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POST APPROVAL CHANGES IN BIOLOGICAL PRODUCTS

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ABSTRACT: The post approval changes are the changes made to biological products that have received an approval and to provide 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. After the approval of NDA or ANDA, the applicant may make post approval changes, provided the changes are reported to the FDA under the appropriate categories. Section 506 A of the Federal Food, Drugs and Cosmetics act and 21 CFR 314.70 provide for three reporting categories of the post approval changes namely: major change, moderate change and minor change. There are many reasons for making changes to pharmaceutical products after the original regulatory approval is obtained. Company change control procedures should detail how changes are evaluated and implemented as well as how the change impacts stability and what data will be needed to support the change. The regulatory group will determine the strategy for submission based on a review of the technical assessment of the change and the appropriate regulatory guidance.

INTRODUCTION: The objective of this study is to classify the changes made to biological products that have received an approval and to provide 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]

Background:

This includes emphasis on applying a science-based and risk-based approach to the pharmaceutical and biological products quality assessment of these products.

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As such, the guidance documents were needed on the information to support quality changes to new biological products which apply a modernized, science-based, and risk-based approach to this area.

Guidance for implementation:

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, sponsors are advised to contact Drug Controller General of India (DCGI).[2]

Reporting Categories [3]:

The following three are the reporting categories under which the changes can be categorized.

A. **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 or effectiveness 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 DCGI 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 be filed, along with the recommended supporting data, to DCGI. The appropriate fee must also be paid, in accordance with the prevailing rules at the time of submission of the notification.

- If, within 30 days of the date of the acknowledgement of receipt of a valid notification, the DCGI has not sent the holder its opinion, the notified shall be deemed to have been accepted by DCGI.

B. 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 or effectiveness of the product.

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

- If, within 15 days of the date of the acknowledgement of receipt of a valid notification, the DCGI has not sent the holder its opinion, the notified shall be deemed to have been accepted by DCGI.

C. 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 or effectiveness of the product.

- The changes included in this reporting category may be implemented by the sponsor without the prior review by DCGI of the data supporting such a change. Supporting data for the Level III changes recommended in this guidance documents should be submitted on annual basis; however, the data on such changes should be available to DCGI within fifteen (15) calendar days, if requested at any time.

Documentation: [4]

A. General Information:

The change examples presented in Quality post approval changes (Biologics) are intended to assist with the classification of changes made to the Quality information. The information summarized in the tables provides recommendations for:

i. The conditions to be fulfilled for a given change to be classified as a Level I, II, or III change. If the conditions outlined for a given change are not fulfilled, the particular change will be assessed by the DCGI in the lights of scientific justification provided by the sponsor and accordingly the level shall be decided.

ii. The supporting data for a given change, either to be submitted to DCGI and/or maintained by the sponsor. Where applicable, the corresponding sections of the application for the supporting data have been identified.

iii. The reporting category (e.g., Supplement, Notifiable Change or Annual Notification). For convenience, the change examples are organized according to the format defined by the DCGI.

B. 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 the DCGI.

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:

i. 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).

ii. Where relevant, a side-by-side comparison of the previously approved and the changed information.

iii. An electronic or hard copy of the Quality Overall Summary or the applicable DCGI Quality Overall Summary template (only those sections affected by the proposed change(s) should be included, sections not affected by the change(s) should be deleted from the QOS).

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 of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved).
Supporting Data - Level III Changes:

Any data that may have been generated by the sponsor in support of a Level III change should be submitted annually but should be available to DCGI within fifteen (15) calendar days, if requested.

C. Stability Testing:

If stability studies are recommended to support a change, these studies should be conducted in accordance with applicable DCGI guidance on:

1. Stability Testing of New Drug Substances and Products.

2. Stability Testing of Existing Drug Substances and Products.

3. Stability Testing of Biotechnological/Biological Products.

Quality Post-Approval Changes (Biologics):

The change examples presented below are intended to assist with the classification of changes made to the Quality information of biologic products.[5, 6, 7, 8]

1. Drug Substance:

TABLE 1: DRUG SUBSTANCE- GENERAL INFORMATION

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the name of the drug substance	1	1-3	Annual Notification

A. 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)).

B. Supporting Data:

1. Product Monograph (e.g., Title Page, Storage and Stability, Composition and Packaging (Part I), and Pharmaceutical Information and Inner and Outer Labels.

2. Information on the changed nomenclature of the drug substance (e.g., Recommended INN, compendial name, chemical name(s)).

3. Evidence that the changed name for the drug substance is recognized (e.g., proof of acceptance by WHO, a copy of the INN list).

