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 2019.

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.

**Submission Guidance:** List of Required documents used by companies to fulfill the submitted variation requests.

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

**Stringent Regulatory Authorities (SRAs):** Regulatory authorities of refence countries that Technical Committee of drug control on 31/12/2009 and 16/9/2021 approved them in a list, and they are chosen according to the WHO criteria and its definition to the SRAs (Annex III).

**Notification Letter:** Letter stating that EDA is notified with the change submitted by the applicant.

**Acceptance Letter:** Letter stating that EDA is initially accepting the change submitted by the applicant and declaring the required studies to be fulfilled.

**Final approval:** Letter stating that EDA approved the change submitted by the applicant after fulfilling the required studies.

**Finished Pharmaceutical Product (FPP):** 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 FPP.

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

**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 FPP 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.

## 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 presented in the (Annex V).

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 variation approval/ acceptance letter.

For All variations when accelerated stability study for 6 months is required, the applicant should place the first production-scale batch of the FPP produced with the new variation into the long-term stability program to be conducted and 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.

### 2.5.2 Variation Evaluation Routes

#### 2.5.2.1 Full Evaluation Route:

Full evaluation will apply to variations subject to EDA full review and assessment prior to the change.
The procedure starts from the date of submission of a valid payment receipt and variation request. Then, the application will undergo initial screening and technical evaluation by the concerned unit of variation.
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 technical evaluation period, the variation administration will determine its decision on the variation request and inform the applicant about the acceptance or rejection of the variation.

| Eligibility Criteria to Full Evaluation Route | Submission Criteria |
|---|---|
| **1- Local / Bulk / Under License Pharmaceutical Products.** | The applicant will submit the variation request and then an acceptance letter will be issued to the applicant stating the Required Studies to be Conducted and submitted for evaluation by EDA administrations.<br>The approved studies with its approvals issued by EDA administrations will be submitted to Variation administration to issue the Final approval on the Variation request. |
| **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:<br>• Valid Certificate of Pharmaceutical Product of country of origin<br>• The approval of other NRA<br>• Verification of Sameness<br>• The studies conducted in country of origin (to be evaluated by EDA administrations).<br>The Variation administration will issue a Notification Letter for the Variation request after assessment of studies by other EDA administrations. |

#### 2.5.2.2 Reliance Evaluation Route:

The variation administration will assess variations that were already approved by other reference countries (SRAs–Annex III), 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 for Reliance Evaluation Route | Submission Criteria |
|---|---|
| **For Imported Finished Product That has been Approved by at least one reference regulatory authority (SRA) or WHO prequalification** | The applicant will Submit the variation request which includes:<br>1.Valid Certificate of Pharmaceutical Product.<br>2. Updated relevant sections of CTD dossier.<br>3. Verification of Sameness* (for example sameness letter).<br>4. Unredacted Assessment report (otherwise justified with evidence).<br>5. Proof of approval from at least one reference regulatory authority.<br><br>The Variation administration will screen these documents in order to issue the Notification Letter for the Variation request. |

*__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.

**Sameness letter:** is a document issued by License Holder to assure same quality of the product, to provide transparency about any potential differences compared to the reference National Regulatory Authority (NRA).

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<br>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 de deemed accepted | IB notification including approval information<br>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.

### 2.5.3 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 FPP.

Such changes can be implemented immediately at the time of submission and they can be considered accepted by receiving a Notification letter stating that the EDA is notified with the change.

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 FPP and must be submitted annually.

Such changes not require prior acceptance and can be implemented directly and the applicant must submit them collectively within 12 months from the date of implementation of the changes and they can be considered accepted by receiving a Notification letter stating that the EDA is notified with 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 FPP.

Such changes can be implemented when the variation is considered accepted and they can be considered accepted by receiving an Acceptance Letter stating the required studies to be fulfilled in order to issue the Final Approval on the variation request.

A letter of acceptance will be issued for all minor variations if and when the variation is considered accepted by the EDA.

**PAC-II:**

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

Such changes can be implemented when the variation is considered accepted and they can be considered accepted by receiving Acceptance Letter stating the required studies to be fulfilled in order to issue the Final Approval on the variation request.

A letter of acceptance will be issued for all major variations if and when the variation is considered accepted by the EDA.

Where necessary, the EDA will update the marketing authorization within 15 working days after ending the technical evaluation 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.

Individual changes normally require the submission of separate variations. Grouping of variations is acceptable under the following circumstances (for example but not limited to):

1. When variations are consequential to each other, e.g. change of coloring agents that requires a new physical character change;
2. When the same change affects multiple FPPs, e.g. addition of a new API manufacturing site for multiple FPPs.

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.

# 3 General Considerations:

## 3.1 Post Market Changes for API Variation for Human Pharmaceutical

### 3.1.1 Administrative Changes Concerning API Variation

| **3.1.1.1 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:**<br>1. The manufacturing site and all manufacturing operations must remain the same. | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

| **3.1.1.2 Deletion of manufacturing sites for an active substance** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| | 1 | 1 | PAC-A |
| **Conditions to be fulfilled:**<br>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:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

### 3.1.2 Quality Changes Concerning API Variation

#### 3.1.2.1 Manufacturer

| 3.1.2.1.1 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- Introduction of a new manufacturer. | 1,2,3 | 1 | PAC-A |
| **B) The Active Substance.** | | | |
| 1- Introduction of a new manufacturer. | | 2,3,4,5 | 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- Introduction of a new site of micronization | 2 | 1 | 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 for the prequalified quality products.
2. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products
3. Analysis of the first production batch of Finished Pharmaceutical product manufactured from the API manufacturer at CADC labs.
4. Results of stability testing generated with a minimum of 6 months Accelerated testing, and to be released to the market by Central Administration of Operation (Inspection Department) after evaluating the results of a minimum of 3 months of the first production batch of Finished Pharmaceutical product manufactured with the new API manufacturer.
5. Comparative in-vitro dissolution study at most suitable medium on first production batch of Finished Pharmaceutical product manufactured from the new API manufacturer 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).

| 3.1.2.1.2 Changes in the manufacturing process of the active substance | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| | 1,2 | 1 | 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.

**Requirements to be fulfilled:**

1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.

| 3.1.2.2 Change in batch size of active substance. | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| | 1,2,3,4,5 | 1 | 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. Test results of at least two batches according to the specifications should be available for the proposed batch size.
3. The change does not adversely affect the reproducibility of the process.
4. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
5. The specifications of the active substance remain the same.

