new supplier where genotype of the animal cannot be confirmed)			

Conditions

1. No change in the acceptance criteria outside of the approved ranges.
2. 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.
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
5. The change does not concern potency testing.
6. The analytical procedure is deleted in-line with the updated pharmacopoeia / Standard; or there is no change in the compliance status of applicable pharmacopoeia / Standard.
7. The change is from a pharmacopoeial assay to another pharmacopoeial assay.
8. The modified analytical procedure maintains or improves performance parameters of the method.

Supporting Data

1. Updated drug substance specifications (3.2.S.4.1).
2. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.S.4.2).
3. Copies or summaries of validation reports, if new analytical procedures are used (3.2.S.4.3).
4. Comparative results demonstrating that the approved and changed analytical procedures are equivalent.
5. Justification of the changed drug substance specifications (e.g., test parameters, acceptance criteria, or analytical procedures) (3.2.S.4.5).

6. Data demonstrating that the change in animals/strains give comparable results with those obtained using the approved animals/strains.
7. Copies of relevant certificate of fitness for use (e.g., veterinary certificate).

3.2.S.5 Reference Standards or Materials

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
23. Change in reference standards or materials used to release the drug substance, involving			
a. qualification of a new reference standard	None	1	Notifiable Change
b. update the reference standards from pharmacopoeial / international standard to an in-house	None	1, 5	Notifiable Change
c. update the reference standards from an in-house to pharmacopoeial / international standard	2	1, 5	Annual Notification
d. Qualification of a new lot of reference standard (except for a bacterial or viral vaccine, bacterial toxin)	2	1, 5	Annual Notification
24. Qualification of a new lot of reference standard against the approved reference standard for a bacterial or viral vaccine, bacterial toxin, involving:			
a. reference standard used in a qualitative test, physicochemical test, semi-quantitative or quantitative biological assay	2	1	Annual Notification
b. Change to reference standard qualification protocol (except for	None	3, 4	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
a bacterial or viral vaccine, bacterial toxin)	4	3, 4	Annual Notification
25. Change to reference standard qualification protocol for a bacterial or viral vaccine, bacterial toxin, involving:			
a. a reference standard used in a qualitative test	None	3, 4	Annual Notification
b. a reference standard used in a physicochemical test, semi-quantitative or quantitative biological assay.	4	3, 4	Annual Notification
26. Extension of reference standard shelf-life / Re-test period	3	2	Annual Notification

Conditions

1. The in -house reference standard is calibrated against an official (e.g., pharmacopoeial/ NIBSC/WHO/EDQM/NCL) reference standard.
2. Qualification of the reference standard is performed according to the approved protocol (i.e. no deviation from the approved protocol).
3. The extension of the shelf-life / re-test is according to an approved protocol.
4. The protocol is considered more stringent (i.e., addition of new tests or tightening of acceptance criteria). If deletion of tests is proposed, the tests proposed to be deleted were not implemented to monitor the quality of the reference standard (e.g., was implemented for research or validation work).

Supporting Data

1. Information demonstrating qualification of the changed reference standards or materials (e.g., source, characterization, certificate of analysis). (3.2.S.5)
2. Summary of stability testing and results to support the extension of reference standard shelf-life. (3.2.S.5)
3. Justification of change to the reference standard qualification protocol.
4. Updated reference standard qualification protocol.
5. Justification for change in the reference standard.

3.2.S.6 Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
27. Change in the primary container closure system(s) for the storage and shipment of the drug substance	None	1-3, 5	Notifiable Change
	1	1, 4, 5	Annual Notification

Conditions

1. Proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (including results of transportation or compatibility studies, if appropriate).

Supporting Data

1. Information on the changed container closure system (e.g., description, specifications) (3.2.S.6).
2. Results of accelerated and a minimum of three (3) months of real time/real temperature testing of the 3 commercial scale batches of changed drug substance (3.2.S.7.3), as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies.
3. Data demonstrating the suitability of the container closure system (for example, extractable/leachable testing) and compliance with pharmacopoeial standards, if applicable.

4. 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).
5. Comparative table of pre and post-change specifications.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
28. Change in the supplier for a primary container involving:			
a. replacement or addition of supplier.	None	1-3	Notifiable Change
	1, 2	None	Annual Notification
b. deletion of supplier.	None	None	Annual Notification

Conditions

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

Supporting Data

1. Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing).
2. Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications).
3. Stability test results from: a) accelerated testing and b) a minimum of three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug substance are available, as well as commitment to notify CDSCO of any failures in the ongoing long term stability studies. (3.2.S.7.3).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
29. Change in the specification/analytical procedure of the primary container system for the Drug Substance, involving:			
a. deletion of test	1, 2	1, 2	Annual Notification
b. addition of test	3	1-3	Annual Notification
c. replacement of an analytical procedure	6, 7	1-3	Annual Notification
d. minor changes to an analytical procedure	4-7	1-3	Annual Notification
e. widening of an acceptance criteria	None	1, 2	Notifiable Change
f. narrowing of an acceptance criteria	8	1	Annual Notification

Conditions

1. The deleted test has been demonstrated to be redundant compared to the remaining tests or is no longer a pharmacopoeial requirement.
2. The change to the specification does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the antigen/drug substance.
3. The change is not necessitated by unexpected recurring events arising during manufacture or because of stability concerns.
4. There is no change in the acceptance criteria outside the approved limits.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been

made to reflect a new pharmacopoeial monograph specification for the container closure component.

Supporting Data

1. Updated copy of the proposed specification for the primary container closure system. (3.2.S.6)
2. Rationale for the change in specification for a primary container closure system.
3. Description of the analytical procedure and, if applicable, validation data. (3.2.S.6)

3.2.S.7 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
30. Change in the shelf life of drug substance or for a stored intermediate of the drug substance, involving:			
a. Extension	None	1-4, 6	Notifiable Change
	1-5	1, 2, 5	Annual Notification
b. Reduction	None	1-5	Notifiable Change
	6	2-4	Annual Notification

Conditions

1. No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance.
2. The approved shelf life is at least 24 months.
3. Full long term stability data are available covering the changed shelf life and are based on stability data generated on at least three production scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes (as defined in ICH's Q1A guideline) 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.

Supporting Data

1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained). (3.2.S.7.3)
2. Proposed storage conditions and shelf life as appropriate.
3. Updated post-approval stability protocol and stability commitment. (3.2.S.7.2)
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 changed shelf life generated on at least three (3) production scale batches). (3.2.S.7.3). For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the drug substance
6. Interim stability testing results and a commitment to notify CDSCO of any failures in the ongoing long term stability studies. Extrapolation of shelf-life should be made in accordance with ICH Q1E guideline. For intermediates, data to show that the extension of shelf-life has no negative impact on the quality of the drug substance (i.e., batch analysis on three (3) commercial scale batches). (3.2.S.7.3).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
31. Change in the labelled storage conditions for the drug substance, involving:			
a. addition of a cautionary statement.	None	1-5	Notifiable Change
	1	1-5	Annual Notification
b. deletion of a cautionary statement.	None	2-4, 6	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
c. addition or change of storage condition for the drug substance (e.g. widening or narrowing of a temperature criterion).	None	1-5	Notifiable Change
	1, 2	2-5	Annual Notification

Conditions

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change consists in the narrowing of a temperature criterion within the approved ranges.