TABLE 2: MANUFACTURING FACILITY [9]

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change to a drug substance manufacturing facility, involving:			
a. replacement or addition of a manufacturing facility and/or manufacturer of the bulk drug substance, the starting material or any intermediate of the drug substance	1-2	1-6, 8-11	Supplement
b. conversion of a drug substance manufacturing facility from single-product to multi-product	3-4	11-12	Notifiable Change
c. introduction of prokaryotes including yeast into a multiproduct eukaryotic fermentation suite	3-4	12-13	Notifiable Change
d. introduction of a different host/media-type into an approved multi-product facility for which a master cleaning protocol for the introduction of new host/media-type has not been approved	None	7,14	Notifiable Change
e. addition of product(s) to an approved multi-product manufacturing area	3-4	11-13	Annual Notification
f. deletion of a manufacturing facility or manufacturer for a starting material, bulk intermediate, or drug substance	None	None	Annual Notification

A. Conditions:

1. No changes have been made to the starting material and the expression system.

2. The production process and controls are the same as those used by the original manufacturer.

3. The addition of product does not involve changes to the validated cleaning and change-over procedures.

4. The addition of product does not involve additional containment requirements.

B. Supporting Data:

1. Updated or new DMF (with a Letter of Access) or relevant drug substance information.

2. Name, address, and responsibility of the changed production facility or facility involved in manufacturing and testing.

3. For drug substances 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).

4. Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the changed drug substance.

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

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

7. Information on the in-process control testing.

8. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug substance.

9. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available, as well as

commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

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.

11. Information on the changed production facility involved in manufacturing and testing, including cleaning and shipping validation, as appropriate.

12. Information describing the change-over procedures for shared product contact equipments and the segregation procedures, as applicable.

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

14. Information on the cleaning procedures (including validation and the master cleaning protocol) demonstrating lack of carry-over or cross-contamination.

TABLE 3: MANUFACTURING PROCESS

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the drug substance manufacturing process, involving:			
a. a critical change	None	1-3, 5-12	Supplement
b. a non-critical change	1-2	1-3, 5-11	Notifiable Change
	1-4	2, 3, 5-7, 9, 10	Annual Notification
Scale-up of the manufacturing process:			
a. at the fermentation stage	5-9	4, 8-11	Notifiable Change
b. at the purification stage	1, 6-7, 10	8-11	Notifiable Change
Change in source/supplier of auxiliary materials/reagents of biological origin (e.g., fetal calf serum, insulin)	None	9, 12, 13	Notifiable Change
Introduction of reprocessing steps	None	7, 9-11	Notifiable Change

A. Conditions:

1. The change does not concern the sterilization procedures 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 for a vaccine.

3. No change in the drug substance specifications.

4. No change in the impurity profile of the drug substance.

5. No change in the proportionality of the raw materials.

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

7. The change does not result in a change to the drug substance specification.

8. The scale-up consists in the addition of identical bioreactors.

9. The change does not affect the purification process.

10. The scale-up is linear.

B. Supporting Data:

1. Updated or new DMF (with a Letter of Access) or relevant drug substance information.

2. Flow diagram of the changed manufacturing process (es) and a brief narrative description of the changed manufacturing process (es).

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.

4. Information on the characterization and testing of the post-production cell bank for recombinant product, or of the drug substance for non-recombinant product.

5. For drug substances 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).

6. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed drug substance.

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

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

9. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug substance.

10. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

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.

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

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

TABLE 4: CHANGES TO THE CELL BANK AND SEED BANK

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Changes to the cell bank:			
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	None	1-8	Supplement
➢ adaptation of a MCB into a new fermentation medium	None	3	Notifiable Change
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, 3, 4	1-2	Annual Notification
Changes to the seed bank:			
a. new Master Seed Bank (MSB)	None	3-9	Supplement
➢ Working Seed Bank (WSB) extended beyond an approved passage level	4		Notifiable Change
b. generation of a new MSB or WSB	2, 3, 4	3, 4	Annual Notification

A. Conditions:

1. The new MCB is generated from a pre-approved Master or Working Cell Bank.

2. The new cell/seed bank is generated from a pre-approved MCB/MSB.

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.

B. Supporting Data:

1. Qualification of the cell bank.

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. 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, in a comparative tabular format, for the new seed lot.

5. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the drug substance derived from the new cell/seed bank.

6. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

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.

8. Supporting non-clinical and clinical data or a request for a waiver of in vivo studies.

9. Supporting clinical data.

TABLE 5: CHANGE INVOLVING MANUFACTURING FACILITY

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in a facility 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	Notifiable Change
b. relocation of equipment to another room in the same facility	1-3	3, 4	Annual Notification
c. modification to a non-critical manufacturing area (e.g., construction of a new warehouse in the facility)	2, 3	3, 6	Annual Notification
d. change in the location of steps in the production process	1	1, 4, 5	Annual Notification

A. Conditions:

1. The change in the location of steps has no impact on the risk of contamination or cross-contamination.

2. The modification has no direct product impact.

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

B. Supporting Data:

1. Information on the in-process control testing.

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. Information demonstrating re-qualification of the equipment or requalification of the change.

