Central Administration for Pharmaceutical Products
General Administration of Human Pharmaceuticals Registration
Administration of Variations of Human Pharmaceuticals Registration

Guideline

GUIDELINES ON
Human Pharmaceuticals Variations
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1 Contents

2 Introduction

The Variation guidelines have been completely updated and expanded, bringing them into line with the principles of the international guidelines.

The Guidelines retain the basic structure and function of the previous variation guidelines, and have been expanded to include the classification of additional post-approval changes and to establish the level of risk inherent to each change.

The guidelines help the reader to understand the considerations necessary to assess the risk of each change, determine the documentation required to support the change and assist in understanding the possible consequences of the listed changes, and may be useful as a risk management tool to promote or enhance best practices within all EDA divisions.

It should be noted that classification of variations may have been changed from the previous guideline's version. In addition, new categories that previously required acceptance of the change prior to implementation, the applicant can now implement the change immediately upon notification.

2.1 Background

This guidance document is technically and structurally inspired by Human Variation Administration in EDA. It is based on the details of various categories of variations for human medicinal products. Mainly, intended to provide supportive information on how to apply an application to implement a change to a product.

This guidance supersedes the guidance published in 2024.

Technical requirements for the different types of variations are set out in these guidelines in order to facilitate the submission of appropriate documentation by applicants and their assessment by Human Variation Administration in EDA and to ensure that variations to the medicinal product do not result in health concerns.

2.2 Objectives

These guidelines are intended to assist applicants with:

1. Classification of changes affects the quality of the active pharmaceutical ingredients (S-Part).
2. Classification of changes affects the finished pharmaceutical products (P-Part).

2.3 Scope

This guidance document is applicable to Human Pharmaceuticals Variations.

2.4 Definitions

Variations: Administrative &/or quality post-authorization changes that take place on the post marketed finished pharmaceutical product or active pharmaceutical ingredients.

Reliance: The act whereby EDA leveraging the assessments and evaluations conducted by trusted other regulatory agencies (SRAs) instead of duplicating the entire evaluation process.

Reliance Evaluation Route is a process where the EDA leveraging the assessments and evaluations conducted by trusted regulatory agencies **Stringent Regulatory Authority** (SRAs) published in EDA website instead of duplicating the entire evaluation process and the variation administration will assess variations that were already approved by other reference countries in accordance with the Egyptian reliance guidelines and state the approval.

Stringent Regulatory Authority (SRA):
A regulatory authority which is:
(a) a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency;
(b) or an ICH observer, being the European Free Trade Association, as Represented by Swiss medic, and Health Canada;
(c) Or a regulatory authority associated with an ICH member through a legally binding, Mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway.

Inquiry Reply Letter: Letter stating that EDA is notified that the applicant will carry out a new variation.

Evaluated Inquiry Reply Letter: Letter stating that EDA is notified that the applicant will carry out a new variation and the required studies to be fulfilled in order to be able to submit the Post Marketing Variation Approval.

Post Marketing Variation Approval: Approval stating that EDA approved the variation submitted by the applicant after submitting all required studies and/or supporting documentation along with its corresponding approvals issued by relevant EDA administrations that ensure the quality, safety & efficacy of the product.

Finished Pharmaceutical Product (FINISHED PRODUCT): The dosage form in the final immediate packaging intended for marketing.

Active Pharmaceutical Ingredient (API): Any active substance or mixture of active substances having pharmacological activity intended to be used in manufacture of Finished Product.

Excipient: Any substance or compound other than API and packaging materials that intended to be used in manufacture of Finished Product.

Container closure system: The sum of packaging components that together contain and protect pharmaceutical product, including primary and secondary packaging components.

Production Batch: A batch of Finished Product manufactured at production scale by using production equipment in a production facility.

Product Competitor: Product with the same APIs, strength and dosage form registered by any other Stringent Regulatory Authority (SRAs).

Marketing Authorization: is the Pharmaceutical Product Registration License.

EDA's approved Reference Countries List: List of reference Countries according to the most updated decisions of the technical committee of drug control.

Original Batch Size: A batch size foreseen when the marketing authorization was granted subsequent addition/ change of a manufacturing site.

2.5 Procedures

2.5.1 Overview on handling variation requests:

The definitions outlined in the following procedures are intended to provide guidance with respect to the classification of quality-related changes. Specific examples of changes are provided in these guidelines. However, it should be noted that a change not covered by these guidelines, should be evaluated through a risk-based assessment.

It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and efficacy of the product. In addition, the applicant is responsible to notify the Variation Administration in EDA in case of any unfavorable out of specification that has negative impact on the quality of the finished pharmaceutical products.

The applicant will apply the variation request according to the submission guidance. The guidance will be updated regularly. The guidance contains sections on which applicant will fulfill according to the type of variation requested. The variation request should be arranged according to the sections listed in the submission guidance.

- In case of Variation request submitted by the applicant for any type of variation change where CADC COA or its composition are not available or couldn't be submitted from CADC, Batch Analysis will be required regardless of the categorization of the procedure type.

- For All variation approvals with No Requirements a grace period of a maximum one-year for implementation of variation will be given to the applicant after issuing the post marketing variation approval.

- For All variations when accelerated stability study is required, the applicant should place the first production-scale batch of the Finished Product produced with the new variation into the long-term stability program. A commitment is given that these long-term stability study will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
- An inspection Report (with supportive documents) from the Central Administration for Inspection on Pharmaceutical Institutions is required for all variation requests submitted as clarification that will undergo a full evaluation route, otherwise justify.

- For All variations (rather than Type II variations) that require Batch Analysis, the following procedure should be followed based on type of variation:
  -If the variation result in change of Finished Product Specification, A batch analysis at CADC labs (At administration of evaluation and approval) is required.
  -If the variation has no impact on Finished Product Specification, A batch analysis at CADC labs (At administration of post approval control) is required.