**Requirements to be fulfilled:**

1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.

| 3.1.2.3 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 |
|---|---|---|---|
| | 1,2,3,4 | 1 | PAC-A |

**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 test procedure remains the same, or changes in the test procedure are minor.
4. 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 changing the frequency of testing (In case of deletion of any in-process tests).

**Requirements to be fulfilled:**

1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.

### 3.1.2.4 Control of Active substance

| 3.1.2.4.1 Change in the specification parameters and/or limits of an active substance | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| a) Tightening of specification limits | 1,2,3 | 1 | PAC-A |
| b) Addition of a new specification parameter to the specification with its corresponding test method | 1,4 | 1 | PAC-N |
| c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 1,2,5 | 1 | 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 Pharmaceutical product | | 2,3,4,5 | PAC-II |
| e) Change outside the approved specifications limits range for the active substance | | 2,3,4,5 | PAC-II |
| f) Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the | | 2,3,4,5 | PAC-II |

| | | | |
|---|---|---|---|
| active substance and/or the Finished Pharmaceutical product | | | |
| g) Addition or replacement of a specification parameter with its corresponding test method as a result of a safety or quality issue | | 2,3,4,5 | PAC-B |
| h) A change in specification of active ingredient from Pharmacopeia to in-house (Tighten of Specification). | 1,2,3,4 | 1 | PAC-N |

**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 test procedure remains the same, or changes in the test procedure are minor.
4. For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with ICH limits, any new impurity control should be in line with the Ph. Eur. or National Pharmacopoeia.
5. 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. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.
2. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products
3. Analysis of the first production batch of Finished Pharmaceutical product manufactured from the API manufacturer at CADC labs.
4. Results of stability testing generated with a minimum of 6 months Accelerated testing, and to be released to the market by Central Administration of Operation (Inspection Department) after evaluating the results of a minimum of 3 months of the first production batch of Finished Pharmaceutical product manufactured with the new API manufacturer.
5. Comparative in-vitro dissolution study at most suitable medium on first production batch of Finished Pharmaceutical product manufactured from the new specification against the innovator product. (Or may be changed to 3 different PH media in addition to the most suitable medium according to category of API & & its BCs Class), If the change affect dissolution.

| 3.1.2.4.2 Change in test procedure for active substance | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| | 1,2 | 1 | PAC-A |
| **Conditions to be fulfilled:**<br>1. There have been no changes of the total impurity limits; no new unqualified impurities are detected.<br>2. Notification/Approval from CADC for new test procedure. | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

**3.1.2.5 Container closure system**

| 3.1.2.5.1 Change in Primary packaging of the active Substance | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| a) Qualitative and/or quantitative composition. | 1,2 | 1 | PAC-A |
| **Conditions to be fulfilled:**<br>1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.<br>2. Approval on stability study for new packaging material from API Manufacturer(s). | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

**3.1.2.6 Stability**

| 3.1.2.6.1 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 | 1 | PAC-N |
| 2-Extension or introduction of a retest period / storage period supported by real time data | 2 | 1 | PAC-N |
| **b) Storage conditions** | | | |
| 1. Change to more restrictive storage conditions of the active substance | 1,2 | 1 | PAC-N |
| 2. Change in storage conditions of the active substance | 1,2 | 1 | PAC-N |

| |
|---|
| **Conditions to be fulfilled:**<br>1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.<br>2. Approval on stability study from API Manufacturer(s). |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. |

**3.1.2.7 CEP**

| **B.III.1 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-A |
| 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-A |
| **Conditions to be fulfilled:**<br>1. New / Updated CEP.<br>2. No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

## 3.2 Post Market Changes for Ownership and Manufacturing Variation for Human Pharmaceutical

### 3.2.1 Administrative Changes Concerning Ownership and Manufacturing Variation

| **3.2.1.1 Change in Name / Address of FPP LH/MAH** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **a) For Local FPPs** | 1 | 1,2 | PAC-N |
| **b) For Imported FPPs** | 1 | 1,2 | PAC-N |
| **Conditions to be fulfilled:**<br>1. FPP LH/MAH must remain the same legal entity. | | | |
| **Requirements to be fulfilled:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of FPP with the new name/Address of the LH/MAH information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of Operation (Inspection Department). | | | |

| **3.2.1.2 Change in Name / Address of Manufacturing sites (including bulk manufacturer, packager & batch releaser)** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **a) For Local FPPs** | 1 | 1,2 | PAC-N |
| **b) For Imported FPPs/Bulk** | 1 | 1,2 | PAC-N |
| **Conditions to be fulfilled:**<br>1. The physical location of the manufacturing site and all manufacturing operations must remain the same. | | | |
| **Requirements to be fulfilled:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of FPP with the new name/Address of Manufacturing sites information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of Operation (Inspection Department). | | | |

| 3.2.1.3 Change in Applicant | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **For Imported FPPs** | 1 | 1 | PAC-N |
| **Conditions to be fulfilled:**<br>1.The applicant shall be authorized for registration. | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

| 3.2.1.4 Modification of Registration license (including but not limited to trade name, shelf life, storage conditions, price, storage site) | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| | 1 | NA | PAC-A |
| **Conditions to be fulfilled:**<br>1. Approval of EDA relevant department(s) on related modification. | | | |

| 3.2.1.5 FPP LH/ MAH Transfer | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **License Holder:** | | | |
| **a) For local FPPs** | 1,2 | 1,2 | PAC-N |
| **b) For Bulk or Under license FPPs** | 1 | 1,2 | PAC-N |
| **c) For Imported FPPs** | 1 | 1,2 | PAC-N |
| **Marketing Authorization Holder** | | | |
| **a) For Bulk or Under license FPPs** | 1 | 1,2 | PAC-N |
| **b) For Imported FPPs** | 1 | 1,2 | PAC-N |
| **Conditions to be fulfilled:**<br>1. The new FPP LH/MAH is a different legal entity.<br>2. A Pharmaceutical FPP 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 for the prequalified quality products.<br>2.Amendment of FPP with the new LH/MAH information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of Operation (Inspection Department). |

| **3.2.1.6 Addition/Change of FPP MAH in Egypt** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| For Imported /Bulk & Under License FPPs | 1 | 1,2 | PAC-N |
| **Conditions to be fulfilled:**<br>1. FPP MAH **in Egypt** must comply with all FPP specifications, composition and all manufacturing operations as mentioned in the FPP CPP from NRA in the country of origin. | | | |
| **Requirements to be fulfilled:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of FPP information if reflected (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of Operation (Inspection Department). | | | |

| **3.2.1.7 Change/addition Supplier of solvent/diluent for a FPP** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| a) Lidocaine | 1,2,3 | 1,2,3 | PAC-B |
| b) Water for injection | 1,2,3 | 1,2 | PAC-N |
| **Conditions to be fulfilled:**<br>1. Solvent from new supplier must be registered.<br>2. Shelf life of solvent from new supplier must comply with shelf life of the FPP.<br>3. Pack of solvent from new supplier must comply with previously approved pack. | | | |
| **Requirements to be fulfilled:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of FPP information if reflected (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of Operation (Inspection Department).<br>3. In use stability study on one production batch. | | | |