4. Information illustrating the manufacturing flow, including the floor plans.

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

6. Information on the changed production facility involved in manufacturing and testing, including cleaning and shipping validation, as appropriate.[3]

TABLE 6: CHANGE INVOLVING EQUIPMENT USED IN MANUFACTURING PROCESS [10]

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in equipment used in drug substance manufacturing process, such as:			
a. Equipment having different specifications from those originally approved	None	1-3	Notifiable Change
b. addition of new product-contact equipment used in a critical step (e.g., change in equipment model for a continuous centrifuge, water bath for inactivation)	None	1-3	Notifiable Change
c. equipment change for an identical/ equivalent equipment	1	3	Annual Notification

A. Conditions:

1. Re-qualification of the equipment follows the original qualification protocol.

B. Supporting Data:

1. Information on the in-process control testing.

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. Information demonstrating re-qualification of the equipment or requalification of the change.

TABLE 7: CHANGE IN CONTROL FOR MATERIAL AND CRITICAL STEPS [11]

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the controls for the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts)	1-5	1-6	Notifiable Change
Change in the controls performed at critical steps used in the manufacture of the drug substance	1-5	1-6	Notifiable Change

A. Conditions:

1. No change in the drug substance specifications.

2. No adverse change in the impurity profile of the drug substance.

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 sterilization procedures of a sterile drug substance.

B. 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 drug substance.

2. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed drug substance.
3. Updated, signed and dated specifications of the drug substance, if affected by the change.

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

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

6. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug substance.

1.1 Characterization:[12]

There are no quality change examples for this section at the present time that has not been addressed in other sections.

1.2 Control of the Drug Substance:

TABLE 8: CONTROL OF THE DRUG SUBSTANCE

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the standard claimed for the drug substance (e.g., from a Professed to pharmacopoeial standard)	None	1-6	Notifiable Change
	1, 2, 3	1-6	Annual Notification
Change in the specifications for the drug substance to comply with an updated pharmacopoeial monograph	1, 2	2-6	Annual Notification

A. Conditions:

1. The change is made exclusively to comply with the (same) pharmacopoeia.
2. No change to the specifications for functional properties of the drug substance.

3. No deletion or relaxation to any of the tests, analytical procedures, or acceptance criteria of the approved specifications.

B. Supporting Data:

1. Product Monograph (e.g., Title Page, Composition and Packaging, and Pharmaceutical Information section) and Inner and Outer Labels.

2. Updated, signed and dated, changed drug substance specifications.

3. Where a House analytical procedure is used and a standard is claimed, results of an equivalency study between the House and compendia methods.

4. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least three (3) batches of the changed drug substance.

5. Justification of the changed drug substance specifications (e.g., demonstration of the suitability of the monograph to control the drug substance, including impurities).

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

Table No. 9: Change in test and acceptance criterion

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
deletion of a test	5	1, 4, 5-6	Notifiable Change
replacement or addition of a test	None	1-6	Notifiable Change
	1-4, 6	1-6	Annual Notification
relaxation of an acceptance criterion	None	1, 4, 5-6	Notifiable Change
tightening of an acceptance criterion	1-4, 6	1, 4, 5-6	Annual Notification

A. 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 deleted analytical procedure has been demonstrated to be redundant with respect to the remaining analytical procedures.
6. The change does not concern sterility testing.

B. Supporting Data:

1. Updated, signed and dated, changed drug substance specifications.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used.
4. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the 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) batches of the changed drug substance.
6. Justification of the changed drug substance specifications (e.g., test parameters, acceptance criteria, or analytical procedures).

TABLE 10: CHANGE IN SPECIFICATIONS FOR THE DRUG SUBSTANCE [13]

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for the drug substance, involving:			
a. deletion of an analytical procedure	1	5	Notifiable Change
b. replacement or addition of an analytical procedure	1, 3	1-5	Notifiable Change
c. minor changes to an approved analytical procedure	1-5	1-5	Annual Notification
a change from a house analytical procedure to a Pharmacopoeial analytical procedure	1-5	1-5	Annual Notification

A. 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. 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 sterility testing.

B. Supporting Data:

1. Updated, signed and dated, changed drug substance specifications.
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used.

4. Comparative results demonstrating that the approved and changed analytical procedures are equivalent.

1.3 Reference Standards or Materials:

TABLE 11: REFERENCE STANDARDS OR MATERIALS

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Qualification of a reference standard	None	1	Notifiable Change
Subsequent qualification of a reference standard	2, 3	1	Annual Notification
Update the reference standards from pharmacopoeial to House	1	1	Notifiable Change
Update the reference standards from House to pharmacopoeial	2, 3	1	Annual Notification

A. Conditions:

1. The House reference standard is validated against an official (e.g., pharmacopoeial) 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 reference standard is not for a bacterial or a viral vaccine.