2.5.2 Categorization of submission of Variation Requests:

The Company submit request according to the following:

- **Variation Inquiry:**
  The applicant submits a request to notify EDA that it will carry out a new variation; the applicant acknowledges full responsibility for conducting all required supporting studies concerning the variation according to last updated version of guidelines.

  EDA issue an Inquiry Reply Letter stating that EDA is notified that the applicant will carry out a new variation.

  EDA maintains the right to fully assess these studies when they are subsequently submitted as part of the Post-Marketing Variation Approval process and may require additional studies or justifications as necessary.

- **Variation Inquiry with Assessment:**
  The applicant submits a request to notify EDA that it will carry out a new variation, and is concurrently requesting which studies should be fulfilled for this variation.

  EDA issue an evaluated inquiry reply letter stating that EDA is notified that the applicant will carry out a new variation and the required studies to be fulfilled in order to be able to submit the Post Marketing Variation Approval.

- **Post-Marketing Variation Approval:**

  The applicant submits a request to the EDA for Post-Marketing Variation Approval. This submission includes all required studies and/or supporting documentation, along with their corresponding approvals issued by the relevant EDA administrations.

  The Variation Administration will then review the complete package to issue the Post Marketing Variation Approval for the requested variation.

2.5.3 Mode of submission:

- **Single PAC:**

  Each distinct Inquiry/post marketing variation approval change necessitates a single submission.

- **Grouped PAC:**

  Grouping of variations is acceptable under the following circumstances (for example but not limited to): When variations are consequential to each other, e.g. change of coloring agents that requires a new physical character change.

For the purposes of classification, an application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both PAC-B and PAC-II will be classified as PAC-II variation.

2.5.4 Variation Evaluation Routes

2.5.4.1 Full Evaluation Route:

Full evaluation will apply to Inquiries &/or Post Marketing variation Approvals subject to EDA full review and assessment.

For Further consultation, the variation request may be subjected to Variation Evaluation committee (VEC) or Technical Committee for Drug Control (TCDC) or both.
By the end of the evaluation period, the variation administration will determine its decision on request and inform the applicant about the acceptance or rejection of variation.

Eligibility Criteria to Full Evaluation Route:

1- Local / Bulk / Under License Pharmaceutical Products.

2-Finished Pharmaceutical Products imported from non-Reference country and not marketed in a reference country:

The applicant will submit the variation request which includes:

- Valid Certificate of Pharmaceutical Product of country of origin
- The approval from country of origin.
- Verification of Sameness letter
- The studies conducted in country of origin (to be evaluated by EDA administrations).

The Variation administration will issue a Post Marketing Variation Approval for the Variation request after assessment of studies by other relevant EDA administrations.

2.5.4.2 Reliance Evaluation Route:

The variation administration will review variations that were already approved by other reference countries in accordance with the Egyptian reliance guidelines.

Reliance on other SRAs involves leveraging the assessments and evaluations conducted by trusted regulatory agencies instead of duplicating the entire evaluation process. However, it does not imply a complete transfer of EDA regulatory responsibility. EDA retains the final decision-making authority regarding the approval of pharmaceutical products within its jurisdiction.

Eligibility Criteria to Reliance Evaluation Route:

1- For Imported Finished Product That has been Approved by at least one reference regulatory authority (SRA) or WHO prequalification

An imported finished product must have been approved by at least one Stringent Regulatory Authority (SRA) that published on EDA's website. or have WHO prequalification.

The applicant will Submit the variation request which includes:

1.Valid Certificate of Pharmaceutical Product.

2. Updated relevant sections of CTD dossier. (However, The non-sequential order of versions of the Common Technical Document (CTD) makes the reliance evaluation unreliable as the company must submit the updated version contains all sequential updates)

3. Verification of Sameness*.

4. Unredacted Assessment report and/or Q&A (otherwise justified).

5. Proof of Approval from at least one reference regulatory authority.

6. Application submitted to the SRA (A linking between the application and the approval from the Reference Authority must be declared (unless otherwise justified)

*__Sameness:__ to ensure identical products (or that where differences exist, these are clearly stated) between the NRA and the reference NRAs, regardless of the approaches or assessment activities conducted by the NRA. The same pharmaceutical product is defined as characterized by:

- the same qualitative and quantitative formulation.
- the same manufacturing site(s) for the drug substance and finished product, including specific block(s)/unit(s), manufacturing chain, processes, control of materials and finished product.
- the same specifications for the excipient(s), drug substance and finished product.
- the same essential elements of product information for pharmaceutical products.

The applicant should therefore confirm and attest that the information (variation dossier) submitted to the EDA is the same as that submitted to reference SRA for the variation (where applicable) along with a copy of the reference SRA decision or other document confirming the final decision of the reference SRA.

When submitting proof of the SRA final decision, EDA acknowledges the different evaluation criteria, variation categorization and approval process between each individual SRA as well as the difference between the SRA and the EDA procedures. Examples but not limited to the below difference between the EMA and FDA evaluation procedures as follows:

	Type of change	Implementation Criteria according to other SRAs	Approval Document
EMA	Type II	Change can only be implemented after approval	Approval letter Assessment report (if available)

	Type IB	If within 30 days following the acknowledgement of receipt of a valid notification, EMA has not sent the applicant an unfavorable opinion, the notification shall be deemed accepted	IB notification including approval information Assessment report (if available)
	Type IA/ Type IAIN	Change can be implemented up to 1 year before submission	Acknowledgement letter
FDA	PAS	After approval	Approval letter
	CBE-30	Change can be implemented 30 days after submission	Approval letter
	CBE-0	Change can be implemented immediately after submission	Approval letter
	Annual report	Up to 1 year before submission	NA

It should remain obvious that changes not evaluated by other SRAs (example but not limited to variations related to climatic zone differences) are still subject to EDA assessment and evaluation.

2.5.5 Categorization of Variation Requests:

These guidelines cover the following categories of variations:

PAC-N:

Variations that could have minimal or no adverse effects on the overall safety, efficacy and quality of the Finished Product.