Supporting Data

1. 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) (3.2.S.7.3).
2. Revised product labelling information (Package Insert, Inner and Outer Labels), as applicable.
3. Proposed storage conditions and shelf life.
4. Justification of the change in the labelled storage conditions/cautionary statement.
5. Updated post-approval stability protocol and stability commitment (3.2.S.7.2).
6. 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). (3.2.S.7.3)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
32. Change to the post-approval stability protocol of the drug substance, involving:			
a. Major / significant change to the	None	1-6	Notifiable

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature.			Change
	1, 4	2-6	Annual Notification
b. addition of time point(s) into the post-approval stability protocol.	None	2, 3	Annual Notification
c. addition of test(s) into the post-approval stability protocol.	2	2-6	Annual Notification
d. deletion of time point(s) from the post-approval stability protocol beyond the approved shelf life.	None	2, 3	Annual Notification
e. deletion of time point(s) from the post-approval stability protocol within the approved shelf life.	3	2-4	Annual Notification

Conditions

1. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
2. The addition of test(s) is not due to stability concerns or to the identification of new impurities.
3. Deletion of time point(s) is made according to ICH Q5C.
4. 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

Supporting Data

1. Proposed storage conditions and shelf life as appropriate.
2. Updated post-approval stability protocol and stability commitment (3.2.S.7.2).
3. Justification of the change to the post-approval stability protocol or stability

commitment.

4. 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). (3.2.S.7.3)
5. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.S.4.2).
6. Validation study reports, if new analytical procedures are used (3.2.S.4.3).

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
33. Change in the description or composition of the drug 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 diluent for lyophilized product)	None	1-12, 16	Supplement
b. addition of a new strength (e.g. 50 mg dose vs 100 mg dose) or change in the concentration of the active ingredient (e.g. 20 unit/mL *vs* 20 unit/2 mL)	None	1, 2-6, 8, 10, 11, 16	Supplement
	1-3, 5	1, 2, 6, 8, 16	Notifiable Change
Note: For these changes that are considered as "New Drugs" as per "The New Drugs and Clinical Trials Rules, 2019, MA holder should submit MA application in Form CT-21/Form CT-18 in SUGAM, with applicable fee, along with supporting documentation as described for the respective post approval change category followed by an amendment / endorsement of current Form 28 D license, as applicable. A declaration to state that no change to other remaining section/s of the MA dossier shall be submitted, as applicable.			
c. addition of a new presentation (e.g. addition of syringes to vial/ prefilled syringe/cartridge/pre-	None	2, 3, 6, 8-10, 13-15	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
filled pen/autoinjector where the approved presentation in a vial or vice a versa, addition of single dose or multi-dose vial)			
d. change in fill volume (same concentration, different volume)	None	2, 6, 8, 10, 11	Supplement
	1, 4	2, 6, 8, 10	Notifiable Change
	1, 4, 5	6, 8, 10	Annual Notification

Conditions

1. No change in dose is recommended
2. New concentration is bracketed by existing approved concentrations
3. More than 2 concentration are already approved (i.e. linear PK/PD profile of the product from at least three different concentration over the bracketed range has been demonstrated and two extreme concentration of the bracketed range have been shown to be bio-equivalent or therapeutically equivalent
4. No changes are classified as major in the manufacturing process to accommodate the new fill volume
5. The change involves narrowing the fill volume while maintaining the lower limit of extractable volume

Supporting Data

1. Updated or new relevant CMC (Module 3 Quality) data of drug product. (3.2.P)
2. Revised Drug Product Labelling information i.e. Package Insert, Inner and Outer Labels, as applicable.
3. Confirmation that information on the drug substance has not changed as a result of the submission (e.g., cross reference(s) should be provided to the previously

approved drug submission, quoting the date approved and file Number(s)) or revised information on the drug substance, if any of the attributes have changed.

4. Description and composition of the dosage form, if there are changes to the composition or dose (3.2.P.1).
5. Discussion of the components of the drug product, as appropriate (e.g., choice of excipients, compatibility of drug substance and excipients, leachates, compatibility with new container closure system)
6. Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation in appropriate CTD sections. (3.2.P.3.2, 3.2.P.3.3. 3.2.P.3.4 & 3.2.P.3.5)
7. Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Regulations) (3.2.P.4).
8. Information on Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used) (3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.3), Batch Analyses (certificate of analysis for three commercial-scale batches should be provided). (3.2.P.5.4). Bracketing for multiple strength products, container sizes and / or fill volumes may be acceptable if scientifically justified (refer ICH Q1D).
9. Information (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed (3.2.P.7).
10. Stability test results from: a) accelerated testing (usually a minimum of three (3) months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and b) three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed drug product, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify CDSCO of any failures 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

(refer to ICH Q1D).

Comparative pre change and post change test results of three (3) months accelerated and real time/real temperature testing on three (3) commercial scale batches of the changed drug product, as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.P.8.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug product may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO.

11. Supporting clinical data or scientific/ clinical justification for not performing additional clinical study
12. Data demonstrating comparability of the new dosage form and/or formulation.
13. Supporting clinical data (usually PK/PD only) or scientific/clinical justification for not performing additional clinical study.
14. The new device (e.g., pre-filled syringes, cartridge or pens), approval letter from the CDSCO, as applicable.
15. Information on container closure system and extractables /leachable if any of components have changed.
16. Duly Signed Form CT-18/Form CT-21 with applicable fee.

3.2.P.1 Description and Composition of the Drug Product: Change to an adjuvant

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
34. Change involving a chemical / synthetic adjuvant			
a. change in supplier of a chemical / synthetic adjuvant	None	3-6	Notifiable Change
	2, 3	4	Annual Notification
b. change in manufacture of a	None	2-6	Notifiable

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
chemical / synthetic adjuvant			Change
	2, 3	8-10	Annual Notification
c. change in release specifications of a chemical/ synthetic adjuvant (including the tests and/or the analytical procedures	None	5, 6, 8-10	Notifiable Change
	2, 4	8-10	Annual Notification
35. Change involving a biological adjuvant			
a. change in supplier of a biological adjuvant.	None	1-8, 11-13	Supplement
b. change in manufacture of a biological adjuvant	None	1-6, 8, 11, 12	Supplement
	1	1-4, 8, 11	Notifiable Change
c. change in the release specifications of a biological adjuvant (including the tests and/or the analytical procedure).	None	5, 6, 8-10, 12	Notifiable Change
	2, 4	8-10	Annual Notification

Conditions

1. The change does not concern the source of the adjuvant.
2. The specification of the adjuvant is equal to or narrow than the approved limits (i.e. narrowing of acceptance criterion).
3. The adjuvant is an aluminium salt.
4. The change in specification consists in the addition of a new test or in a minor change to an analytical procedure.

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

changed adjuvant.

2. Flow diagram of the proposed manufacturing process (es), a brief narrative description of the proposed manufacturing process (es), and information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed adjuvant.
3. Process validation and/or evaluation studies (e.g., for manufacturing of the adjuvant).
4. Description of the general properties, characteristic features and characterization data of the product
5. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) commercial scale batches of the drug product with the approved and changed adjuvant, as applicable. (3.2.P.5.4).
6. Results of accelerated and a minimum of three (3) months of real time/real temperature testing on three (3) batches of the changed adjuvant as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.P.8.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug product may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO.
7. Supporting non-clinical and clinical data or scientific/clinical justification for not performing additional clinical studies if in vitro tests are sufficient to prove comparability.
8. Updated copy of the proposed specification for the adjuvant (3.2.P.4.1).
9. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.P.4.2).
10. Validation study reports, if new analytical procedures are used (3.2.P.4.3).
11. Information assessing the risk with respect to potential contamination with adventitious agents (e.g. impact on the viral clearance studies, BSE/TSE risk).
12. Comparability of the pre- and post-change adjuvant with respect to physicochemical properties, biological activity, purity, impurities and contaminants, as appropriate. Nonclinical and/or clinical bridging studies may

occasionally be required when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies should be determined on a case-by-case basis, taking into consideration the quality comparability findings, the nature and level of knowledge of the adjuvant, existing relevant nonclinical and clinical data, and aspects of vaccine use.