B. Supporting Data:

1. Information demonstrating qualification of the changed reference standards or materials (e.g., source, characterization, certificate of analysis).

1.4 Container Closure System

TABLE 12: CONTAINER CLOSURE SYSTEM

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the container closure system(s) for the storage and shipment of the drug substance	1	1,2,3	Notifiable Change
	1, 2	1	Annual Notification

A. Conditions:

1. Results demonstrate that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.

2. The change does not concern a sterile drug substance.

B. Supporting Data:

1. Information on the changed container closure system (e.g., description, specifications).

2. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug substance, or longer if less than three (3) time points are available, as well as commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

3. Demonstration of compatibility if the drug substance is a liquid

1.5 Stability:[14]

TABLE 13: STABILITY

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the re-test period (or shelf life) for the drug substance, involving:			
a. Extension	1,4,5,6	1-4,6	Notifiable Change
	1,2,3,5,6	1,2,5	
b. Reduction	1, 5	1-5	Notifiable Change
Addition of storage condition for the drug substance	1	1-5	Notifiable Change

A. 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. 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 production scale batches. If the proposed shelf life is beyond the available long term data, the extrapolation is in accordance with ICH's Q1E guideline.

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

6. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.

B. Supporting Data:

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

2. Proposed storage conditions and re-tests period (or shelf life, as appropriate).

3. Updated post-approval stability protocol and stability commitment.

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

5. Results of stability testing (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).

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 not generated on at least three (3) production scale batches) and a commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

TABLE 14: CHANGE IN THE LABELLED STORAGE CONDITIONS

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the labelled storage conditions for the drug substance, involving:			
addition of a cautionary statement	None	1	Notifiable Change
deletion of a cautionary statement	1	1	Notifiable Change
relaxation of a temperature criterion	None	1	Notifiable Change
tightening of a temperature criterion	1	1	

A. Conditions:

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

B. Supporting Data:

1. If applicable, stability testing results to support the change to the storage conditions.

TABLE 15: CHANGE TO THE POST APPROVAL STABILITY PROTOCOL

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change to the post-approval stability protocol or stability commitment	None	1-4	Notifiable Change

Conditions:

None

B. Supporting Data:

1. Proposed storage conditions and re-tests period (or shelf life, as appropriate).

2. Updated post-approval stability protocol and stability commitment.

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.

5. Drug Product:[15]

TABLE 16: DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Addition of a dosage form or strength	1	1-13	Supplement

Conditions:

1. None of the excipients are prohibited by the DCGI regulation.

B. Supporting Data:

1. Supporting clinical or comparative bioavailability data or a request for a waiver of in vivo studies, e.g,

2. Letters of Access (e.g., Drug Master Files (DMFs)), if new excipients are included.

3. Product Monograph (e.g., Title Page, Storage and Stability, Dosage Forms, Composition and Packaging, and Pharmaceutical Information section) and Inner and Outer Labels.

4. Confirmation that the information on the drug substance has not changed (e.g., cross reference(s) should be provided to the previously approved drug submission, including brand name of the drug product, manufacturer's/sponsor's name, submission type, control number, date approved) or revised information on the drug substance, if any of the attributes have changed.

5. Description and composition of the dosage form.

6. Discussion of the components of the drug product (e.g., choice of excipients, compatibility of drug substance and excipients), comparative in vitro testing for the approved and changed products, discussion of any in vitro and/or in vivo studies.

7. Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation.

8. Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the DCGI Regulations).

9. Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used), and Batch Analyses (certificate of analyses for one production scale batch).

10. Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.

11. Stability Summary and Conclusions, e.g., for a new dosage form and new strength: results of a minimum of six (6) months of accelerated and six (6) months of long term testing of the changed drug product (including a minimum of three time points).

12. Updated post-approval stability protocol and stability commitment to place the first production scale batch of each strength of the changed product into the long term stability programme (bracketing and matrixing could be applied, if scientifically justified).

13. Executed Production Documents for one batch of each new dosage form or strength, Master Production Documents for the new dosage form or strength.

TABLE 17: CHANGE IN THE DESCRIPTION OR COMPOSITION OF THE DRUG PRODUCT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the description or composition of the drug product, involving:			
a. addition of a dosage form or change in the formulation (e.g., change in the amount of excipient, new diluents for lyophilized product)	1	1-12	Supplement
b. addition of a new strength (e.g., 50 mg dose vs 100 mg dose)	None	2-12	Supplement
c. change in the concentration of the active ingredient (e.g., 20 unit/mL vs 20 unit/2 mL)	None	2-11, 13	Supplement
d. addition of a new presentation (e.g., addition of syringes to vials)	None	1-11, 13, 14	Notifiable Change

Conditions:

1. None of the excipients are prohibited by the Food and Drug Regulations.

B. Supporting Data:

1. Letters of Access (e.g., Drug Master Files (DMFs)), if new excipients are included.

2. Product Monograph (e.g., Title Page, Storage and Stability, Dosage Forms, Composition and Packaging, and Pharmaceutical Information section) and Inner and Outer Labels.