It should be highlighted that PAC-N may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

PAC-A:

Variations that could have minimal or no adverse effects on the overall safety, efficacy and quality of the Finished Product and must be submitted annually. the applicant may submit them collectively within 12 months from the date of implementation of the changes.

It should be highlighted that PAC-A may be rejected in specific circumstances with the consequence that the applicant must cease to apply the already implemented variation.

PAC-B:

Variations that may have minor effects on the overall safety, efficacy and quality of the Finished Product.

PAC-II:

Variations that could have major effects on the overall safety, efficacy and quality of the Finished Product.

Where necessary, the EDA will update the marketing authorization within 15 working days after complete reviewing of package by sending an acceptance email for the variation request stating that the marketing authorization is under update and will be issued within 15 working days.

3 General Considerations:

3.1 Administrative Changes

3.1.1. Change in Name / Address of Finished Product LH/MAH	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
	1	1,2	PAC-N
Conditions to be fulfilled: 1. Product LH/MAH must remain the same legal entity.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Finished Product Information with the new name/Address of the LH/MAH (i.e. Inner leaflet and/or mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.1.2. Change in name of the active substance or of an excipient	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
	1	1,2	PAC-N
Conditions to be fulfilled 1. The active substance/excipient must remain the same.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Product Information (i.e. Inner leaflet and/or mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.1.3. Change in the name and/or address	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Manufacturer of the active substance (API)	1	1	PAC-N
b) Manufacturer of starting material, reagent or intermediate used in the manufacture of the active substance.	1	1	PAC-A
Conditions to be fulfilled: 1. The physical location of the manufacturing site and all manufacturing operations must remain the same.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change.			

3.1.4. Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or storage site of finished product.	**Conditions to be fulfilled**	**Requirements to be fulfilled**	**Procedure type**
a) Active Substances	1	1	PAC-A
b) Finished Product. (including manufacturer/ packager/storage site, etc.)	1	1,2	PAC-A
Conditions to be fulfilled: 1. There should at least remain one site/manufacturer, as previously authorized, performing the same			

function as the one(s) concerned by the deletion.
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Finished Product information if reflected (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.

3.1.5. Change in Name / Address of Manufacturing sites (including bulk manufacturer, packager, quality control testing & batch releaser)	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
	1	1,2	PAC-N
Conditions to be fulfilled: 1. The physical location of the manufacturing site and all manufacturing operations must remain the same.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Finished Product information with the new name/Address of Manufacturing sites (i.e. Inner leaflet and/or mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.1.6. Change in Applicant for Registration	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
For Imported Finished Products	1	1	PAC-N
Conditions to be fulfilled: 1. The applicant shall be authorized for registration.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change.			

3.1.7. Modification of Registration license (including but not limited to trade name, price, storage site)	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
	1	NA	PAC-A

Conditions to be fulfilled: 1. Approval of EDA relevant department(s) on related modification.

3.1.8. Finished Product LH/ MAH Transfer	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
License Holder:			
a) For local Finished Product	1,2	1,2	PAC-N
b) For Bulk or Under license Finished Product	1	1,2	PAC-N
c) For Imported Finished Product	1	1,2	PAC-N
Marketing Authorization Holder:			
a) For Bulk or Under license Finished Product	1	1,2	PAC-N
b) For Imported Finished Product	1	1,2	PAC-N
Conditions to be fulfilled: 1. The new Finished Product LH/MAH is a different legal entity. 2. A Pharmaceutical Finished Product shall undergo a LH transfer for all its strengths			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2.Amendment of Finished Product information with the new LH/MAH (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.1.9. Addition/Change of Finished Product MAH in Egypt	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
For Imported /Bulk & Under License Finished Products	1	1,2	PAC-N
Conditions to be fulfilled: 1. Finished Product MAH **in Egypt** should comply with all Finished Product specifications, composition and all manufacturing operations as mentioned in the Finished Product CPP from NRA in the country of origin.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Finished Product information if reflected (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.1.10. Addition/Change of Marketing Rights Holder of Finished Product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
For Local License Finished Products	1	1,2	PAC-N
Conditions to be fulfilled: 1. The product License Holder must remain the same. 2. Marketing Rights Holder and License Holder should be different Legal entities.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Finished Product information if reflected (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.1.11.Change/addition of solvent/diluent manufacturer supplied for a Finished Product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Lidocaine or other solvent	1,2,3,4	1,2,3	PAC-B
b) Water for injection	1,2,3	1,2	PAC-N
Conditions to be fulfilled: 1. Solvent from new supplier must be registered. 2. Shelf life of solvent from new supplier must comply with shelf life of the Finished Product. 3. Pack of solvent from new supplier must comply with previously approved pack. ٤. Composition and Specification of solvent from new supplier must comply with previously approved .			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Finished Product information if reflected (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions. 3. In use stability study as per ICH Q1 guidelines, otherwise justify.			

3.2 Quality Changes:

3.2.1 Active substance

3.2.1.1. Change in the manufacturer	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
A) Starting material/reagent/intermediate used in the manufacturing process of the active substance.			
1- Addition or Replacement of a new manufacturer.	1,2,3	1,2	PAC-N
B) The Active Substance.			
1- Addition or Replacement of a new manufacturer.			PAC-II
2- Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	1,2,3	1	PAC-A
3- Addition or replacement of a manufacturing site responsible for micronisation of the active substance	2	1,2	PAC-A
Conditions to be fulfilled: 1. No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. 2. The specifications of the active substance are unchanged. 3.The particle size specification of the active substance and the corresponding analytical method remain the same.			
Requirements to be fulfilled: 1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change. 2. Batch analysis data of at least two batches of the active substance from API supplier, manufactured according to the currently approved and proposed process.			