### 3.2.2 Quality Changes Concerning Ownership and Manufacturing Variation

#### 3.2.2.1 Site changes

| **Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **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 | PAC-B |
| **b) Primary packaging site** | 1,2,3,4,5 | 1,2,3,4,5 | PAC-B |
| **c) Secondary packaging site (Non-Functional)** | 2,4,5 | 1,2 | PAC-N |
| **d) Batch release site** | 2 | 1,2 | PAC-N |
| **e) 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 FPP specifications.
2. The proposed site appropriately authorized (To perform the specified operation for the concerned FPP)
3. The change does not concern a sterile FPP.
4. No change in FPP container closure system.
5. Manufacturing at the new site shall be in a compliance with cGMP if available.

**Requirements to be fulfilled:**

1.Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.

2.Amendment of FPP with the new manufacturer / packager /Batch release site if reflected information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of Operation (Inspection Department).

3. Batch analysis for first three consecutive production batches manufactured/packed at the new site at CADC labs.

4. Comparative in-vitro dissolution tests at 3 different PH media (1.2, 4.5, 6.8) & most suitable medium on one production batch manufactured/packed at the new 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 three batches from the proposed manufacturing site.

### 3.2.2.2 Batch Size Changes

| **Scaling up or down of FPP production batch size** | 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 (IR).** | 1,2,3,4 | 1,5 | PAC-B |
| **b) Scaling up/down to and including a factor of 10 folds for Modified Release (MR).** | | 1,4,5 | PAC-II |
| **c) Scaling up more than factor of 10 folds for Immediate Release (IR)** | 1,2,4 | 1,2,3,5 | PAC-B |
| **d) Scaling up more than a factor of 10 folds for Modified Release (MR).** | | 1,2,3,4,5 | PAC-II |

**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.
4. API BCs Class is not Classified as Category IV,otherwise justified

**Requirements to be fulfilled:**

1.Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.
2. Batch analysis for first three consecutive production batches manufactured with the new batch size at CADC labs.
3. Results of stability testing generated with a minimum of 6 months Accelerated testing, and to be released to the market by Central Administration of Operation (Inspection Department) after evaluating the results of a minimum of 3 months of the first production batch of Finished Pharmaceutical product manufactured with the new batch size.
4. 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 new batch size against a batch manufactured with the old batch size or against the innovator product. (Or Bioequivalence study according to category of API)
5. Process validation reports for three batches of the proposed batch size.

## 3.3 Post Market Changes for Specification & Composition Variation:

### 3.3.1 Administrative Changes Concerning Specification & Composition Variation

| **3.3.1.1 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**<br>1. The active substance/excipient must remain the same. | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of Product Information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of operation (Inspection Department). | | | |

### 3.3.2 Quality Changes Concerning Specification & Composition Variation

#### 3.3.2.1 Description and composition

| **3.3.2.1.1 Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **a) Change in imprints, embossing or other markings** | 1,2,5 | 1 | PAC-N |
| **b) Deletion of a score line** | 2,4 | 1,4 | PAC-N |
| **c) Addition of a score line** | 1,2,3 | 2,3,4 | PAC-B |
| | 1,2,3,4 | 1,4 | PAC-B |
| **Conditions to be fulfilled**<br>1. The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP.<br>2. Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring. | | | |

| |
|---|
| 3. Addition of a score line from a product is consistent with a similar change in the competitor product from any reference country.<br>4. The scoring is not intended to divide the FPP into equal doses.<br>5. Any product markings used to differentiate strengths should not be completely deleted. |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>3. Batch Analysis for first production batch at CADC labs.<br>4. Amendment of Product Information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of operation (Inspection Department). |

| **3.3.2.1.2 Change in the shape or dimensions of the pharmaceutical form** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **Non-scored Tablets** | 1,2 | 1,3 | PAC-B |
| **Scored Tablets** | | 1,2,3 | PAC-II |
| **Conditions to be fulfilled**<br>1. End of shelf-life specifications of the product have not been changed except for dimensions.<br>2. The qualitative or quantitative composition and mean mass remain unchanged. | | | |
| **Requirements to be fulfilled:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Batch Analysis for first production batch at CADC labs.<br>3. Comparative in-vitro dissolution study at most suitable medium on first production batch of Finished Pharmaceutical product manufactured from the new shape/dimension 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). | | | |

| 3.3.2.1.3 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 | 1,2,3 | PAC-B |
| 2. Increase or reduction | 1,2,3 | 1,2 | 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 IV) | 1,2,3,6 | 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 | | 1,2,3,4 | 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 | | 1,2,3,4 | PAC-II |
| 4. Replacement of a single excipient with a comparable excipient with the same functional characteristics and same quantity at a similar level. | | 1,3,4 | 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.<br>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.<br>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:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Batch Analysis for first production batch at CADC labs.<br>3. Result of stability testing generated on one production batch with a minimum of 6 months accelerated testing, and to be released to the market by central administration of operation (Inspection department) after evaluating the result of a minimum of 3 months.<br>4. Comparative in-vitro dissolution study at 3 different PH media (1.2,4.5,6.8) & most suitable medium (D3/4) on one production batch against the innovator product. (Or Bioequivalence study according to category of API). |

| **3.3.2.1.4 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 | 1,2,3 | PAC-B |
| b) Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism | | 1,2,3,4 | 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.