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 Control Number(s)) or revised information on the drug substance, if any of the attributes have changed.

4. Description and composition of the dosage form.

5. Discussion of the components of the drug product, as appropriate (e.g., choice of excipients, compatibility of drug substance and excipients).

6. Batch Formula, Description of Manufacturing Process and Process Controls, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation.

7. Control of Excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited by the Food and Drug Regulations).

8. Specification(s), Analytical Procedures (if new analytical methods are used), Validation of Analytical Procedures (if new analytical methods are used), and Batch Analyses (certificate of analyses for three (3) batches).

9. Discussion (including description, materials of construction, summary of specifications) on the container closure system, if any of the components have changed.

10. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug product, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

11. Executed Production Documents for one batch of each new dosage form or strength, Master Production Documents for the new dosage form or strength.

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

13. Supporting clinical data (usually PK/PD only) or a request for a waiver of in vivo studies.

14. For a new device (e.g., pre-filled syringes or pens), information to the Medical Device Bureau to qualify the proposed device.

Conditions:

1. The change does not concern the source of the adjuvant.

B. Supporting Data:

1. Product Monograph (title page, "Dosage Forms, Composition, and Packaging" section).

2. Inner and Outer Labels.

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 adjuvant.

4. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the changed adjuvant.

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

6. Description of the general properties, characteristic features and characterization data of the product.

7. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the drug product with the approved and changed adjuvant, as applicable.

8. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed adjuvant, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

9. Supporting non-clinical and clinical data.

TABLE 19: CHANGE IN DILUENT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in diluent, involving:			
a. replacement or addition of a source of a diluent	None	1-3	Notifiable Change
b. deletion of a diluent	None	None	Annual Notification

Conditions:

None

B. 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) batches of the approved and changed diluent.

3. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed diluent, or longer if less than three (3) time points are available, and updated stability of the product reconstituted with the new diluent.

TABLE 20: MANUFACTURE [16]

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Changes involving a drug product manufacturer/manufacturing facility:			
a. replacement or addition of a drug product manufacturing facility	None	1-11	Supplement
b. replacement of a formulation/filling suite	1, 2, 3, 6,7	1-11	Notifiable Change
c. addition of an identical formulation/filling suite	1	1-11	Notifiable Change
d. replacement of a secondary packaging/ labeling/storage and distribution facility	2-3	1, 2, 4	Annual Notification
e. deletion of a drug product manufacturing facility	None	None	Annual Notification
Scale-up of the manufacturing process at the formulation/filling stage	4-7	5-8,12	Notifiable Change

A. Conditions:

1. The formulation/filling facility is a DCGI approved facility.
2. No change in the composition, manufacturing process or drug product specifications.
3. No change in the container/closure system.
4. The scale-up uses the same approved equipments.
5. 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).
6. The change should not be a result of unexpected events arisen during manufacture or because of stability concerns.
7. The change does not affect the sterilization procedures of a sterile drug product.

B. Supporting Data:

1. GMP and Establishment License information.

2. Updated or new DMF (with a Letter of Access) or relevant drug product information.

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

7. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) batches of the approved and changed drug product.

8. Results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing of the changed drug product, or longer if less than three (3) time points are available as well as commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

9. Information on the changed production facility involved in manufacturing and testing of the drug product, including cleaning and shipping validation, as appropriate.

10. Information describing the change-over procedures for shared product contact equipments or the segregation procedures, as applicable.

11. Results of the environmental monitoring studies in classified areas.

12. Master Production Documents for each proposed strength, batch size, and manufacturing facility.

TABLE 21: CHANGE IN A FACILITY INVOLVED IN THE MANUFACTURE OF A DRUG PRODUCT

	Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
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	1, 2, 3	1-3	Notifiable Change
b.	conversion of production and related area(s) from campaign to concurrent for multiple product manufacturing areas	1	1-2	Notifiable Change

c. introduction of new product into an approved multiproduct formulation/ filling suite	2, 3	1-3	Annual Notification

Conditions:

1. The manufacturing process is a closed process.

2. The newly introduced product has the same prophylactic, therapeutic or related classification.

3. The maximum allowable carry-over is not affected by the introduction of the new product.

B. 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 equipments or the segregation procedures, as appropriate.

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

TABLE 22: CHANGE IN EQUIPMENT USED IN DRUG PRODUCT MANUFACTURING PROCESS

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in equipment used in drug product manufacturing process, such as:			
addition of new product-contact equipment used in a critical step (e.g., lyophilizer)	None	1-3	Notifiable Change
product-contact equipment change from dedicated to shared (e.g., formulation tank, lyophilizer)	None	1, 3, 4	Notifiable Change

Conditions:

None

B. Supporting Data:

1. Information on the in-process control testing.

2. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product, including technology transfer validation, equipment qualification, and 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.