13. Evidence of facility GMP compliance.

3.2.P.1 Description and Composition of the Drug Product: Change to a diluent

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
36. Change to the diluent, involving:			
a. replacement or addition of a source of a diluent	None	1-6, 12	Notifiable Change
	1-3	2, 4, 5	Annual Notification
b. change in manufacturing process of a diluent	None	2-6	Notifiable Change
	1, 3	2-5	Annual Notification
c. change in specification of a diluent (Eg. deletion or replacement or addition of test)	None	2, 5, 7-11	Notifiable Change
	5-10	2, 5, 7-11	Annual Notification
d. tightening of an acceptance criteria	5, 6	2, 5, 7-11	Annual Notification
e. relaxation of an acceptance criteria	5, 7-10	2, 5, 7-11	Notifiable Notification
f. change in facility used to manufacture a diluent (same	1, 2	2, 4, 6	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
company)			
g. addition of a diluent filling line	1, 2, 4	2, 4, 6	Annual Notification
h. addition of a diluent into an approved filling line	1, 2	2-5, 13	Annual Notification
i. deletion of a diluent	None	None	Annual Notification

Conditions

1. The diluent is water for injection or a salt solution (including buffered salt solutions) (i.e. it does not include an ingredient with a functional activity, such as a preservative) and there is no change to its composition.
2. After reconstitution, there is no change in the final product specification outside the approved limits.
3. The proposed diluent is commercially available in the NRA country.
4. The addition of the diluent filling line is in an approved filling facility.
5. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
6. The change is within the range of approved acceptance criteria.
7. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
8. Acceptance criterion for any Class 3 residual solvent is within the ICH limits.
9. The change to the specifications does not result in a potential impact on the performance of the drug product.
10. The change does not concern sterility testing.

Supporting Data

1. Demonstration that the changed diluent results in the same properties of the product as with the approved diluent.

2. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) commercial scale batches of the approved and changed diluent.
3. Results of accelerated and a minimum of three (3) months of real time/real temperature testing (3.2.P.8.3) of the changed diluent and updated stability of the product reconstituted with the new diluent (3.2.P.8.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed diluent may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO.
4. 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).
5. Updated copy of the proposed specification for the diluent (3.2.P.5.1).
6. Evidence that the facility is GMP-compliant.
7. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.P.5.2).
8. Copies or summaries of validation reports, if new analytical procedures are used (3.2.P.5.3).
9. Where a house analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the house and compendial method.
10. Justification of the changed diluent specifications (e.g. demonstration of the suitability of the monograph to control the diluent, including degradation products.
11. Demonstration that consistency of quality and of the production process is maintained.
12. Revised product labelling information (Package Insert, Inner and Outer Labels), as applicable.
13. Cleaning procedures (including data in a summary validation report) demonstrating lack of carryover / cross contamination.

3.2.P.2 Pharmaceutical Development

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
37. Change in the approved design space, involving :			
a. establishment of a new design space	None	1	Supplement
b. expansion of the approved design space	None	1	Supplement
c. reduction in the approved design space (any change that reduces or limits the range of parameters used to define the design space	1	1	Annual Notification
Conditions			
1. The reduction in design space is not necessitated by recurring problems having arisen during manufacture.			
Supporting Data			
1. Pharmaceutical development data to support the establishment or changes to the design space (3.2.P.2)			

3.2.P.3 Manufacture

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
38. Changes involving a drug product manufacturing facility / premise (site):			
a. replacement or addition of a drug product manufacturing facility / suite in new geographical site / premises. (including formulation / filling and primary packaging)	None	1-10	Supplement
	1-6	1, 3, 4, 6, 7-10	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Note: For these changes, MA holder shall submit MA application in Form CT-21/Form CT-18 in SUGAM with applicable fees along with supporting documentation as described for the post approval change category, for addition of manufacturing facility/suite, for a drug product, in a new geographical site/ premises. CDSCO will issue a No Objection Certificate for obtaining an amendment / endorsement of the current Form 28 D license, as applicable. A declaration to state that no change to other remaining section/s of the MA dossier, including impact on safety/efficacy, shall be submitted, as applicable.			
b. replacement of a formulation / filling suite.	None	3-6, 8-14	Supplement
	1, 7	3, 4, 6-10, 12-13	Notifiable Change
c. addition of an equivalent formulation / filling suite	1	3, 4, 6, 8-10	Notifiable Change
d. replacement or addition of a secondary packaging including secondary functional packaging / labelling / storage and distribution facility	2, 3	1-4	Annual Notification
e. qualification of a new room or change in classification of an existing room.	8, 9	11-13	Annual Notification
f. deletion of a drug product manufacturing facility	10	None	Annual Notification
g. modification to a manufacturing area or modification to an existing service/system (e.g., change to WFI systems or HVAC	8, 9	11-13	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
systems, moving a wall)			

Conditions

1. The formulation/filling facility is approved facility or site (premises) is approved by licensing authority.
2. No change in the composition, manufacturing process or drug product specifications.
3. No change in the container/closure system and storage conditions.
4. The same validated manufacturing process is used.
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the one of those already approved at the site and uses the similar/ comparable filling process/equipment.
6. The Site / Premise are under same Quality system oversight and owned by same legal entity.
7. The new formulation/filling suite is equivalent to the approved formulation/filling suite.
8. The change has no impact on the risk of contamination or cross-contamination.
9. The modification has no product impact.
10. The deletion should not be due to critical deficiencies in manufacturing (for example, recurrent out-of-specification events, environmental failures, etc.).

Supporting Data

1. Evidence that the facility is GMP-compliant.
2. Updated relevant drug product CMC (3.2.P) Sections.
3. Confirmation that information on the drug product has not changed as a result of the submission (e.g., other than change in facility) or revised information on the drug product, if any of the attributes have changed.
4. Name, address, and responsibility of the changed 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 changed drug product.

6. Process validation and/or evaluation studies (3.2.P.3.5) or the proposed validation protocol of the changed drug product is acceptable, but data could be requested, including technology transfer validation, equipment qualification, media fills, as appropriate, bracketing for multiple strength products, container sizes and /or fills may be acceptable if scientifically justified (refer ICH Q1D).
7. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) commercial scale batches of the approved and changed drug product (3.2.P.5.4), Bracketing for multiple strength products, container sizes and /or fills may be acceptable if scientifically justified (refer ICH Q1D).
8. Results of 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 changed drug product as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.P.8.3). Bracketing for multiple strength products, container sizes and /or fills may be acceptable if scientifically justified (refer to ICH Q1D).
9. Rationale for considering the proposed formulation/filling suite as equivalent.
10. Commitment to place the first batch of the drug product manufactured using the proposed formulation/filling suite into the stability programme, and to notify CDSCO of any failures in ongoing long-term stability studies.
11. Information demonstrating re-qualification of the equipment or re-qualification of the change (e.g. operational qualification, performance qualification), as appropriate.
12. Information on the proposed production facility involved in the manufacture of the drug 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.
13. Results of the environmental monitoring studies in classified areas.
14. 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.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
39. Change in a facility involved in the manufacture of a drug product, such as:			
a. conversion of a drug product manufacturing facility from single-product to multiproduct	None	1-3	Notifiable Change
b. conversion of production and related area(s) from campaign to concurrent for multiple product manufacturing areas	1	1, 2, 4	Notifiable Change
c. introduction of new product into an approved multiproduct formulation / filling suite	2-4	1-4	Annual Notification

Conditions

1. The manufacturing process is a closed process.
2. The newly introduced product does not introduce significantly different risk issues (i.e., cytotoxic drugs to cytokine manufacturing area).
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. Information on the cleaning procedures (including validation) 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 there are no revisions, the manufacturer should state that no changes were made to the changeover procedures.