**Requirements to be fulfilled:**

1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.
2. Batch Analysis for first production batch at CADC labs.
3. Result of stability testing generated on one production batch with a minimum of 6 months accelerated testing, and to be released to the market by central administration of operation (Inspection department) after evaluating the result of a minimum of 3 months.
4. Comparative in-vitro dissolution study at 3 different PH media (1.2,4.5,6.8) & most suitable medium (D3/4) on one production batch against the innovator product. (Or Bioequivalence study according to category of API).

### 3.3.2.2 Control of Finished Pharmaceutical product

| 3.3.2.2.1 Change in the specification parameters and/or limits of the Finished Pharmaceutical product | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| a) Tightening of specification limits | 1,2 | 1 | PAC-A |
| b) Addition of a new specification parameter to the specification with its corresponding test method | 1 | 2,3,4 | 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-N |

**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 for the prequalified quality products.
2. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.
3. Batch Analysis for first production batch at CADC labs.
4. Comparative in-vitro dissolution study at 3 different PH media (1.2,4.5,6.8) & most suitable medium (D3/4) on one production batch against the innovator product. (Or Bioequivalence study according to API category), If the added test affect dissolution.

| **3.3.2.2.2 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** | | | |
| 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 |
| **Conditions to be fulfilled:**<br>1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.<br>2.Approval from Stability Administration for proposed Change. | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2.Amendment of Product Information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of operation (Inspection Department). | | | |

| 3.3.2.2.3 Change in test procedure for the Finished Pharmaceutical product | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| | 1 | 1 | PAC-N |
| **Conditions to be fulfilled:**<br>1.Notification/Approval from CADC for new test procedure. | | | |
| **Requirements to be fulfilled:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

### 3.3.2.3 Container closure system

| 3.3.2.3.1 Change in Primary packaging of the Finished Pharmaceutical product | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| **a) Qualitative and quantitative packaging composition (within the same packaging type)** | | | |
| 1. Solid & Semi-solid and non-sterile liquid pharmaceutical forms | 1 | 1,3 | PAC-B |
| 2. Sterile medicinal products | | 1,2,3 | PAC-II |
| **b) Change to a new type of Packaging container. (Such as glass to plastic, or strip to jar,etc….)** | | 1,2,3 | PAC-II |
| **Conditions to be fulfilled**<br>1. The change only concerns the same packaging container type (e.g. blister to blister). | | | |
| **Requirements to be fulfilled:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Batch Analysis for first production batch at CADC labs<br>3. Result of stability testing generated on one production batch with a minimum of 6 months accelerated testing, and to be released to the market by central administration of operation (Inspection department) after evaluating the result of a minimum of 3 months. | | | |

| 3.3.2.3.2 Change in shape of the container | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| a) Non-sterile medicinal products | 1,2 | 1 | PAC-N |
| c) Sterile medicinal products | | 1,2,3 | PAC-II |
| **Conditions**<br>1. No change in the qualitative or quantitative composition of the container.<br>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:**<br>1. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Batch Analysis for first production batch at CADC labs<br>3. Result of stability testing generated on one production batch with a minimum of 6 months accelerated testing, and to be released to the market by central administration of operation (Inspection department) after evaluating the result of a minimum of 3 months. | | | |

| 3.3.2.3.3 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 medicinal products.** | 1,2 | 2,3,4,5,6 | PAC-II |
| **d) Change/Addition in the fill weight/fill volume of non- sterile multi-dose medicinal products** | 1,2 | 2,3,4,6 | PAC-B |

| |
|---|
| **Conditions to be fulfilled:**<br>1. New pack size should be consistent with the posology and treatment duration & similar change in the competitor product from any reference country.<br>2. The primary packaging material remains the same.<br>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:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>3. Amendment of Product Information (i.e., Inner leaflet and mock up) that will be followed up by Central Administration of operation (Inspection Department).<br>4. Pricing<br>5. Batch Analysis for first production batch at CADC labs.<br>6. Result of stability testing generated on one production batch with a minimum of 6 months accelerated testing, and to be released to the market by central administration of operation (Inspection department) after evaluating the result of a minimum of 3 months. |

| **3.3.2.3.4 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:**<br>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:**<br>1. No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products.<br>2. Amendment of Product Information (i.e. Inner leaflet and Mock up) that will be followed up by Central Administration of operation (Inspection Department). | | | |

| **3.3.2.3.5 Change in supplier of packaging components or devices.** | Conditions to be fulfilled | Requirements to be fulfilled | Procedure type |
|---|---|---|---|
| a) Deletion of a supplier | 1 | 1 | PAC-A |
| b) Replacement or addition of a supplier | 1,2,3,4 | 1 | PAC-N |
| **Conditions to be fulfilled**:<br>1. No deletion of packaging component or device.<br>2. The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.<br>3. The specifications and quality control method are at least equivalent.<br>4. The sterilization method and conditions remain the same, if applicable. | | | |
| **Requirements to be fulfilled:**<br>1.No requirements needed, just amendment of the relevant section(s) of the dossier concerning the change for the prequalified quality products. | | | |

**History of Change:**

| Versions (Effective Date) | Updated Sections | Summary of changes |
|---|---|---|
| 15 November 2023 | Update in Scope of Variation Evaluation Routes. | Current Change(s):<br>* 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. |
| 3 June 2023 | The guidelines have undergone a comprehensive update and expansion, aligning them with international principles. | Current Change(s):<br>* Incorporation of the classification of additional post-approval changes and determining the inherent risk level associated with each change.<br>* Classification of types variations have been changed from the previous guideline's version.<br>* Previously, certain categories required acceptance of the change before implementation. Now, the applicant can implement the change immediately upon notification.<br>* The full evaluation route and reliance evaluation route have been clarified. |
| 2 February 2019 | Updating Types of variation. | Current Change(s):<br>* Updating types of variation.<br>* Updating the requirements to be fulfilled according to the type of change. |
| 1 March 2018 | New Document | First edition of variation guidelines. |

# 4 References


- EMA Guidelines by European commission in Official Journal of the European Union volume 56 dated on 2 August 2013.
- WHO guidelines on variations to a prequalified product (Annex III).
- Egyptian Variation Guidelines Second Edition 2019.
- 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
- Technical Committee of Drug Control on 31/12/2009 & 16/9/2021.