3.2.1.2. Changes in the manufacturing process of the active substance	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Minor change in the manufacturing process of the active substance	1, 2, 3, 4, 5	1, 2	PAC-A
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product			PAC-II
c) Minor change to the restricted part of an Active Substance Master File		1, 2	PAC-B
d) Deletion of a manufacturing process	6,7	1	PAC-A
Conditions to be fulfilled:			

1. No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. 2. The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. 3. The specifications of the active substance or intermediates are unchanged. 4. The change is fully described in the open part of an Active Substance Master File, if applicable. 5. The change does not refer to the restricted part of an Active Substance Master File. 6. The deletion shouldn't be due to critical deficiencies concerning manufacturing. 7. There should at least remain one manufacturing process as previously authorized.
Requirements to be fulfilled: 1-Amendment of the relevant section(s) of the dossier concerning the change. 2. Batch analysis data of at least two batches of the active substance from API supplier, manufactured according to the currently approved and proposed process.

3.2.1.3. Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) An increase to the originally approved batch size	1,2,4,5	1,2	PAC-A
b) Downscaling of the approved batch size	1,2,3,4	1,2	PAC-A
Conditions to be fulfilled: 1. Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment. 2. The change does not adversely affect the reproducibility of the process. 3. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 4. The specifications of the active substance/intermediates remain the same. 5. The active substance is not sterile.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Batch analysis data of at least two batches of the active substance or intermediate as appropriate from API supplier, manufactured to both the currently approved and the proposed sizes.			

3.2.1.4. Change to in-process tests or limits applied during the manufacture of the active substance	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Minor change of in-process control limits	1, 2, 3, 4	1	PAC-A
b) Addition of new in-process control and limits with its corresponding analytical procedure	1, 2	1, 2	PAC-A
c) Deletion of a non-significant or obsolete in-process control	1, 2, 5	1, 2	PAC-A
d) Widening of the approved in-process control limits, which may have a significant effect on the overall quality of the active substance			PAC-II
e) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance			PAC-II
f) Replacement of an in-process control with its corresponding analytical procedure		1, 2	PAC-B

Conditions to be fulfilled:

1. The change is not a consequence of any commitment from previous assessments to review specification limits.
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. The in-process control does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing or water content.

Requirements to be fulfilled:

1. Amendment of the relevant section(s) of the dossier concerning the change.
2. Batch analysis data of at least two batches of the active substance for all specification parameters from API supplier.

3.2.1.5. Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change within the specification acceptance criteria	1, 2, 3, 4	1	PAC-A
b) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5	1, 2, 3, 4	PAC-A
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2, 6	1, 2	PAC-A
d) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			PAC-II
e) Change outside the approved specifications limits range for the active substance			PAC-II
f) Change outside the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product			PAC-II
g) Addition or replacement of a specification parameter with its corresponding test method as a result of a safety or quality issue		1, 2, 3, 4	PAC-B

Conditions to be fulfilled:

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a PAC-II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. For any material, the change does not concern a genotoxic impurity.
6. The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.

Requirements to be fulfilled:

1. Amendment of the relevant section(s) of the dossier concerning the change.
2. Details of any new analytical method and validation data, where relevant.

3. Batch analysis data of at least two batches of the active substance for all specification parameters from API supplier. 4. If the quality characteristics of the active substance are changed in a way that may impact the dissolution profile of the finished product, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification.

3.2.1.6 Change in analytical procedure for active substance	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
Change to an analytical procedure (including replacement or addition) for an active substance.		1,2	PAC-B
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Comparative validation results or if justified comparative analysis results showing that the current analytical procedure and the proposed one are equivalent.			

3.2.1.7. Change in immediate packaging of the active substance	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change in immediate packaging of non-liquid active substance	1, 2	1,2	PAC-A
b) Change in immediate packaging of sterile liquid active substance			PAC-II
c) Change in immediate packaging of nonsterile liquid active substance		1,2	PAC-B
Conditions to be fulfilled: 1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties. 2. The active substance is not a sterile active substance.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of long-term testing of the Active Substance, A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the			

Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3.2.1.8. Change in the specification parameters and/or limits of the immediate packaging of the active substance	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change of specification acceptance criteria	1, 2, 3, 4	1	PAC-A
b) Addition of a new specification parameter to the specification with its corresponding test method	1, 2	1	PAC-A
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2	1	PAC-A
d) Replacement of a specification parameter as a result of a safety or quality issue		1	PAC-B
Conditions to be fulfilled: 1. The change is not a consequence of any commitment from previous assessments to review specification limits unless it has been previously assessed and agreed as part of a follow-up measure. 2. The change does not result from unexpected events arising during manufacture of the packaging material c during storage of the active substance. 3. Any change should be within the range of currently approved limits. 4. The analytical procedure remains the same, or changes in the analytical procedure are minor.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change.			

3.2.1.9. Change in analytical procedure for the immediate packaging of the active substance	**Conditions to be fulfilled**	**Requirements to be fulfilled**	**Procedure type**
a) Minor changes to an approved analytical procedure	1,2	1,2	PAC-A
b) Other changes to an analytical procedure (including replacement or addition)	1	1,2	PAC-A
c) Deletion of an analytical procedure if an alternative analytical procedure is already authorized	3	1	PAC-A
<u>Conditions:</u> 1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.			

2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). 3.There is still an analytical procedure registered for the specification parameter.
Requirements: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.

3.2.1.10. Change in the retest period/storage period or storage conditions of the active substance.	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Retest period/storage period			
1. Reduction	1,3	1	PAC-A
2-Extension or introduction of a retest period / storage period supported by real time data	2,3	1	PAC-B
b) Storage conditions			
1. Change to more restrictive storage conditions of the active substance	1,2,3	1	PAC-A
2. Change in storage conditions of the active substance	1,2,3	1	PAC-B
c) Change to an approved stability protocol	1,2	1	PAC-A
Conditions to be fulfilled: 1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing. 3. Result of stability study from API manufacturer(s) supported by real time data.			
Requirements to be fulfilled: 1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change.			