3. Information on the product(s) which share the same equipment (e.g., therapeutic classification).
4. Risk assessment summary.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
40. Changes involving a drug product manufacturing process:			
a. critical change with high potential to have an impact on the quality of final product	None	1-6	Notifiable Change
b. non critical change with low potential to have impact on the quality of the of final product	1-4	1-5	Annual Notification
c. addition of a new step (e.g. filtration step)	4	1-7	Notifiable Change
d. scale-up of the manufacturing process at the formulation / filling stage (e.g. Increase in Blend size or increase of batch size loaded in the lyophilizer)	2, 4-6	1, 3-5, 8, 10	Notifiable Change
e. addition of a new scale bracketed by the approved scales or Scale-down of the manufacturing process at the formulation / filling stage	2, 4-7	1, 3-5, 8, 9	Annual Notification

Conditions

1. No change in the drug product specifications.
2. The change does not affect the method of sterilization of the drug product.
3. No change in the excipients / preservative.
4. The change is not necessitated by unexpected events arising during

manufacture or because of stability concerns.

5. The scale-up or scale down uses the similar/ comparable approved equipment (Note: Change in equipment size is not considered as using similar/comparable equipment).
6. Any changes to the manufacturing process and/or to the in-process controls are only those necessitated by the change in batch-size (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized).
7. Change does not affect the lyophilization step. If the proposed change affects the lyophilization cycle, then lower and upper cycle should be validated.

Supporting Data

1. Flow diagram of the changed manufacturing process (es) and a brief narrative description of the changed manufacturing process (es) (3.2.P.3.3).
2. Information on the quality and controls of the materials (e.g., excipients) used in the manufacture of the changed drug product (3.2.P.4).
3. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed drug product (3.2.P.3.4).
4. Process validation and/or evaluation studies (e.g., for aseptic processing and sterilization) (3.2.P.3.5).
5. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) commercial scale batches of the approved and changed drug product (3.2.P.5.4).
6. Results of accelerated and three (3) months of real time/real temperature testing on three (3) commercial scale batches of the changed drug product as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.P.8.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug product may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO.
7. Information on leachable and extractables, as applicable.
8. Rationale for regarding the equipment as similar or comparable, as applicable.
9. Commitment to place the first production batch of the final product manufactured

using the proposed scale into the stability programme, and to notify the CDSCO if any failure in the ongoing stability studies.

10. The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
41. Change in equipment used in drug product manufacturing process, such as:			
a. replacement or addition of new equipment used in a critical step (e.g., lyophilizer, formulation tank, filling line and head)	None	1-3, 5, 7-9	Notifiable Change
	1	1, 3, 5, 6	Annual Notification
b. product contact equipment change from dedicated to shared (e.g., formulation tank, lyophilizer)	None	1, 3, 4	Notifiable Change
	2, 3	1, 3, 4, 10	Annual Notification

Conditions

1. Replacement of equipment with equivalent equipment; the change is considered “Like to Like” (i.e. in terms of product contact material, equipment size, operating principle).
2. The site is approved as multi-product facility by CDSCO.
3. The change has no impact on the risk of cross-contamination and is supported by validated cleaning procedures.

Supporting Data

1. Information on the in-process control testing, as applicable.
2. Process validation and/or evaluation studies (3.2.P.3.5) or the proposed

validation protocol of the changed drug product, including technology transfer validation, equipment qualification, media fills, as appropriate.

3. Information demonstrating qualification of the equipment or qualification of the change.
4. Information on the cleaning procedures (including validation) demonstrating lack of carry-over or cross-contamination.
5. Information on new equipment and comparison of similarities and differences regarding operating principles and specifications between the new and the replaced equipment.
6. Rationale to support the equipment as similar/ comparable, as applicable.
7. Description of 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 drug product. (3.2.P.3.3)
8. Description of the batches and the summary of in-process controls and release testing results as quantitative data in a comparative tabular format for at least three commercial scale batches of the pre-change and post change drug product. (3.2.P.3.3)
9. Results of accelerated and three (3) months of real time/real temperature testing on three (3) commercial scale batches of the changed drug product as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.P.8.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug product may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO
10. Information describing the change-over procedures for the shared product-contact equipment

Description of Change Conditions	Conditions to be Fulfilled	Supporting Data	Reporting Category
42. Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates			
a. Deletion of an in-process test which may have a significant effect on the overall quality of the drug product	None	1, 2, 4-6, 8, 11	Notifiable Change
b. deletion of a non-significant in process test	1, 4, 5, 7, 10, 13	2, 11, 12	Annual Notification
c. replacement or addition of an in- process test	1-4, 6-8	1, 2, 4, 6, 8	Annual Notification
d. relaxation of an acceptance criterion	None	1, 2, 4, 6, 7, 10, 11	Notifiable Change
	1, 7, 8	2, 6, 8, 11	Annual Notification
e. tightening of an acceptance criterion	1, 2, 7, 12	1, 12	Annual Notification
f. addition or replacement of an in-process test as a result of a quality and safety issue	None	1-4, 6, 8, 10,11	Notifiable Change
g. change in in-process control testing site. Note: Transfer of in-process control testing to a different facility within a GMP compliant site is not considered to be a reportable change but it is treated as a minor GMP change (Level IV) and reviewed during inspections.	1, 6-9, 11	9	Annual Notification
Conditions			

1. The change is not necessitated by unexpected 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. The changed test does not affect the sterility of a sterile drug product. or no change in the principle of the sterilization procedures of the drug product.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. The replaced or added analytical procedure maintains or tightens precision, accuracy, specificity, sensitivity.
7. No change in the impurity profile of the final product outside the approved limits.
8. No change in final product specification outside the approved limits.
9. No change in the in-process control limits outside the approved limits.
10. The deleted test is not for a viral clearance/removal step.
11. No Level II changes are made to the approved in-process tests and/or acceptance criteria.
12. Test procedure remains the same, or changing in test procedures are minor.
13. The test does not concern a critical attribute (for example, content, impurities, any critical physical characteristics or microbial purity).

Supporting Data

1. Description of the changed process controls or acceptance criteria (comparative table of current and proposed change).
2. Description of the changed process controls or acceptance criteria of the critical steps and intermediates (3.2.P.3.4).
3. Method validation for any new analytical procedure. (3.2.P.5.3)
4. Copies or summaries of analytical procedures, if new analytical procedures are used. (3.2.P.5.2)
5. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least one production scale batch (3.2.P.5.4).
6. Rationale/justification for change in process test and limits supported by data.

7. Data to show that the relaxation has not a negative impact on the quality of the batch. Results for at least one (1) batch are required.
8. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) commercial scale batches of the approved and changed drug product (3.2.P.5.4). Batch data on next two full production batches should be made available on request and reported by the MA holder if out-side specification (with proposed actions). Use of smaller scale batch may be acceptable, where justified.
9. Evidence that the new company/facility is GMP-compliant.
10. Updated Drug Product specification if changed (3.2.P.5.1)
11. Description of the batches and summary of in-process control and release testing results as quantitative data, in a comparative tabular format for three commercial scale batches of the pre-change and post change drug product (CoA should be provided) (3.2.P.3.5 and 3.2.P.5.4).
12. Justification/risk assessment showing that the attributes is non-significant.

3.2.P.4 Control of Excipients

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
43. Change in the standards / monograph for Excipients			
a. change in the standard / monograph claimed for the excipient (e.g., from an in-house to pharmacopoeial standard)	None	1-4	Notifiable Change
	1-3	1-4	Annual Notification
b. change in the standard claimed for the excipient (e.g., from pharmacopoeial standard to in-house)	None	1-4	Notifiable Change

Conditions

1. The change is made exclusively to comply with the (applicable) Pharmacopoeia/ Standard.

2. No change to the specification for the functional properties of the excipient (e.g., particle size distribution) outside the approved range, or that results in a potential impact on the performance of the drug product.
3. No deletion of or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specification except to comply with pharmacopoeial standard/ monograph.