# 5 Annexes

## Annex I: Glossary

| | |
|---|---|
| **EDA** | Egyptian Drug authority |
| **FPP** | 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** |

## Annex III: EDA's approved list of reference countries.

The current list consists of 22 countries that EDA can rely on their regulatory authorities includes:

- **Australia (TGA)**
- **Austria (Bundesamt für Sicherheit im Gesundheitswesen)**
- **Belgium (afmps)**
- **Canada (Health Canada)**
- **Denmark (The Danish Medicines Agency)**
- **Finland (FIMEA)**
- **France (ANSM)**
- **Germany (Pharm Net)**
- **Iceland (Lyfjastofnun- Icelandic Medicines Agency)**
- **Ireland (HPRA)**
- **Italy (AIFA)**
- **Japan (Ministry of Health, Labour and Welfare (MHLW))**
- **Luxembourg**
- **Netherland (CBG)**
- **New Zealand (medsafe)**
- **Norway (Legemiddelverket)**
- **Portugal (infarmed)**
- **Spain (aemps)**
- **Sweden (lakemedelsverket)**
- **Switzerland (Swiss medic)**
- **United Kingdom (MHRA)**
- **United States of America (Food & Drug Administration)**

## Annex IV: 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

## Annex V: Submission Guidance

**I- Common Administrative Documents:**

**(Should be submitted with all variations in addition to Relevant Documents (Section 5) According to the Variation Type)**

| Section (1)<br>Variation Application form + Payment Receipt | |
|---|---|
| **1** | **Variation Application form.**<br>Signed and Stamped |
| **2** | **Payment Receipt.** |

| Section (2)<br>EDA License & Approvals | |
|---|---|
| **1** | **EDA Valid Registration License**<br>▪ If Final & invalid: Valid Approval for registration renewal.<br>▪ If Tentative & invalid: License validity extension approval or approval for submission from Tent. to final. |
| **2** | Any other EDA or Variation approvals or any Exemptions for the product. |
| **3** | Minister decree 600 exemption (If needed). |
| **4** | Any Previous Stability Approvals (Accelerated Stability or Long-term Stability). |
| **5** | Leaflet of the product and innovator. |
| **6** | EDA labs certificate of analysis. |
| **7** | EDA labs composition certificate. |
| **8** | Updated Pricing License |

| Section (3)<br>Other Documents (In Case of Imported / UL Products) | |
|---|---|
| **1** | ▪ **Valid CPP (With All Attachment):**<br>Authenticated by the Health Authority in COO, Chamber of commerce or Notary & Egyptian consulate/embassy.<br>**OR**<br>▪ **Electronic CPP**<br>& Declaration Letter from The Applicant Clarifies the Authorized Link for its **Online Verification** |

| | |
|---|---|
| 2 | **Declaration Letter from LH/MAH in COO**<br>▪ Clarifies The Changes.<br>if The Change(s) **stated in The CPP** The Declaration Should be Signed and stamped<br>& if The Change(s) **doesn't stated in The CPP** ( for 2ry Packager / Batch Release Site),<br>The Declaration Letter should be **Authenticated** from Chamber of commerce or Notary & Egyptian consulate/embassy. |
| 3 | **Declaration Letter from LH/MAH in COO signed and stamped**:<br>▪ Stating the reasons of change. |
| 4 | **CTD:**<br>▪ Part related to required change. |

| Section (4)<br>Applicant Documents | |
|---|---|
| 1 | **Last Updated Commercial Register** |
| 2 | **Last Updated Toll Card**<br>***** In case of toll companies |
| 3 | **Last Updated Manufacturing License**<br>***** In case of local companies |
| 4 | **Scientific Office License**<br>*****In case of scientific office |
| 5 | **In Case of Imported Finished Human Pharmaceutical Product if the applicant is either Scientific Office or Company the following documents to be submit:**<br>***Scientific Office:**<br>**a) "Authorization letter for the Scientific Office to register finished Imported Human Pharmaceutical Products"**<br>issued by Evaluation Unit of registration requests for human pharmaceuticals.<br>**b) Declarations Letter** Clarifying the Company's profile Code signed & stamped<br>***Company:**<br>**Declarations Letter** Clarifying the Company's profile Code describing its activity as "Company Authorized for Registration"<br>And if not Available The company must apply to systems & information unit for creating a company profile to be able to submit variation requests<br>**N.B.: If Applicant Change for the Imported finished Pharmaceutical Product is needed** kindly submit separate Fulfilled file (as check list) for the Applicant change |

**II) Relevant Documents According to the Variation Type of API Manufacturer Variations (Section 5):**

**( It should be noted that the required Fees is 1000 LE / each Variation / Supplier)**

| | 1- Change in the name and/or address of: a manufacturer of the active substance / starting material, reagent or intermediate used in the manufacture of the active substance. (Signed & stamped) |
|---|---|
| **1** | Recent API Manufacturer certificate with the new name as the same address mentioned in old name certificate, submit one of the following:<br>▪ GMP.<br>▪ ISO 9001 – 2015 (for Minerals, Vitamins and Extracts only).<br>▪ CPP.<br>▪ Written confirmation letter.<br>▪ Quality module 3 (S-Part) 3.2.S.2.1 section in case of GMP is not available ( For Prequalified products).<br>**In case of new name certificate is not including API:**<br>Complete & recent API manufacturer license (or CPP for Korea) with the same new name certificate address & mentioning the API(s) name. |
| **2** | 1. API Manufacturer certificate with the old name as the same address mentioned in new name certificate, submit one of the following:<br>▪ GMP.<br>▪ ISO 9001 – 2015 (for Minerals, Vitamins and Extracts only).<br>▪ CPP.<br>▪ Written confirmation letter. |
| **3** | **In case of local API(s) manufacturer(s), Submit one of the following:**<br>▪ API Manufacturer License issued from Egyptian Drug Authority mentioning the API production line.<br>▪ Data Certificate with API Manufacturer name issued from Egyptian Drug Authority mentioning the API production line. |
| **4** | **In case of the new name GMP is not issued yet:**<br>**Declaration letter** from the authority which is responsible for the manufacturer inspection declares the name change without changing the manufacturing site (location). |
| **5** | **In case of different addresses between the old & new names API manufacturer(s) certificates without change in location:**<br>Layout for the API manufacturer clarifying the entrances of the manufacturer. |