3.2.1.11. Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability for an active substance.	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
1. New certificate from an approved manufacturer	1, 2	1	PAC-A
2. Updated certificate from an already approved manufacturer	1, 2	1	PAC-N
3. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free	1, 2	1	PAC-B
4. Deletion of certificate(s) of suitability (CEP)		1	PAC-A
Conditions to be fulfilled: 1. New/ Updated CEP. 2. No Adverse change in qualitative and quantitative impurity profile or in physico-chemical properties.			
Requirements to be fulfilled: 1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change.			

3.2.2 Finished Product:

3.2.2.1. Change or addition of imprints, bossing (embossing/debossing) or other markings including replacement, or addition of inks used for product marking	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change in imprints, embossing or other markings	1,2,5	1,3	PAC-N
b) Deletion of a score line	2,4	1,3	PAC-N
c) Addition of a score line	1,2,3	1,2,3	PAC-B
	1,2,3,4	1,3	PAC-B
Conditions to be fulfilled 1. The change does not affect the stability or performance characteristics (e.g. release rate) of the Finished Product.			

2. Finished Product release and end shelf-life specifications have not been changed (except for appearance). 3. Addition of a score line from a product is consistent with a similar change in a product from any reference country. 4. The scoring is not intended to divide the Finished Product into equal doses. 5. Any product markings used to differentiate strengths should not be completely deleted.
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Batch Analysis for first production batch at CADC labs. 3. Amendment of Product Information (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.

3.2.2.2. Change in the shape or dimensions of the pharmaceutical form	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Immediate release tablets, capsules, suppositories and pessaries.	1,2,3	1,3	PAC-N
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses.		1,2,3	PAC- B
Conditions to be fulfilled 1. Release & End of shelf-life specifications of the product have not been changed except for dimensions. 2. The qualitative or quantitative composition and mean mass remain unchanged. 3. The change does not relate to a scored tablet that is intended to be divided into equal doses.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Comparative in-vitro dissolution study at most suitable medium on first pilot or production batch of Finished Pharmaceutical product manufactured from the new shape/dimension against the old batch of product with old shape and dimension. (Or may be changed to 3 different PH media in addition to the most suitable medium or Bioequivalence study according to category of API & its BCs Class), otherwise justify. 3. Amendment of Product Information (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.2.2.3. Changes in the composition (excipients) of the Finished Pharmaceutical product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Changes in components of the flavoring or coloring system			
1. Addition, deletion or replacement	1,2,3,4,5,6	1,2,3	PAC-B
2. Increase or reduction	1,2,3	1,3	PAC-B
b) other excipients			
1. Any minor adjustment of the quantitative composition of the Finished Pharmaceutical product with respect to excipients (according to Annex III)	1,2,5,6	1,3	PAC-B
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product			PAC-II
3. Any new excipient that includes the use of materials of animal origin for which assessment is required of viral safety data or TSE risk			PAC-II
4. Replacement of excipient(s) with a comparable excipient(s) with the same functional characteristics.		1,2,3,4	PAC-B

Conditions to be fulfilled

1. No change in functional characteristics of the pharmaceutical form, e.g. disintegration time, dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the Finished Pharmaceutical product formulation.
3. The Finished Pharmaceutical product specification has only been updated in respect of appearance/odor/taste and if relevant, deletion of an identification test.
4. Any new component does not include the use of materials of animal origin for which assessment is required of viral safety data or compliance with the current Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human Medicinal Products.
5. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for pediatric formulations.

6. The change is not the result of stability issues and/or should not result in potential safety concerns, i.e. differentiation between strengths.
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Batch Analysis for first production batch at CADC labs. 3. Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated and 3 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). 4.Comparative in-vitro dissolution study at most suitable medium on first pilot or production batch of Finished Pharmaceutical product manufactured with new composition against the innovator product. (Or may be changed to 3 different PH media in addition to the most suitable medium or Bioequivalence study according to category of API & its BCs Class

3.2.2.4 Change in coating weight of oral dosage forms or change in weight of capsule shell	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Solid oral pharmaceutical forms.	1,2,3	1,3	PAC-B
b) Gastro-resistant pharmaceutical forms where the coating is a critical factor for the release mechanism.		1,2,3,4	PAC-B
c) Modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism.			PAC-II
Conditions to be fulfilled: 1. The coating is not a critical factor for the release mechanism. 2. The Finished Pharmaceutical product specification has only been updated in respect of weight and dimensions, if applicable. 3.The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one.			

Requirements to be fulfilled

1. Amendment of the relevant section(s) of the dossier concerning the change.
2. Batch analysis for two production batch at CADC lab.
3. Results of stability testing generated on at least two pilot- or production scale batch with a minimum of 3 months of accelerated and 3 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
4. Comparative in-vitro dissolution tests at 3 different PH media (1.2, 4.5, 6.8) & most suitable medium on one production batch with new composition against the innovator product. (Or Bioequivalence study according to category of API).

3.2.2.5 Change in the manufacturing site for part or all of the manufacturing process of the Finished Product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Addition or replacement of a Site where any manufacturing operation(s) take place except batch control and/or release testing and Primary / secondary packaging.	1,2,4,5	1,2,3,4,5,6	PAC-B
b) Addition or replacement of a Site responsible for any manufacturing operation(s) of finished product.			PAC-II
c) Addition or replacement of a site for Imported finished products and /or sites which requires initial GMP inspection.			PAC-II
d) Addition or replacement of Primary packaging site	1,2,3,4,5	1,2,3,5,6	PAC-B
e) Addition or replacement of Secondary packaging site (Non-Functional)	2,4,5	1,2	PAC-N
f) Addition or replacement of Batch release site/ Quality control testing	2	1,2	PAC-N

g) Addition or replacement of Storage site	2	1,2	PAC-N

Conditions to be fulfilled

1. No change in batch formula, description of manufacturing process, equipment class, process controls, control of critical steps & intermediates or Finished product specifications.
2. The proposed site appropriately authorized (To perform the specified operation for the concerned Finished product)
3. The change does not concern a sterile finished product.
4. No change in finished product container closure system.
5. Manufacturing at the new site shall be in a compliance with cGMP.