Supporting Data

1. Updated excipient specifications (3.2.P.4.1).
2. Where a In-house analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the In-house and compendial methods.
3. Justification of the changed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product) (3.2.P.4.4). Comparative table/description wherever applicable of current and proposed specifications
4. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
44. Change in the specifications used for release of the excipient, involving: **Note: This change excludes adjuvants**			
a. deletion of a test	None	1-4	Notifiable Change
	5, 7	1-4	Annual Notification
b. replacement of a test	None	1-4	Notifiable Change
	1-4, 6, 8, 9	1-4	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
c. addition of a test	None	1-4	Notifiable Change
	4	1-3	Annual Notification
d. relaxation of an acceptance criterion	None	1-4	Notifiable Change
	1, 3, 4, 6	1-4	Annual Notification
e. tightening of an acceptance criterion	1-4, 6, 10	1-4	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. Acceptance criterion for residual solvents are within the recognized or approved acceptance limits (for example, within ICH limits for class 3 residual solvent or pharmacopoeial requirements).
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
6. The change to the specifications does not affect the functional controls of the excipient (e.g., particle size distribution) nor result in a potential impact on the performance of the drug product.
7. An alternative test analytical procedure is already authorized for this specification attributes/test.

8. Results of method validation demonstrate that the proposed analytical procedures are at least equivalent to the approved analytical procedure.
9. The replaced analytical procedures maintain or improves precision, accuracy, specificity and sensitivity.
10. The analytical procedures remain the same, or changes in the test procedure are minor.

Supporting Data

1. Updated excipient specifications (3.2.P.4.1).
2. Where an In-house analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the In-house and compendial methods.
3. Justification of the changed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product) (3.2.P.4.4).
4. Demonstration that consistency of quality and of the production process is maintained.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
45. Change in the analytical procedures used for the excipient, involving: **Note: This change excludes adjuvants**			
a. deletion of an analytical procedure	None	1, 3, 4	Notifiable Change
	6	1	Annual Notification
b. replacement or addition of an analytical procedure	None	1-4	Notifiable Change
	3-5	1-4	Annual Notification
c. minor changes to an approved	1, 2	1-4	Annual

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
analytical procedure			Notification
d. a change from an In-house analytical procedure to a Pharmacopoeial analytical procedure	None	1, 2	Annual Notification

Conditions

1. No change in the approved acceptance criteria.
2. 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.
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. The replaced analytical procedure maintains or improves precision, accuracy, specificity and sensitivity.
5. The change is within the range of approved acceptance criteria or has been made to reflect the new pharmacopoeial monograph specification for the excipient.
6. An alternative analytical procedure is already authorized for the specification parameter/ test and this procedure has not been added through a minor change submission.

Supporting Data

1. Updated excipient specifications (3.2.P.4.1).
2. Where an In-house analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the In-house and compendial methods.
3. Justification of the changed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the drug product) (3.2.P.4.4).

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

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
46. Change in the source or manufacture of the excipient,			
a. change in the source of an excipient from a vegetable or synthetic source to a TSE risk or viral risk (e.g. human / animal source)	None	2-7	Supplement
b. change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	None	1, 3, 5, 6	Notifiable Change
c. replacement in the source of an excipient from a TSE risk source to a different TSE risk source (e.g., different country of origin, different animal species)	6, 7	2-7	Annual Notification
d. change in manufacture of a biological excipient Note: excludes biological adjuvants, refer to adjuvant specific changes for details.	None	3-7, 9	Supplement
	2, 3	2, 3, 5-7	Notifiable Change
	1-3	2, 3, 5	Annual Notification
e. change in the supplier for a plasma-derived excipient (e.g. human serum albumin)	None	3, 8	Supplement
	4, 5	5, 6, 9	Notifiable Change

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
f. change in supplier for an excipient of non-biological origin or of biological origin (excluding plasma-derived excipient)	None	2, 3, 5-7	Notifiable Change
	1, 5, 6	3	Annual Notification
g. change in excipient testing site **Note:** Transfer of testing to a different facility within GMP compliant site is not considered to be reportable change but it is treated as a minor GMP change (Level IV) and is reviewed during inspection	1	10	Annual Notification

Conditions

1. No change in the specifications of the excipient or drug product outside the approved limit.
2. The change does not concern a human plasma-derived excipient.
3. Properties of the changed excipient are not different from those of the approved excipient.
4. The human plasma-derived excipient from the new supplier is an approved medicinal product and no manufacturing changes were made by the supplier of the new excipient since its last approval by CDSCO.
5. The excipient does not influence the structure / conformation of the active ingredient.
6. The TSE risk source is covered by TSE certificate/declaration of suitability and is of the same or lower TSE risk as the previously approved material.
7. Any new excipient does not require the assessment of viral safety data.

Supporting Data

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Details of the source or the excipient (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 changed 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 changed excipient (3.2.P.3.3)
5. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) commercial scale batches of the drug product without changed excipient and of the drug product with the changed excipient (3.2.P.5.4).
6. Results from the stability testing (3 months accelerated testing and 3 months real time/temperature) on three batches of the drug product with the changed Excipient (3.2.P.8.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug product may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO.
7. Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk). (3.2.A.2)
8. Complete manufacturing and clinical safety data to support the use of the proposed human plasma derived excipient.
9. Letter from supplier certifying that no changes were made to the plasma-derived excipient compared to the currently approved corresponding medicinal product.
10. Evidence that the new company/facility is GMP compliant.

3.2.P.5 Control of Drug Product

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
47. Changes in standard / monograph (specifications) claimed for the drug product, involving			
a. a change from a pharmacopoeial standard/ monograph to in-house standard	None	1-3, 5-7	Notifiable Change
b. change in the standard claimed for the drug product (e.g., from an in-house standard to pharmacopoeial standard/monograph or from one pharmacopoeial standard / monograph to a different pharmacopoeial standard/monograph)	None	1-6	Notifiable Change
	1, 3	1-3, 6, 7	Annual Notification
c. change in the specification for the drug product to comply with an updated pharmacopoeial monograph. Note: Change in specifications and an analytical procedure for the Drug Product to comply with an updated pharmacopoeial monograph within 6 months of Pharmacopoeia update should be captured under Level IV changes	1, 2	1-3, 6, 7	Annual Notification

Conditions

1. The change is made exclusively to comply with the pharmacopoeia.
2. No change to the specification that results in a potential impact on the performance of the drug product.
3. No deletion of or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specification except to comply with

pharmacopoeial standard/ monograph.

Supporting Data

1. Revised Drug Product Labelling information, i.e. Package Insert and Inner and Outer Labels, as applicable.
2. Updated, drug product specifications (3.2.P.5.1).
3. Where an In-house analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the In-house and compendial methods.
4. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least two batches (minimum pilot scale) of the drug product tested according to the changed specification (3.2.P.5.4).
5. Justification of the changed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products) (3.2.P.5.6).
6. Demonstration that consistency of quality and of the production process is maintained.
7. Copies or summaries of validation reports, if new analytical procedures are used (3.2.P.5.3).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
48. Change in the drug product release / shelf life specification, involving:			
a. for sterile products, replacing the sterility test with process parametric release	None	1, 2, 5, 8-10	Supplement
b. deletion of a test	None	2, 9, 10	Notifiable Change
	7	2, 9, 10	Annual Notification
c. replacement or addition of a test	None	2-7, 9, 10	Notifiable Change

	1, 2, 8	2-4, 9	Annual Notification
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	11, 12	Notifiable Change
e. relaxation of an acceptance criterion	None	2, 9, 10	Notifiable Change
	1, 3-6	2, 9, 10	Annual Notification
f. tightening of an acceptance criterion	1, 2, 4, 9	2	Annual Notification

Conditions

1. The change is not necessitated by unexpected 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. Acceptance criterion for any Class 3 residual solvent is within the ICH limits.
5. The change to the specifications does not result in a potential impact on the performance of the drug product.
6. The change does not concern sterility or potency testing.
7. The test is deleted in-line with the updated Pharmacopoeia/ Standard; or there is no change in the compliance status of applicable Pharmacopoeia/ Standard (E.g. The deleted test is the abnormal toxicity test / general safety test).
8. The addition of test is not to monitor new impurity species.
9. The method of analysis is the same (i.e. a change in column length, temperature, but not a different type of column or method) and no new impurities are detected.