| 2- Deletion of manufacturing sites for an active substance (Signed & stamped / Digitally signed / Electronically signed) | |
|---|---|
| **1** | For **Current** API manufacturer(s)**, Submit one of the following:**<br>▪ GMP.<br>▪ ISO 9001 – 2015 (for Minerals, Vitamins and Extracts only).<br>▪ CPP.<br>▪ Written confirmation letter. |
| **2** | For **Current local** API manufacturer(s)**, Submit one of the following:**<br>▪ API Manufacturer License issued from Egyptian Drug Authority mentioning the API production line.<br>▪ Data Certificate with API Manufacturer name issued from Egyptian Drug Authority mentioning the API production line. |

| 3- Change in the API manufacturer (Signed & stamped) | |
|---|---|
| **a.** | **Introduction of a new manufacturer:** |
| **1** | **For API manufacturer(s) to be added, Submit one of the following:**<br>▪ GMP.<br>▪ ISO 9001 – 2015 (for Minerals, Vitamins and Extracts only).<br>▪ CPP.<br>▪ Written confirmation letter.<br>**N.B.:** the submitted certificate is required to be complete, recent, mentioning the API(s) manufacturer name & its address & the API(s) name(s).<br>**N.B.: if the submitted certificate does not mention the API(s) name:**<br>Submit a complete, recent API(s) manufacturer license (or CPP for Korea) with the same address of GMP certificate & mentioning the API(s) name. |
| **2** | **For the current API manufacturer(s), Submit one of the following:**<br>▪ GMP.<br>▪ ISO 9001 – 2015 (for Minerals, Vitamins and Extracts only).<br>▪ CPP.<br>▪ Written confirmation letter.<br>**N.B.:** the submitted certificate is required to mention the API(s) manufacturer name & its address. |
| **3** | **In case of local API(s) manufacturer(s), Submit one of the following:**<br>**For current & required to be added manufacturer(s) , Submit one of the following:**<br>▪ API Manufacturer License issued from Egyptian Drug Authority mentioning the API production line.<br>▪ Data Certificate with API Manufacturer name issued from Egyptian Drug Authority mentioning the API production line. |

| | |
|---|---|
| **4** | **API(s) manufacturer(s) CoA(s)**, it should fulfill the following:<br>▪ With the same specification of the API in the Product Registration License Composition.<br>▪ Matching with API monograph in all tests and specification limits ranges.<br>▪ Mentioning the expiry date or re-test date.<br>▪ Particle size test range in numbers & solubility test are required if the API particle size will be changes or clarified in the Product Registration License Composition. |
| **5** | **In case of the submitted CoA on manufacturer letterhead Different from the API manufacturer:** Relationship Declaration Letter between the two manufacturers is required. |
| **6** | Updated Pharmacopeia Monograph for API(s). |
| **7** | **In case of API is Pellets/Premix/Granules:** Composition on API manufacturer letterhead & matching with Product Registration License Composition. |
| **8** | **In case of Pellets specification is <u>not In-house</u>:** Justification on API manufacturer letterhead. |
| **9** | Commitment on API manufacturer letterhead declares that: There is no adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. |
| **b.** | **Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place:** |
| **1** | Comparison between current & proposed changes. |
| **2** | Commitment on API manufacturer letterhead declares that: The specifications of the active substance are unchanged , The particle size specification of the active substance and the corresponding analytical method remain the same. |
| **c.** | **Introduction of a new site of micronization:** |
| **1** | Comparison between current & proposed changes. |
| **2** | Commitment on API manufacturer letterhead declares that: The particle size specification of the active substance and the corresponding analytical method remain the same. |

| 4- Changes in the manufacturing process of the active substance (Signed & stamped) | |
|---|---|
| **1** | Comparison between current & proposed changes. |
| **2** | Commitment on API manufacturer letterhead declares that: there is no adverse change in qualitative and quantitative impurity profile or in physico-chemical properties & The specifications of the active substance are unchanged. |

| 5- Change in batch size of active substance (Signed & stamped) | |
|---|---|
| **1** | Comparison between current & proposed changes. |
| **2** | Commitment on API manufacturer letterhead declares that: The change does not adversely affect the reproducibility of the process, does not a result of unexpected events arising during manufacture or because of stability concerns & The specifications of the active substance remain the same. |

| 6- Change to in-process tests or limits applied during the manufacture of the active substance (Signed & stamped) | |
|---|---|
| **1** | Comparison between current & proposed changes. |
| **2** | Commitment on API manufacturer letterhead declares that: The change does not result from unexpected events arising during manufacture ,The test procedure remains the same, or changes in the test procedure are minor & The specification parameter does not concern a critical parameter. |

| 7- Change in the specification parameters and/or limits of an active substance (Signed & stamped) | |
|---|---|
| **1** | COAs for current and proposed changes. |
| **2** | Comparison between current & proposed changes. |
| **3** | Commitment on API manufacturer letterhead declares that: The change does not result from unexpected events arising during manufacture , The test procedure remains the same, or changes in the test procedure are minor & The specification parameter does not concern a critical parameter. |

| 8- Change in test procedure for active substance (Signed & stamped) | |
|---|---|
| **1** | Comparison between current & proposed changes. |
| **2** | Approval from CADC on new test procedure. |
| **3** | Commitment on API manufacturer letterhead declares that: There have been no changes of the total impurity limits; no new unqualified impurities are detected. |

| 9- Change in Primary packaging of the active Substance (Signed & stamped) | |
|---|---|
| **1** | Comparison between current & proposed changes. |
| **2** | Approval on stability study of New packaging material from API Manufacturer. |

| 10- Change in the retest period/storage period or storage conditions of the active substance (Signed & stamped) | |
|---|---|
| **a) Retest period / storage period:** **1. Reduction** | |
| **1** | Comparison between current & proposed changes. |
| **2** | Commitment on API manufacturer letterhead declares that: The change should not be the result of unexpected events arising during manufacture or because of stability concerns. |
| **2. Extension or introduction of a retest period / storage period supported by real time data.** | |
| **1** | Comparison between current & proposed changes. |
| **2** | Approval on stability study from API Manufacturer. |
| **b) Storage conditions:** | |
| **1** | Comparison between current & proposed changes. |
| **2** | Approval on stability study from API Manufacturer. |
| **3** | Commitment on API manufacturer letterhead declares that: The change should not be the result of unexpected events arising during manufacture or because of stability concerns. |