Requirements to be fulfilled:

1. Amendment of the relevant section(s) of the dossier concerning the change.
2.Amendment of Finished product information with the new manufacturer / packager /Batch release site if reflected (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.
3. Batch analysis for the first three consecutive production batches manufactured/packed at the proposed site.
4. Comparative in-vitro dissolution tests at 3 different PH media (1.2, 4.5, 6.8) & most suitable medium on the first production batch manufactured/packed at the proposed site against a batch manufactured/packed at the old site (must be previously validated if not available, tests must be done against the innovator product). (Or Bioequivalence study according to category of API).
5. Process validation reports for the first three production batches from the proposed manufacturing site.
6. A commitment is given that a long-term stability study on first production batch will be conducted and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

N.B :

***Please Refer to Updated Regulations of Addition/ Change of manufacturing site published on 3/8/2025 (Except For Imported Finished Products).**

***If the manufacturing site and the immediate packaging site are different, conditions of transport and bulk storage should be specified and validated through the Central Administration for Inspection on Pharmaceutical Institutions.**

3.2.2.6. Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Minor change in the manufacturing process	1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5	PAC-B
b) Major changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			PAC-II
c) Introduction of a non-standard terminal sterilization method			PAC-II
d) Introduction or change in the overage that is used for the active substance			PAC-II
e) Change in the holding time and/or storage condition of an intermediate or Bulk product used in manufacturing of the finished product.		1,4,6	PAC-B

Conditions to be fulfilled

1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.
2. Either the change relates to an immediate release solid oral dosage form/oral solution or to non-sterile solution.
3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.
4 The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.
5. The specifications of the finished product or intermediates are unchanged.
6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.

Requirements to be fulfilled:

1. Amendment of the relevant section(s) of the dossier concerning the change.
2. For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.
3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action).

4. Batch analysis data on a minimum of two batch manufactured to both the currently approved and the proposed process.
5. Results of stability testing generated on at least one pilot- or production scale batch with a minimum of 3 months of accelerated and 3 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
6. Data to validate the proposed change in holding time and/or storage condition of the intermediate or bulk product (minimum of two batches at pilot or commercial scale). Composition of the intermediate or bulk container should be described and its specification stated.

3.2.2.7. Change in the batch size of the finished product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Scaling up/down to and including a factor of 10 folds for Immediate Release oral pharmaceutical forms or non-sterile solutions**.**	1,2,3	1,4	PAC-B
b) Scaling up/down to and including a factor of 10 folds for pharmaceutical forms manufactured by complex manufacturing process e.g Modified Release (MR), etc.			PAC-II
c) Scaling up more than factor of 10 folds for Immediate Release oral pharmaceutical forms	1,2,3	1,2,3,4,5	PAC-B
d) Scaling up more than a factor of 10 folds for pharmaceutical forms manufactured by complex manufacturing process e.g Modified Release (MR), etc.			PAC-II
e) The change requires assessment of the comparability or the change in			PAC-II

batch size requires a new bioequivalence study			

Conditions to be fulfilled

1. The change does not affect the reproducibility and/or consistency of the product.
2. Changes to the manufacturing method and/or to the in-process controls are ONLY those necessitated by the change in batch size, e.g., use of different-sized equipment
3. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.

Requirements to be fulfilled:

1.Amendment of the relevant section(s) of the dossier concerning the change.
2. Batch analysis for two production batch manufactured with the new batch size at CADC labs.
3. Results of stability testing generated on at least one pilot- or production scale batch with a minimum period of 3 months of accelerated stability. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).
4. Process validation reports for first three batches of the proposed batch size.
5. If the batch size is changed in a way that may impact the dissolution profile of the finished product, Comparative in-vitro dissolution study at 3 different PH media (1.2, 4.5, 6.8); most suitable medium on one production batch manufactured with the proposed batch size against a batch manufactured with the current batch size or against the innovator product. (Or Bioequivalence study according to category of API).

3.2.2.8. Change to in-process tests or limits applied during the manufacture of the finished product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Minor changes of in-process limits	1, 2, 3, 4	1	PAC-N
b) Addition of a new test(s) and limits	1, 2	1, 2	PAC-N
c) Deletion of a non-significant in-process test	1, 2,5	1	PAC-N
d) Deletion of an in-process test which may have a			PAC-II

significant effect on the overall quality of the finished product			
e) Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product			PAC-II
f) Addition or replacement of an in-process test as a result of a safety or quality issue		1, 2, 3	PAC-B
Conditions to be fulfilled 1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a PAC- II variation procedure). 2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits. 3. Any change should be within the range of currently approved limits. 4. The analytical procedure remains the same, or changes in the analytical procedure are minor. 5. The in-process test does not concern the control of a critical parameter, e.g.: assay, impurities (unless a particular solvent is definitely not used in the manufacture) any critical physical characteristics (particle size, bulk, tapped density, etc.) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Batch analysis data on two production batches of the finished product for all specification parameters. 3. If the in-process tests are changed in a way that may impact the dissolution profile of the finished product, Comparative in-vitro dissolution study at 3 different PH media (1.2, 4.5, 6.8); most suitable medium on one production batch manufactured with the proposed in process tests against a batch manufactured with the current in process tests or against the innovator product. (Or Bioequivalence study according to category of API) is required.			

3.2.2.9. Change in the specification attribute and/or acceptance criteria of an excipient	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change within the approved specification acceptance criteria.	1, 2, 3, 4	1	PAC-A

b) Addition of a new specification attribute to the specification with its corresponding test method	1, 2, 5	1, 2	PAC-A
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2, 6	1	PAC-A
d) Change outside the approved specifications limits range			PAC-II
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			PAC-II
f) Addition or replacement of a specification parameter with its corresponding test method, as a result of a safety or quality issue		1, 2	PAC-B

Conditions to be fulfilled

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a PAC- II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. The change does not concern a genotoxic impurity.
6. The specification parameter does not concern the control of a critical parameter, e.g.:

-impurities (unless a particular solvent is definitely not used in the manufacture of the excipient)
-any critical physical characteristics (particle size, bulk, tapped density, etc.)
-identity test (unless there is a suitable alternative control already present)
-microbiological control (unless not required for the particular dosage form

Requirements to be fulfilled:

1. Amendment of the relevant section(s) of the dossier concerning the change.
2. Batch analysis data on two production batches of the excipient for all specification parameters.