Supporting Data

1. Process validation and/or evaluation studies (3.2.P.3.5) or the proposed validation protocol of the changed drug product.
2. Updated drug product specifications (3.2.P.5.1).
3. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.P.5.2).
4. Copies or summaries of validation reports, if new analytical procedures are used (3.2.P.5.3).
5. Where an In-house analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the In-house and compendial methods.
6. Information demonstrating qualification of the method and comparability with the approved method.
7. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least two batches (minimum pilot scale) of the drug product tested according to the changed specifications (3.2.P.5.4).
8. Description of the batches, certificates of analyses, and summary of results, of a sufficient number of batches to support the process parametric release (3.2.P.5.4).
9. Justification of the changed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products) (3.2.P.5.6).
10. Demonstration that consistency of quality and of the production process is maintained.
11. Copies of relevant certificate of fitness for use (e.g., veterinary certificate).
12. Data demonstrating that the change in animals gives comparable results with those obtained using the approved animals.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
49. Change in the analytical procedures of drug product, involving:			
a. deletion of an analytical procedure and/or an acceptance criteria	None	1, 2-4	Notifiable Change
	5	1, 2-4	Annual Notification
b. replacement or addition of an analytical procedure	None	1, 3, 5-7	Notifiable Change
	1, 3, 4, 6-8	1, 3, 5-7	Annual Notification
c. minor changes to an approved analytical procedure	1-4, 8	3, 5-7	Annual Notification
d. change from an In-house analytical procedure to a Pharmacopoeial analytical procedure	1-4, 8	1, 5, 6	Annual Notification

Conditions

1. No change in the approved acceptance criteria.
2. 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.
3. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
4. The change does not concern sterility testing.
5. The analytical procedure is deleted in-line with the updated Pharmacopoeia/ Standard; or there is no change in the compliance status of applicable Pharmacopoeia/ Standard.
6. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.

7. The change is from a pharmacopoeial assay to another pharmacopoeial assay or marketing authorization holder has demonstrated an increase understanding of the relationship between method parameters and method performance define by a systematic development approach including robustness studies.
8. The change does not concern the potency testing.

Supporting Data

1. Updated drug product specifications (3.2.P.5.1)
2. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least two batches (minimum pilot scale) of the drug product tested according to the changed specification (3.2.P.5.4).
3. Justification for the change to the analytical procedure (e.g. demonstration of suitability of the analytical procedure to monitor the drug product).
4. Demonstration that consistency of quality and of the production process is maintained.
5. Copies of summaries of analytical procedures, if new analytical procedures are used (3.2.P.5.2).
6. Copies of summaries of validation/qualification reports, if new analytical procedures are used (3.2.P.5.3).
7. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
50. Changes affecting the quality control (QC) testing of the final product (release and stability), involving :			
a. transfer of the QC testing responsibilities for a non - pharmacopoeial assay (in-house) to a new company	None	1, 2	Notifiable Change
	2 - 4	1, 2	Annual Notification
b. transfer of the QC testing responsibilities for a	None	1, 2	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
pharmacopoeial assay to a new company			
c. transfer of the QC testing responsibilities for a pharmacopoeial assay or a nonpharmacopoeial assay to a different site **Note #1:** Change in specifications and an analytical procedure for the Drug Product to comply with an updated pharmacopoeial monograph within 6 months of Pharmacopoeia update requires no reporting. **Note #2:** Transfer of testing to a different facility within GMP compliant site is not considered to be reportable change but it treated as a minor GMP change (Level IV) and is reviewed during inspection.	1	1, 2	Annual Notification
d. introduction of additional laboratory in a facility to perform drug product testing	None	2	Annual Notification

Conditions

1. The new QC testing site/facility is under the central quality assurance .
2. The transfer is within a facility approved in the current MA for the performance of other test
3. The transferred quality control test is not a potency assay or bioassay.
4. There is no change in the test methods.

Supporting Data

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

2. Information demonstrating technology transfer validation and equipment qualification, as appropriate.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
51. Changes in the control strategy of the drug product, involving:			
a. Change from end-product testing to upstream controls for some test(s) (e.g., Real-Time Release Testing, Process Analytical Technology)	None	1-5	Supplement
b. Addition of a new Critical Quality Attribute (CQA) in the control strategy	None	1-5	Notifiable Change
c. Deletion of a Critical Quality Attribute (CQA) from the control strategy	None	1, 5	Notifiable Change

Conditions

None

Supporting Data

1. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed product (3.2.P.3.4).
2. Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after CDSCO approval), if changed (3.2.P.5.1).
3. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.P.5.2).
4. Copies or summaries of validation reports, if new analytical procedures are used (3.2.P.5.3).
5. Justification and supporting data for each proposed change to the control

strategy.

3.2.P.6 Reference Standards or Materials

Description of Change	Condition to be Fulfilled	Supporting Data	Reporting Category
52. Change in reference standards or materials used to release the drug product, involving			
a. qualification of a Reference Standard	None	1	Notifiable Change
b. update the reference standards from pharmacopoeial to in-house	1	1, 5	Notifiable Change
c. update the reference standards from in -house to pharmacopoeial	2, 3	1, 5	Annual Notification
d. qualification of a new lot of reference standard (except for a bacterial or viral vaccine, bacterial toxin)	2	1, 5	Annual Notification
53. Qualification of a new lot of reference standard against the approved reference standard for a bacterial or viral vaccine, bacterial toxin, involving.			
a. reference standard used in a qualitative test, physicochemical test, semi-quantitative or quantitative biological assay	2	1	Annual Notification
54. Change to the reference standard qualification protocol[1] (except for a bacterial or viral vaccine, bacterial toxin)	None	2, 3	Notifiable Change
	5	2, 3	Annual Notification
55. Change to reference standard qualification protocol for a bacterial or viral vaccine, bacterial toxin involving:			

Description of Change	Condition to be Fulfilled	Supporting Data	Reporting Category
a. a reference standard used in a qualitative test	None	3, 5	Annual Notification
b. a reference standard used in a physicochemical test, a semi-quantitative or quantitative biological assay.	5	3, 5	Annual Notification
56. Extension of the shelf-life / re-test period of the reference standard	4	4	Annual Notification

Conditions

1. The In-house reference standard is validated against an official (e.g., pharmacopoeial/ NIBSC/WHO/EDQM/NCL) reference standard.
2. Qualification of the reference standard is performed according to the approved protocol (i.e. no deviation from the approved protocol).
3. The change is necessitated due to Pharmacopoeial requirement to meet with the regulatory requirements.
4. The extension of the shelf-life of the reference standard is carried out in accordance with an approved protocol.
5. The protocol is considered more stringent (i.e., addition of new tests or tightening of acceptance criteria). If deletion of test is proposed, the tests proposed to be deleted were not implemented to monitor the quality of the reference standard (e.g., was implemented for research or validation work.).

Supporting Data

1. Information demonstrating qualification of the changed reference standards or materials (e.g., source, characterization, certificate of analysis).
2. Justification of the change to the reference standard qualification protocol.
3. Updated reference standard qualification protocol.
4. Summary of stability testing and results or retest data to support the extension of the reference standard shelf-life.