| 11- Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability (Signed & stamped) | |
|---|---|
| | **For an active substance:** |
| **a.** | **New certificate from an approved manufacturer** |
| **b.** | **Updated certificate from an already approved manufacturer** |
| **c.** | **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** | Comparison between current & proposed changes. |
| **2** | New / Update CEP. |
| **3** | Commitment on API manufacturer letterhead declares that: there is no adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. |

| 12- Documents for API(s) manufacturer(s) final approval (Signed & stamped) | |
|---|---|
| **1** | Copy of preliminary approval for API(s) manufacturer(s) addition (If the API manufacturer is not mentioned in the Product Registration License). |
| **2** | Copy of 1st production batch withdrawal report for the API(s) manufacturer(s). |
| **3** | Declaration letter on company's letterhead that the production batch no. …. is the first production one. |
| **4** | Copy of EDA labs. Certificate of analysis on the 1st production batch for API(s) manufacturer(s). |
| **5** | Copy of EDA labs. Composition (in case of registration analysis). |
| **6** | Copy of accelerated stability study on the 1st production batch for API(s) manufacturer(s). |
| **7** | Copy of comparative in – vitro study on the 1st production batch for API(s) manufacturer(s). |
| **8** | API manufacturer GMP certificate with address. |

**N.B.:** In case of API(s) Specifications Change/Clarification and/or the API is BCS Class II or IV & the Dosage Form is Solid or Suspension, Submit a separate Fulfilled PDF file on the same link according to this requirement.

| 13- Documents for API(s) Specifications and/or Particle size change or clarification (Signed & stamped / digitally signed) | |
|---|---|
| **1** | Old composition + New composition with new specs and/or Particle Size on company's letterhead. |
| **2** | **In case of particle size clarification:**<br>An inspection report stating that the production before was using API with particle size: |
| **3** | **In case of there is no need to clarify/change the API Particle size:**<br>A scientific justification on company's letterhead. |

## II- Relevant Documents According to Ownership & Manufacturing Variations (Section 5):

| 1- Change in Name of FPP LH ( Local Products ) | |
|---|---|
| | **Fees:** 1000 L.E. |
| | **Last Updated Commercial Register of The Company.**<br>Mentions the **New** Name of The Company. |
| | **Declaration Letter**<br>With list of all products affected by this name change.<br>*Signed & stamped. |
| | **Declaration Letter**<br>The proposed company trade name in English<br>*Signed & stamped. |

| 2- Change in Name / Address of FPP LH/MAH (Imported/ UL / Bulk Products ) | |
|---|---|
| | **Fees:** 1000 L.E |
| | **Declaration Letter**<br>From LH/MAH<br>Stating that it's the **same** legal entity with no change in LH/MAH, product specifications, quality, composition, manufacturing site & process.<br>Authenticated from Chamber of commerce or Notary & Egyptian consulate/embassy |

| 3- Change in Name of Manufacturing Sites ( Local Products ) | |
|---|---|
| | **Fees:** 1000 L.E. |
| | **Last Updated Factory License**<br>**Released from EDA**<br>"Stating the New Name of the Manufacturing site" |
| | **Declaration Letter**<br>With list of all products affected by this name change.<br>*Signed & stamped. |

| 4- Change in Name / Address of Manufacturing sites (Imported/ UL / Bulk Products) | |
|---|---|
| | **Fees:** 1000 L.E. |
| | **No Change Declaration Letter**<br>From LH<br>Stating that there's NO Change in the physical location of the manufacturing site, manufacturing process, quality & composition of the product. |

| | |
|---|---|
| | Authenticated from Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Certificate of Good Manufacturing Practice (GMP)**<br>For the Site with the NEW Name/Address<br>Valid<br>Authenticated from Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Certificate of Good Manufacturing Practice (GMP)**<br>For the Site with the OLD Name/Address<br>Authenticated from Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Official document from a relevant official body**<br>In case of changing address Justifying the change in address |

| 5- Change in Applicant For Registration ( Imported/ UL / Bulk Products ) | |
|---|---|
| | **Fees for Imported FPP:**<br>In Case of Transfer from Scientific office to Company: 6000 L.E.<br>In Case of Transfer from Company to Scientific Office: 16000 LE.<br>In Case of Transfer from Scientific Office to Scientific Office: 11000 LE.<br>**Fees For UL & Bulk FPP:** 1000 L.E. |
| | **In Case of Imported Finished Human Pharmaceutical Product if the applicant is either Scientific Office or Company the following documents to be submitted:**<br>***Scientific Office:**<br>**a) "Authorization letter for the Scientific Office to register Finished Imported Human Pharmaceutical Products"** issued by Evaluation Unit of registration requests for human pharmaceuticals.<br>**b) Declarations Letter** Clarifying the Company's profile Code signed & stamped<br>***Company:**<br>**Declarations Letter** Clarifying the Company's profile Code describing its activity as "Company Authorized for Registration"<br>And if not Available The company must apply to Systems & Information Unit for creating a Company Profile to be able to submit variation requests<br>**N.B.: If Applicant Change for the Imported Finished Pharmaceutical Product is needed** kindly submit separate Fulfilled file (as check list) for the Applicant change**.** |
| | **Termination letter**<br>From LH<br>The Product Trade Name & Reg. no. is mentioned<br>Name & address of old Applicant mentioned<br>Authenticated from chamber of commerce from country of origin & the Egyptian consulate/embassy<br><br>**Or Waiver**<br>From Old Applicant |

| | |
|---|---|
| | The product trade name & reg. no. is mentioned<br>Authenticated from Bank |
| | **Authorization Letter**<br>From LH<br>The Product Trade Name & Reg. no. is mentioned<br>Name & address of new Applicant mentioned<br>Clarifying its responsibilities for Registration, all Regulatory activities & signing contracts.<br>Authenticated from chamber of commerce from country of origin or Notary & the Egyptian consulate/embassy<br>OR<br>**Agency Agreement between LH and New Applicant**<br>The Product Trade Name & reg. no. is mentioned<br>Name & address of New Applicant mentioned (as written in its commercial register)<br>Clarifying its responsibilities for registration & all regulatory activities.<br>Authenticated from chamber of commerce from country of origin or Notary & the Egyptian consulate/embassy |
| | **Commercial Register** for Old Applicant<br>**OR**<br>**Scientific Office License** In case of scientific office |
| | **For UL FPP**<br>**Manufacturing contract**<br>Between New Applicant & Manufacturer.<br>Authenticated from Chamber of Commerce, Egyptian Consulate/Embassy, EDA Legal Affairs and Bank |
| | **Attached Annex**<br>Mentioning the product name & reg. no. |