3.2.2.10. Change in the specification attributes and/or limits of the Finished Pharmaceutical product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change within the approved specification acceptance criteria.	1,2	1	PAC-A
b) Addition of a new specification parameter to the specification with its corresponding test method	1	2,3	PAC-B
c) Deletion of a non-significant specification parameter (e.g., deletion of an obsolete parameter such as odor and taste or identification test for a coloring or flavoring material)	1,3	1	PAC-A
d) Change outside the approved specifications limits range			PAC-II
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			PAC-II

Conditions to be fulfilled

1. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
2. Any change should be within the range of currently approved limits.
3. The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example: assay, impurities or critical physical characteristics.

Requirements to be fulfilled:

1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change.
2. Amendment of the relevant section(s) of the dossier concerning the change.
3. Batch Analysis on two production batches of Finished Product at CADC labs.

3.2.2.11. Change in Analytical procedure for the Finished Pharmaceutical product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
	1	1	PAC-A

Conditions to be fulfilled:

1. Notification/Approval from CADC for new analytical procedure.

Requirements to be fulfilled:
1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change.

3.2.2.12. Change in immediate packaging of the Finished Pharmaceutical product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Qualitative and quantitative composition of an approved container			
1. Solid pharmaceutical forms	1	1,2	PAC-B
2.Semi-solid and non-sterile liquid pharmaceutical forms		1,2	PAC-B
3. Sterile pharmaceutical products.			PAC-II
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			PAC-II
b) Change in type of container or addition of a new container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		1,2	PAC-B
2. Sterile pharmaceutical products.			PAC-II
C) Deletion of a container			
Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	2	1	PAC-B

Conditions to be fulfilled
1. The change only concerns the same packaging container type (e.g. blister to blister).
2. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.

Requirements to be fulfilled:
1. Amendment of the relevant section(s) of the dossier concerning the change.
2. Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated and 3 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).

3.2.2.13. Change in the specification attribute and/or acceptance criteria of the immediate packaging of the finished product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change of specification acceptance criteria.	1, 2, 3, 4	1	PAC-N
b) Addition of a specification attribute to the specification with its corresponding analytical procedure.	1, 2	1, 2	PAC-N
c) Deletion of a non-significant specification or obsolete specification attribute	1, 2	1	PAC-N
d) Replacement of a specification attribute with its corresponding analytical procedure.		1, 2	PAC-B
Conditions to be fulfilled: 1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a PAC- II variation procedure). 2. The change does not result from unexpected events arising during manufacture. 3. Any change should be within the range of currently approved acceptance criteria. 4. The analytical procedure remains the same, or changes in the analytical procedure are minor.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Batch analysis data on two batches of the immediate packaging for all specification parameters from supplier.			

3.2.2.14. Change in analytical procedure for the immediate packaging of the finished product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Minor changes to an approved analytical procedure	1	1,2	PAC-A
b) Other changes to an analytical procedure (including replacement or addition)		1,2	PAC-A

c)Deletion of an analytical procedure if an alternative analytical procedure is already authorized	2	1	PAC-A
Conditions 1. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method). 2. An alternative analytical procedure is already authorized for the specification parameter.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure			

3.2.2.15.Change in shape of the container	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Non-sterile medicinal products	1,2	1,2,3	PAC-B
c) Sterile medicinal products		1,2,3	PAC-B
Conditions 1. No change in the qualitative or quantitative composition of the container. 2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the Finished Pharmaceutical product.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Sample of the old and new container/closure system. 3. In case of a change in the head space or a change in the surface/volume ratio, Results of stability testing generated on at least two pilot- or production scale batches with a minimum of 3 months of accelerated and 3 months of long-term testing. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).			

3.2.2.16.Change in pack size of the Finished Pharmaceutical product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change in the number of units (e.g., tablets, ampoules, etc.) in a pack	1,2	2,3,4	PAC-B
b) Deletion of pack size(s)	3	1	PAC-A

c) Change/Addition in the fill weight/fill volume of sterile multidose pharmaceutical products.			PAC-II
d) Change/Addition in the fill weight/fill volume of non- sterile multi-dose medicinal products	1,2	2,3,4,5	PAC-B
Conditions to be fulfilled: 1. New pack size should be consistent with the posology and treatment duration & similar change in the competitor product from any reference country. 2. The primary packaging material remains the same. 3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the product information leaflet.			
Requirements to be fulfilled: 1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of the relevant section(s) of the dossier concerning the change. 3. Amendment of Product Information (i.e., Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions. 4. Pricing 5. Results of stability testing generated on at least one pilot- or production scale batch with a minimum of 3 months of accelerated. A commitment is given that the long-term stability study on first production batch will be finalized and that data will be provided immediately to the Variation Administration if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action).			

3.2.2.17. Change in any part of the (primary) packaging material not in contact with the Finished Pharmaceutical product formulation (such as color of flip-off caps, color code rings on ampoules, change of needle shield (different plastic used)	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Change that affects the product information	1	1,2	PAC-N

b) Change that does not affect the product information	1	1	PAC-A
Conditions to be fulfilled: 1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the Finished Pharmaceutical product			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2. Amendment of Product Information (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

3.2.2.18. Change in manufacturer, sterilization process or supplier of packaging components (when mentioned in the dossier).	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Addition or replacement of a manufacturer or supplier	1,2,3,4	1	PAC-A
b) Addition or replacement of a site responsible for sterilization of a packaging component, and/or a change to the sterilization process		1	PAC-B
Conditions to be fulfilled: 1. No deletion of packaging component or device. 2. The qualitative and quantitative composition of the packaging components/device and design specifications remain the same. 3. The specifications and quality control method are at least equivalent. 4. The sterilization method and conditions remain the same, if applicable.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change.			