5. Justification for change in the reference standard.

3.2.P.7 Container Closure System

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
57. Change in primary container closure component, involving			
a. modification of a container closure system (e.g., new coating, adhesive, stopper, prefilled syringe with attached needle, prefilled syringe with separate needle). Note: The addition of a new container closure system (e.g., addition of a pre-filled syringe where the currently approved presentation is only a vial) is considered a change in presentation.	None	1-7	Notifiable Change
	1-3	3	Annual Notification
	4	3, 6	Annual Notification
b. deletion of a container closure system	None	1	Annual Notification
c. change from a reusable container to a disposable container with no changes in product contact material (e.g. change from reusable pen to disposable pen)	None	1, 3-4, 6	Notifiable Change

Conditions

1. No change in the type of container closure or materials of construction.
2. The container closure shape dimensions or specifications are equivalent.
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 dimensions).
4. The modified part is not in contact with the Drug Product

Supporting Data

1. Revised Product Labelling information i.e. Package Insert and Inner and Outer Labels, as appropriate.
2. For sterile products, process validation and/or evaluation studies (3.2.P.3.5).
3. Information on the proposed changed container closure system, as appropriate (e.g., description, materials of construction of primary/secondary packaging components, specifications) (3.2.P.7).
4. Summary of stability testing and results of minimum three months of accelerated and a minimum of three (3) months of real time/real temperature testing on three (3) commercial scale batches of the changed drug product stored in the proposed container as well as commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies (3.2.P.8.3). Matrixing, bracketing, the use of smaller scale batches and use of fewer than 3 batches for stability testing of proposed changed drug product may be acceptable if scientifically justified (refer ICH Q1D) by the manufacturer /MA holder to CDSCO.
5. Summary of release testing results as quantitative data, in a comparative tabular format, for at least three consecutive commercial-scale batches of the pre-change and post-change drug product. Comparative pre-change test results do not need to be generated concurrently; relevant historical testing results are acceptable. Bracketing for multiple-strength products, container sizes and/or fills may be acceptable if scientifically justified.
6. Information demonstrating suitability of the changed container/closure system (e.g., results from last media fills, preservation of protein integrity, and maintenance of the sterility in multi-dose container).
7. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity test.

Description of Change Conditions	Conditions to be Fulfilled	Supporting Data	Reporting Category
58. Change in the supplier for a primary container closure component, involving:			
a. replacement or addition of a supplier	None	1-3	Notifiable Change
	1, 2	3, 4	Annual Notification
b. deletion of a supplier	None	None	Annual Notification

Conditions

1. There is no change in the type of container closure, materials of construction; and container closure shape, dimensions, specifications (or are equivalent) or in the sterilization process for a sterile container closure component.
2. No change in the specifications of the container closure component outside of the approved ranges.

Supporting Data

1. Data demonstrating the suitability of the container closure system (e.g., extractable/ leachable testing).
2. For sterile products, process validation and/or evaluation studies (3.2.P.3.5).
3. Information on the changed container closure system (e.g., description, materials of construction of primary packaging components, specifications) (3.2.P.7).
4. Certificate of analysis, or equivalent, for the container provided by the new supplier and comparison with certificate of analysis, or equivalent, for the approved container.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
59. Change in the specifications for a primary container closure component or functional secondary container closure component, involving:			
a. deletion of a test	4, 5	1, 2	Annual Notification
b. replacement or addition of a test	None	1	Notifiable Change
	1-3	1, 2	Annual Notification
c. relaxation of an acceptance criterion	None	1, 2	Notifiable Change
d. tightening of an acceptance criterion	1, 2	1	Annual Notification

Conditions

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. The change is within the range of previously 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. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeial requirement.
5. 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.

Supporting Data

1. Updated changed specifications, for the primary or functional secondary container closure component (3.2.P.7).
2. Rationale for the change in specification for a primary container closure component.

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
60. Change in the analytical procedures for a primary container closure component or functional secondary container closure component			
a. deletion, replacement or addition of an analytical procedure	3	1-3	Notifiable Change
	3, 4	1-3	Annual Notification
b. minor changes to an analytical procedure	1-4	1-3	Annual Notification

Conditions

1. No change in the approved acceptance criteria outside the approved limits.
2. The analytical procedure is of the same type.
3. Results of method validation demonstrate that the proposed new or modified analytical procedure is at least equivalent to the approved analytical procedure.
4. The new or modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

Supporting Data

1. Updated changed specifications. (3.2.P.7)
2. Description of the analytical procedure and, if applicable, validation data.
3. Rationale for the change in specification for a primary container closure component.

3.2.P.8 Stability

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
61. Change in the shelf life for the drug product, involving:			
a. extension (includes extension of shelf-life of the Drug Product as packaged for sale, and hold	None	1-4, 6, 7	Notifiable Change
	1-3, 4, 5	1, 2, 5, 7	Annual

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
time after opening and after dilution or reconstitution)			Notification
b. reduction (includes reduction as packaged for sale, after opening, after dilution or reconstitution)	None	1-4, 5, 7	Notifiable Change
	6	2-4, 7	Annual Notification

Conditions

1. No change to the container closure system in direct contact with the drug product or to the recommended storage conditions of the drug product.
2. The approved re-test period (or shelf life) is at least 24 months.
3. Full long term stability data are available covering the changed re-test period (or shelf life) and are based on stability data generated on at least three production scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes (as defined in ICH's Q1A guideline) 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.

Supporting Data

1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained) (3.2.P.8.3).
2. Proposed storage conditions and re-test period (or shelf life, as appropriate).
3. Updated post-approval stability protocol and stability commitment (3.2.P.8.2).
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing on both upright and inverted samples, except for lyophilized products (i.e., full real time/real temperature stability data covering the changed re-test period (or shelf life) generated on at least three (3) production scale batches) (3.2.P.8.3).

6. Results of stability testing (i.e., less than full real time/real temperature stability data covering the changed re-test period (or shelf life) and/or generated on less than three (3) production scale batches), (3.2.P.8.3) and a commitment to submit the stability report when completed and to notify CDSCO of any failures in the ongoing stability studies. Full long term stability data are not available covering the changed shelf life or are not based on stability data generated on at least three batches, the extrapolation is in accordance with ICH's Q1E guideline.
7. Updated product labeling information, as applicable

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
62. Change in the labelled storage conditions for the drug product or the diluted or reconstituted product, involving:			
a. addition of a cautionary statement (e.g. DO NOT FREEZE)	None	1, 2, 4, 5	Notifiable Change
	1	1, 2, 4, 5	Annual Notification
b. deletion of a cautionary statement (e.g. DO NOT FREEZE)	None	1, 2, 4, 6	Notifiable Change
c. addition or change of storage condition for the drug product, diluent or reconstituted drug product (e.g. relaxation or tightening of temperature criterion)	None	1-5	Notifiable Change
	1, 2	1-4	Annual Notification

Conditions

1. The change is not necessitated by unexpected 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 labelling information (Package Insert, Inner and Outer Labels), as applicable.
2. Proposed storage conditions and shelf-life.
3. Updated post-approval stability protocol and stability commitment (3.2.P.8.2).
4. Justification of the change in the labelled storage conditions/cautionary statement.
5. Results of stability testing under appropriate stability conditions covering the proposed shelf-life, generated on one (1) commercial scale batch unless otherwise justified (3.2.P.8.3).
6. Results of stability testing under appropriate conditions covering the proposed shelf-life, generated on at least three (3) commercial scale batches unless otherwise justified (3.2.P.8.3).

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
63. Change to the post-approval stability protocol or stability commitment of final product, involving			
a. major change to the post-approval stability protocol or stability commitment, such a deletion of a test, replacement of an analytical procedure, or change in storage temperature	None	1-7	Notifiable Change
	1, 4	2, 3, 5, 6	Annual Notification
b. addition of time point (s) into the post-approval stability protocol	None	2, 3	Annual Notification
c. addition of test (s) into the post-approval stability protocol	1	2, 3, 5, 6	Annual Notification
d. deletion of time point (s) from the post-approval stability protocol	5	2, 3, 7	Annual Notification

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
beyond the approved shelf life			
e. deletion of the time(s) from the post-approval stability protocol within the approved shelf-life	2	2, 3, 7	Annual Notification
f. replacement of the sterility testing by the container closure system integrity testing	None	2, 3, 5-7	Notifiable Change
	3	2, 3, 7	Annual Notification

Condition

1. The addition of the test(s) is not due to stability concerns or to the identification of new impurities.
2. The approved shelf–life of the final product is at least 24 months.
3. The method used to demonstrate the integrity of the container/closure system has already been approved as part of a previous application.
4. 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.
5. Deletion of the time-points is done according to relevant guideline (i.e. ICH Q5C).