TABLE 23: CHANGE IN THE CONTROLS APPLIED DURING THE MANUFACTURING PROCESS OR ON INTERMEDIATES

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates			
a. deletion of a test	None	1, 4-5	Notifiable Change
			Annual Notification
	5	1, 4-5	
b. replacement or addition of a test	None	1-5	Notifiable Change
			Annual Notification
	1-4	1-5	
c. relaxation of an acceptance criterion	None	1-5	Notifiable Change
d. tightening of an acceptance criterion	1-4	1-5	Annual Notification

A. 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 change does not affect the sterilization procedures of a sterile drug product.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.

B. Supporting Data:

1. Description of the changed process controls or acceptance criteria.
2. Description of the changed process controls or acceptance criteria of the critical steps and intermediates.
3. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product.
4. Description of the batches, certificates of analyses, and summary of results, in a tabular format, for at least one production scale batch.
5. Master Production Documents.

TABLE 24: CHANGE IN THE APPROVED PROTOCOL FOR PROCESS VALIDATION

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the approved protocol for process validation and/or evaluation studies	1	1	Notifiable Change
	1, 2	1	Annual Notification

A. Conditions:

1. The change is to a protocol approved by DCGI.
2. The change does not affect the sterilization procedures of a sterile drug product.

B. Supporting Data:

1. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product.

TABLE 25: CONTROL OF EXCIPIENTS

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the standard claimed for the excipients (e.g., from a House to pharmacopoeial standard)	None	1-4	Notifiable Change
	1, 2, 3	1-4	Annual Notification
Change in the specification for the excipient to comply with an updated pharmacopoeial monograph	1, 2	1-4	Annual Notification

A. Conditions:

1. The change is made exclusively to comply with the (same) pharmacopoeia.
2. No change to the specification for the functional properties of the excipient (e.g., particle size distribution) 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.

B. Supporting Data:

1. Updated excipient specifications.

2. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the 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).

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

TABLE 26: CHANGE IN THE SPECIFICATIONS FOR THE EXCIPIENT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for the excipient, involving:			
a. deletion of a test	None	1-4	Notifiable Change
	5	1-4	Annual Notification
b. replacement or addition of a test	None	1-4	Notifiable Change
	1-4,6	1-4	Annual Notification
c. relaxation of an acceptance criterion	None	1-4	Notifiable Change
	1,3-4,6	1-4	Annual Notification
d. tightening of an acceptance criterion	1-4, 6	1-4	Annual Notification

A. 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 deleted test has been demonstrated to be redundant with respect to the remaining tests.

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.

B. Supporting Data:

1. Updated excipient specifications.

2. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the 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).

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

TABLE 27: CHANGE IN THE SPECIFICATIONS FOR THE EXCIPIENT, INVOLVING THE ANALYTICAL PROCEDURES

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for the excipient, involving the analytical procedures:			
a. deletion of an analytical procedure	None	1, 3-4	Notifiable Change
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 analytical procedure	1-5	1-4	Annual Notification
d. a change from a House analytical procedure to a Pharmacopoeial analytical procedure	1-5	1-4	Annual Notification

A. 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. 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 sterility testing.

B. Supporting Data:

1. Updated excipient specifications.

2. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the 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).

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

TABLE 28: CHANGE IN THE SOURCE OF AN EXCIPIENT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the source of an excipient from a vegetable or synthetic source to a TSE risk (e.g., animal) source	None	2, 3	Supplement
Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source	1, 2	1, 3, 5, 7	Notifiable Change
Change in manufacture of a biological excipient	1-3	4-9	Notifiable Change
	2,3	2,3,5-7	Notifiable Change
	1-3	2,3,5-7	Annual Notification

Conditions:

1. No change in the specifications of the excipient or drug product.

2. The change does not concern a human plasma-derived excipient.

3. Properties of changed excipients are same as approved excipient.

B. 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.

5. Description of the batches, certificates of analyses, and summary of results, in a comparative tabular format, for at least three (3) production scale batches of the changed excipient and of the drug product with the changed excipient.