3.2.2.19. Change of a secondary packaging component of the finished product (including replacement or addition or deletion),	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type

when mentioned in the dossier			
	1,2,3,4	1	PAC-A
Conditions to be fulfilled: 1. The secondary packaging does not play a functional role on the stability of the finished product, or if it does, it is not less protective than the approved one 2. The changed packaging component must be adequate for the storage of the finished product at the authorised conditions. 3. The change should not be due to critical deficiencies of the former packaging component. 4. The change is not a result of any unexpected events arising during manufacture or storage of the finished product			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change.			

3.2.2.20. Change in the shelf-life or storage conditions of the Finished Pharmaceutical product	Conditions to be fulfilled	Requirements to be fulfilled	Procedure type
a) Reduction of the shelf life of the Finished Pharmaceutical product			
1. As packaged for sale	1	1,2	PAC-N
2. After first opening	1	1,2	PAC-N
3. After dilution or reconstitution	1	1,2	PAC-N
b) Extension of the shelf life of the Finished Pharmaceutical product			
1. As packaged for sale (supported by real time data)	2	1,2	PAC-N
2. After first opening (supported by real time data)	2	1,2	PAC-N
3. After dilution or reconstitution (supported by real time data)	2	1,2	PAC-N
c) Change in storage conditions of the Finished Pharmaceutical product or the diluted/reconstituted product	2	1,2	PAC-N
d) Change in stability protocol	1	1	PAC-N
Conditions to be fulfilled: 1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 2. Result of stability study for proposed Change according to requirement for post approval stability study submission issued by stability general administration.			
Requirements to be fulfilled: 1. Amendment of the relevant section(s) of the dossier concerning the change. 2.Amendment of Product Information (i.e. Inner leaflet and/or Mock up) that will be followed up by Central Administration for Inspection on Pharmaceutical Institutions.			

4 References

- EMA Guidelines by European commission in Official Journal of the European Union volume 56 dated on September 2025.
- WHO guidelines on variations to a prequalified product (Annex III) 2013.
- Egyptian Variation Guidelines Fifth Edition 2024.
- Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, November 1995
- EDA's approved Reference Countries List according to the most updated decisions of the technical committee of drug control

5 Annexes

Annex I: Glossary

EDA	Egyptian Drug authority
FINISHED PRODUCT	Finished Pharmaceutical Product
CPP	Certificate of pharmaceutical products
cGMP	Current Good Manufacturing Practice
WHO	World Health Organisation
COA	Certificate of Analysis
NRA	National Regulatory Authority
SRAs	Stringent regulatory authorities
LH	License Holder
MAH	Marketing Authorization Holder
BE	Bioequivalence
CADC	Central Administration of Drug Control
NTI	Narrow Therapeutic Index
IR	Intermediate Release
MR	Modified Release

API	Active Pharmaceutical Ingredient

Annex II: NTI (Narrow Therapeutic Index) List.

Narrow Therapeutic Drugs	
Aminophylline	**Ethosuximide**
Carbamazepine	**Flecainide**
Clindamycin	**Isoprenaline**
Clonidine	**Levoxyine**
Dyphylline	**Methotrexate**
Disopyramide	**Phenobarbital**
Ethinyl Estradiol	**Sirolimus**
Guanethidine	**Sulfonylurea Antidiabetic Drugs Compounds**
Isoetharine Mesylate	**Tacrolimus**
Isoproterenol	**Zonisamide**
Lithium Carbonate	**Valproic Acid**
Metaproterenol	**valproate Sodium**
Minoxidil	**Warfarin Sodium**
Oxtriphylline	**Cyclosporine**
Phenytoin	**Digitoxin**
Prazosin	**Digoxin**
Primidone	**Aprindine**
Procainamide	**Clonazepam**
Quinidine Gluconate	**Theophylline compounds**
Colchicine	

Annex III: Minor adjustment of the quantitative composition.

Are evaluated according to Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.
Link: https://rb.gy/jceyn

6 History of Change:

Versions (Effective Date)	Updated Sections	Summary of changes
1 March 2018	New Document	First edition of variation guidelines.
2 February 2019	Updating Types of variation.	Current Change(s): * Updating types of variation. * Updating the requirements to be fulfilled according to the type of change.
3 June 2023	The guidelines have undergone a comprehensive update and expansion, aligning them with international principles.	Current Change(s): * Incorporation of the classification of additional post-approval changes and determining the inherent risk level associated with each change. * Classification of types variations have been changed from the previous guideline's version. * Previously, certain categories required acceptance of the change before implementation. Now, the applicant can implement the change immediately upon notification. * The full evaluation route and reliance evaluation route have been clarified.

4 November 2023	Update in Scope of Variation Evaluation Routes.	Current Change(s): * Update Scope of Full Evaluation route to clarify the eligibility & Submission criteria for Finished Pharmaceutical Products imported from non-Reference country and not marketed in a reference country.
5 August 2024	*Editorial change in Scope of Variation Evaluation Routes. *Remove annex III *Update Variation Application Form of Post Marketed Human Products	Current Change(s): * Editorial change in eligibility & Submission criteria for Finished Pharmaceutical Products imported from non-Reference country and not marketed in a reference country. *As an Update list of EDA's approved list of reference countries according to Technical Committee Decisions is published on EDA Website. * Updated Version of application
6 December 2025	*Update Introduction	Current Change(s): *The entire introduction has undergone a full content update, including expanded definitions, mode of submission, etc.

	* Change in classification of general Considerations	* General Considerations classified into (Administrative Changes and Quality Changes).
	* Addition/Update of Administrative & Quality Changes.	* Addition/Update of Administrative & Quality Changes in the following: • Update in variations sub-classification. • Change in conditions and requirements to be fulfilled. • Change in procedure type.