Supporting Data

1. Proposed storage conditions and shelf life.
2. Updated post-approval stability protocol and stability commitment (3.2.P.8.2).
3. Justification of the change to the post-approval stability protocol or stability commitment.
4. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment. (3.2.P.8.3)
5. Copies or summaries of analytical procedures, if new analytical procedures are used (3.2.P.5.2).
6. Validation study reports, if new analytical procedures are used (3.2.P.5.3).
7. Comparative results demonstrating that the approved and proposed analytical

procedure are equivalent.

5. POST-APPROVAL CHANGE MANAGEMENT PROTOCOL-PACMP

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
a. Introduction of a post-approval change management protocol related to DS and/or DP	None	1-3	Notifiable Change
b. Deletion of an approved post-approval change management protocol related to DS and/or DP	1	3, 4	Annual Notification
c. Minor changes to an approved change management protocol	None	3, 4	Notifiable Change

Conditions

1. The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.

Supporting Data

1. Description of the proposed change
2. Change management protocol
3. Amendment of the relevant CTD CMC sections
4. Justification for the proposed change

6. EFFICACY POST APPROVAL CHANGES

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
1. Change in the efficacy parameter			
a. Addition of a new therapeutic indication and/or modification of an approved one	1	1-5	Supplement
Note: The changes that are considered as "New Drugs" as per "The New Drugs and Clinical Trials Rules, 2019, MA holder should submit the MA application in Form CT-21/Form CT-18 in SUGAM with applicable fee along with supporting documentation as described for the respective post approval change category, followed by amendment / endorsement of current Form 28 D license, as applicable. Note: A declaration to state that no change to other remaining section/s of the MA dossier, shall be submitted, as applicable.			
b. Deletion of a therapeutic indication	None	3	Notifiable Change
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	Supplement
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 Package Insert (PI) with proposed change,
4. Published data or relevant literature supporting the proposed change, if any.
5. Duly signed Form CT-18 or Form CT-21, with applicable fees (challan)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
2. 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	Supplement

Note: The changes that are considered as "New Drugs" as per "The New Drugs and Clinical Trials Rules, 2019, MA holder should submit the MA application in Form CT-21/Form CT-18 in SUGAM with applicable fee along with supporting documentation as described for the respective post approval change category, followed by amendment / endorsement of current Form 28 D license, as applicable.

Note: A declaration to state that no change to other remaining section/s of the MA dossier, shall be submitted, as applicable.

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 PI with the proposed change.
4. Published data or relevant literature supporting the proposed change, if any.
5. Duly signed Form CT-18 or Form CT-21, with applicable fees (challan)

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
3. Other changes related to safety and efficacy, involving			
a. change to add information on shedding and transmission	1	1-4	Notifiable Change
b. change in the recommended dose and/ or dosing schedule (addition or modification new vaccination regimen)	None	1-4	Supplement
c. change to use in specific risk groups (e.g. use in pregnant women or immunocompromised patients)	1	1-4	Notifiable Change
d. change to add information on co-administration with other vaccines or medicines	1	1-4	Notifiable Change
e. change to add a new delivery device	1	1-4	Supplement
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	Notifiable Change

Conditions
1. No change in strength, dosage form and indication.
Supporting Data
1. Published 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 PI 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 vaccine against human influenza or COVID-19	None	1-3	Notifiable Change
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.			

7. ADMINISTRATIVE CHANGES

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 Marketing Authorization for DS and / or	1	1, 2	Notifiable Change

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
DP.			

Conditions

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

Supporting data

1. Approval for change of name as per statutory requirements.
2. Notification of new name in the form of a MA holder signed letter if the manufacturer is sold or merged with another company. Note that if address changes due to manufacturing facility change then MA application needs to be resubmitted with fresh quality; safety and efficacy data according to the manufacturing facility change requirements

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
2. Company sale, purchase, merger	1	1-3	Notifiable Change

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 information.

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
3. Change in the (invented) name of the product.	1	1, 2	Notifiable Change
Conditions			
1. The name is as per the updated Pharmacopeia.			
Supporting data			
1. Copy of the updated Pharmacopeia monograph. 2. Revised product labelling information (Package Insert, Inner and Outer Labels), as applicable.			

8. PRODUCT LABELLING 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:

1. Addition of an adverse event that is identified to be consistent with a causal association to biological product concerned.
2. Change in the frequency of occurrence of a given adverse reaction.
3. Addition of a contraindication or a warning (e.g. identification of a specific subpopulation as being at greater risk, such as persons with a concomitant condition or taking concomitant medicines, or a specific age group). These changes may include the provision of recommended risk-management actions (e.g. required testing prior to vaccination, specific monitoring following vaccination, ensuring patient awareness of certain risks).

In some cases, the safety-related changes listed above may be urgent and may require rapid implementation (e.g. addition of a contraindication or a warning). To

allow for speedy processing of such requests, the submission for these changes should be labelled as “Urgent Product Labelling Information Changes”.

9. APPENDICES

Appendix 1: Examples of Level IV Changes but not limited to

- Non-critical changes to the licensed application including spelling mistakes, editorial changes and remediations made to documents such as Validation Summaries and/or Reports, Analytical Procedures, SOPs, Production Documentation Summaries, QOS, for added clarity that have no impact to affect the safety, efficacy and quality of the product.
- Replacement of the membrane (filter) used during the UF/DF step.
- Replacement or addition of filter housing.
- Change in stopper cap colour for an injectable product.
- Modification to pretreatment stages of a WFI system, including purified water systems used solely for pretreatment in WFI production.
- Change in the floor plan that does not affect production process or contamination precautions.
- Addition of vial reject chute.
- Change in the in-process controls performed at non-critical manufacturing steps or change to a non-critical manufacturing area (see Glossary).
- Transfer of in-process control testing to a different facility within a GMP-compliant site
- Transfer of raw material / packaging material testing to a different facility within GMP compliant site.
- Transfer of Pharmacopoeial testing of drug substance / drug product to a different facility within GMP compliant site.
- Rooms upgrades, such as installation of improved finishes on floors/walls.
- Addition of a new GMP storage warehouse for raw materials, master and working cell banks and drug substance.
- Installation of non-process-related equipment or rooms to improve the facility, such as warehousing refrigerators or freezers.

- Replacement of equipment with identical equipment (non-product contact equipment).
- Introduction of additional laboratory in a facility to perform drug substance testing.
- Change in supplier for non-critical excipients.
- Change in tertiary packaging components of drug substance or drug product that do not affect stability.
- Minor changes to the layout of the product labelling information items or revision of typographical errors without changing the content of the label.

Appendix 2: ANNUAL REPORT FORM (Minor Changes)

January _____ to December_____

1.	Manufacturing site(s) or Area(s) involved	
2.	Product(s) involved	
3.	Description of change	
4.	Rationale of change	
5.	Reference to CDSCO guidelines	Conditions**:**

6.	Implementation date	
7.	Cross reference to validation protocols and/ or SOP's/STP's/ Spec's (If relevant)	
8.	Relevant data from studies and tests performed (Impact of change assessed)	

Submitted by: **Date:**

Appendix 3: Glossary

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.).

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:

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.

Similar Biologics:

“Similar biologic” means a biological product which is similar in terms of quality, safety and efficacy to reference biological product licenced or approved in India, or any innovator product approved in International Council of Harmonisation (ICH) member countries.

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, that any procedure, process, equipment, material, activity or system will consistently produce a result meeting

predetermined acceptance criteria. 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.

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.

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