6. Results from the stability testing of the changed excipient.

7. Results from the stability testing of the drug product with the changed excipient.

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

9. Supporting comparative clinical data (usually PK/PD only).

TABLE 29: CONTROL OF DRUG PRODUCT [17]

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the standard claimed for the drug product (e.g., from a Professed to pharmacopoeial standard)	None	1-6	Notifiable Change
	1, 2, 3	1-6	Annual Notification
Change in the specification for the drug product to comply with an updated pharmacopoeial monograph	1, 2	2-6	Annual Notification

A. Conditions:

1. The change is made exclusively to comply with the (same) 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.

B. Supporting Data:

1. Product Monograph (e.g., Title Page, Composition and Packaging (Part I), and Pharmaceutical Information (Part II) section) and Inner and Outer Labels.

2. Updated, signed and dated, changed drug product specifications.

3. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the 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.

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).

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

TABLE 30: CHANGE IN THE SPECIFICATIONS FOR THE DRUG PRODUCT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for the drug product, 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	2,7,9,10	Notifiable Change
c. replacement or addition of a test	None	2-5,7,9,10	Notifiable Change
	1-6	2-5,7,9,10	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	6,7,11	Notifiable Change
e. relaxation of an acceptance criterion	None	2,5,7,9,10	Notifiable Change
	1, 3-6	2,5,7,9,10	Annual Notification
f. tightening of an acceptance criterion	1-2	2,5,7,9,10	Annual Notification

A. 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.

B. Supporting Data:

1. Process validation and/or evaluation studies or the proposed validation protocol of the changed drug product.

2. Updated, signed and dated, changed drug product specifications.

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

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

5. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the 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.

8. Description of the batches, certificates of analyses, and summary of results, of a sufficient number of batches to support the process parametric release.

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).

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).

TABLE 31: CHANGE IN THE SPECIFICATIONS FOR THE DRUG PRODUCT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for the drug product, involving:			
a. deletion of an analytical procedure	None	1,3-5	Notifiable Change
b. replacement or addition of an analytical procedure	None	1-5	Notifiable Change
c. minor changes to an approved analytical procedure	1-4	1-5	Annual Notification
d. a change from a house analytical procedure to a Pharmacopoeial analytical procedure	1-4	1-5	Annual Notification

A. 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.

B. Supporting Data:

1. Updated, signed and dated, changed drug product specifications.

2. Where a House analytical procedure is used and a Pharmacopoeial standard is claimed, results of an equivalency study between the House and compendial methods.

3. 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.

4. Justification of the changed drug product specifications (e.g., demonstration of the suitability of the monograph to control the drug product, including degradation products).

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

TABLE 32: CHANGES AFFECTING THE QUALITY CONTROL TESTING

	Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Changes affecting the quality control (QC) testing:				
a.	transfer of the QC testing responsibilities for a non-pharmacopoeial assay (in-house) to a new company	None	1, 2	Notifiable Change
b.	transfer of the QC testing responsibilities for a pharmacopoeial assay (in-house) to a new company	None	1, 2	Annual Notification
c.	transfer of the QC testing responsibilities for a pharmacopoeial or a non-pharmacopoeial assay to a different facility (same company)	1	1, 2	Annual Notification
d.	introduction of additional laboratory facility in a facility to perform drug product testing	None	2	Annual Notification

A. Conditions:

1. The new QC testing site/facility is under the same QA/QC oversight.

B. Supporting Data:

1. Updated or new DMF (with a Letter of Access provided in Module 1) or relevant drug product information.

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

TABLE 33: REFERENCE STANDARDS OR MATERIALS

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Qualification of a reference standard	None	1	Notifiable Change
Subsequent qualification of a reference standard	2, 3	1	Annual Notification
Update the reference standards from pharmacopoeial to House	1	1	Notifiable Change
Update the reference standards from House to pharmacopoeial	2, 3	1	Annual Notification

A. Conditions:

1. The House reference standard is validated against an official (e.g., pharmacopoeial) 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 reference standard is not for a bacterial or a viral vaccine.

B. Supporting Data:

1. Information demonstrating qualification of the changed reference standards or materials (e.g.,

source, characterization, certificate of analysis).

TABLE 34: CONTAINER CLOSURE SYSTEM

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Modification of a container closure system (e.g., new coating, adhesive, stopper)	None	1-7	Notifiable Change
	1-3	1-7	Annual Notification
Change from approved single-dose container to multi-dose container	None	1-7	Notifiable Change
Deletion of a container closure system	None	1, 3	Annual Notification

A. Conditions:

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

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

3. The change is made only to improve quality of the container (e.g., increase thickness of the glass vial).

B. Supporting Data:

1. Product Monograph (e.g., Title Page, Storage and Stability, Dosage Forms, Composition and Packaging) and Inner and Outer Labels.

2. For sterile products, process validation and/or evaluation studies.

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

4. Stability Summary and Conclusions, e.g.,

✓ For a moderate change to the container closure system (e.g., change in fill weight / fill volume): 3 months long term/3 months accelerated data and, where applicable, results of photo stability studies.

✓ For a minor change to the container closure system: stability data at the time of filing would not be necessary (see below).

5. Updated post-approval stability protocol and stability commitment to place the first production scale batch of each strength of the changed product into the long term stability programme (bracketing and matrixing could be applied, 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.

TABLE 35: CHANGE IN THE SUPPLIER FOR A CONTAINER CLOSURE COMPONENT

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

A. Conditions:

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

2. The change does not concern a sterile container closure component.

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

TABLE 36: CHANGE IN THE SPECIFICATIONS FOR A PRIMARY CONTAINER CLOSURE COMPONENT

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

A. 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.

B. Supporting Data:

1. Updated changed specifications, including justification.

TABLE 37: CHANGE IN THE SPECIFICATIONS FOR A PRIMARY CONTAINER CLOSURE COMPONENT, INVOLVING ANALYTICAL PROCEDURES

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the specifications for a primary container closure component, involving analytical procedures:			
a. deletion, replacement or addition	3	1, 2	Notifiable Change
b. minor changes	1-5	1, 2	Annual Notification

A. Conditions:

1. No change in the approved acceptance criteria.

2. The analytical procedure is of the same type.

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 sterility testing.

B. Supporting Data:

1. Updated changed specifications, including justification.

2. Description of the analytical procedure and, if applicable, validation data.

TABLE 38: CHANGE IN THE RE-TEST PERIOD FOR THE DRUG PRODUCT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the re-test period (or shelf life) for the drug product, involving:			
a. Extension	1,4,5,6	1-4,6	Notifiable Change
	1,2,3,5,6	1,2,5	Annual Notification
b. Reduction	1, 5	1-5	Notifiable Change
Addition of storage condition for the drug product	1	1-5	Notifiable Change

A. 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. Full long term stability data are not available covering the changed retest period (or shelf life) or are not based on stability data generated on at least three production scale batches. If the proposed re-test period (or shelf life) is beyond the available long term data, the extrapolation is in accordance with ICH's Q1E guideline.

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

6. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.

B. Supporting Data:

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

2. Proposed storage conditions and re-test period (or shelf life, as appropriate).

3. Updated post-approval stability protocol and stability commitment.

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

5. Results of stability testing (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).

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), and a commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

TABLE 39: CHANGE IN THE LABELED STORAGE CONDITIONS FOR THE DRUG PRODUCT OR THE DILUTED OR RECONSTITUTED PRODUCT

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the labeled storage conditions for the drug product or the diluted or reconstituted product, involving:			
1. addition of a cautionary statement	None	1	Notifiable Change
2. deletion of a cautionary statement	1	1	Notifiable Change
3. relaxation of a temperature criterion	None	1	Notifiable Change
4. tightening of a temperature criterion	1	1	Annual Notification

A. Conditions:

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

B. Supporting Data:

1. If applicable, stability testing results to support the change to the storage conditions.

TABLE 40: CHANGE TO THE POST-APPROVAL STABILITY PROTOCOL

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change to the post-approval stability protocol or stability commitment	None	1-4	Notifiable Change

A. Conditions:

None

B. Supporting Data:

1. Proposed storage conditions and shelf life.

2. Updated post-approval stability protocol and stability commitment.

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.

TABLE 41: EFFICACY

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the Efficacy parameter:			
a. New indication	1	1-4	Supplement

A. Conditions:

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

B. Supporting Data:

1. Published Phase-I, Phase-II and Phase-III data along with preclinical data.

2. Copy of EMEA approval with new indication or any other regulatory certificate issued by NRA or country of origin with new indication.

3. Copy of approved PI with new indication.

4. Published data or relevant literature on new indication.

TABLE 42: CHANGE IN THE ROUTE OF ADMINISTRATION

Description of Change	Conditions to be Fulfilled	Supporting Data	Reporting Category
Change in the route of administration:			
a. New route of administration	1	1-4	Supplement

A. Conditions:

1. No change in strength, dosage form and indication.

B. Supporting Data:

1. Published Phase-I, Phase-II and Phase-III data along with preclinical data.

2. Copy of EMEA approval with new indication or any other regulatory certificate issued by NRA or country of origin with new route of administration.

3. Copy of approved PI with new route of administration.

4. Published data or relevant literature on new route of administration.

CONCLUSION: In the process of developing the new product, the batch size used in earliest human studies is small. The sizes of the batches is gradually increased which is known as scale up and the changes made after approval in composition, manufacturing process, manufacturing equipment, and change of site are known as post approval changes.

After the approval of NDA or ANDA, the applicant may make post approval changes, provided the changes are reported to the FDA under the appropriate categories. In the present scenario, the post approval change application filing has been done under second category i.e., supplemental change. The applicant needs to get approval from the drug regulatory authority for the change being done within 15 days of its filing the application.

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