| 6- Modification of Registration License | |
|---|---|
| | **Fees:** 1000 L.E. |
| | **EDA Approval**<br>Of the required change to be updated in the registration license issued from relevant EDA department |

| 7- FPP LH Transfer ( Local Products ) | |
|---|---|
| | **Fees:** 5000 L.E. |
| | **Ownership Waiver**<br>From Old LH to New LH<br>Authenticated from Real Estate Registry at Ministry of Justice<br>Authenticated from EDA Legal Affairs<br>Product trade name, strength, dosage form & reg.no. is mentioned |
| | **Manufacturing contract** |

| | |
|---|---|
| | Between New LH & Manufacturing Site<br>Valid<br>Authenticated from Bank & EDA Legal Affairs |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **3 Copies Composition declaration**<br>On New LH head letter<br>Identical to the one attached with the registration license or to the latest finally approved composition<br>Signed & stamped |
| | **Declaration Letter (Template 1)**<br>From Old LH<br>FPP does not have any other strengths of the same dosage form or other dosage forms either registered or under registered products.<br>Signed & stamped. |
| | **Declaration Letter (Template 2)**<br>From New LH<br>FPP does not have any other strengths of the same dosage form or other dosage forms either registered or under registered products.<br>Signed & stamped. |
| | **Declaration Letter (Template 3)**<br>Stating all registered & under-registrations human FPP with their active ingredients owned by the new owner company<br>In case of Toll companies<br>Signed & stamped. |
| | **Declaration Letter**<br>The new LH is committed to provide all safety data related to the product since its placement in market - when needed in addition to implementing all its vigilance activities. |
| | **1st Marketing Permission Report**<br>For the products registered under the ministerial decree 425/2015 & 645/2018. |

| 8- FPP LH/ MAH Transfer ( Imported/ UL / Bulk Products ) | |
|---|---|
| | **Fees:** 5000 L.E. |
| | **Declaration Letter**<br>From New LH/MAH<br>Stating the ownership transfer<br>Ensuring that there is **NO CHANGE** in product composition, specification, manufacturing process and container/closure system.<br>The product trade Name & Reg. no. is mentioned. |

| | |
|---|---|
| | Authenticated from Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Authorization Letter**<br>From New LH to the current applicant.<br>The product trade name & reg. no. is mentioned<br>Name & address of applicant mentioned<br>Clarifying its responsibilities for registration & all regulatory activities<br>Authenticated from chamber of commerce or Notary & the Egyptian consulate/embassy |
| | **For UL FPP**<br>**Manufacturing contract**<br>Between New LH/MAH & Manufacturer.<br>Authenticated from Chamber of Commerce, Egyptian Consulate/Embassy, EDA Legal Affairs and Bank<br>If the contract is between the applicant & manufacturer: A letter from LH/MAH authorizing the applicant to sign contracts |
| | **For Bulk FPP**<br>**Packaging contract**<br>Between New LH/MAH & Packager.<br>Authenticated from Chamber of Commerce, Egyptian Consulate/Embassy, EDA Legal Affairs and Bank<br>If the contract is between the applicant & packager: A letter from LH/MAH authorizing the applicant to sign contracts |
| | **Attached Annex**<br>Mentioning the product name & reg. no.<br>Authenticated from Bank & EDA Legal Affairs |

| 9- Addition/Change of FPP MAH in Egypt ( Imported/ UL / Bulk Products ) | |
|---|---|
| | **Fees:** 5000 L.E. |
| | **Declaration Letter**<br>From LH in COO<br>Product name, reg.no. mentioned<br>Appointing the New MAH in Egypt clarifying its full responsibilities including but not limited to **the right to sell the product in Egypt**<br>Authenticated from Chamber of commerce & Egyptian consulate/embassy |
| | **Applicant Authorization Letter**<br>From New MAH in Egypt<br>Product name, reg.no. mentioned<br>Name & address of applicant mentioned matching with Commercial Register<br>Clarifying its responsibilities for registration & all regulatory activities<br>Authenticated from chamber of commerce & the Egyptian consulate/embassy |

| | |
|---|---|
| | **NO CHANGE Declaration Letter**<br>From New MAH in Egypt<br>Ensuring that there is **NO CHANGE** in product composition, specification, manufacturing process and container/closure system.<br>Authenticated from chamber of commerce & the Egyptian consulate/embassy |

| 10- Change/addition Supplier of Solvent / Diluent for a FPP ( Local / UL Products ) | |
|---|---|
| | **Fees:** 1000 L.E. |
| | **EDA Valid Registration License of solvent**<br>If Final & invalid: Approval for registration renewal<br>If Tentative & invalid: License validity extension approval or approval for submission from Tent. To final |
| | **In Case of Lidocaine Addition/Change:**<br>Composition of Lidocaine the old and new Supplier<br>Previously approved stability study and AR for the old lidocaine Supplier |
| | **Declaration Letter:**<br>Of The Pack Type from the OLD supplier. |
| | **For UL FPP**<br>**Letter of Variation**<br>From product LH in COO<br>Stating the required variation<br>Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary |

| 11- Replacement of a Manufacturing/Packaging site (Local / UL Products ) | |
|---|---|
| | **Fees:**<br>1st site: 3000 L.E<br>2nd site: 5000 L.E<br>3rd site: 10000 L.E<br>4th site: 20000 L.E<br>**N.B: For Transferring the storage site refer to the fees of storage site transfer** |
| | **Waiver**<br>From Old Manufacturing/Packaging Site<br>Mentioning the product name & reg. no.<br>Stating his approval of transferring manufacturing/packaging of the product to a new manufacturing site<br>Authenticated from Bank & EDA Legal Affairs<br>**OR Termination letter**<br>From LH to Old Manufacturing/Packaging Site signed & Stamped<br>With proof of delivery. |
| | **Manufacturing/Packaging contract** |

| | |
|---|---|
| | Between LH/Applicant & New Manufacturer/Packager.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs.<br>In case of a foreign party signing the contract: Authentication from chamber of commerce or Notary& Egyptian embassy/consulate |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Manufacturing site license:**<br>Production line &/or area needed for manufacturing the product is present. |
| ` | **Last Updated Commercial Register**<br>Of the new manufacturing site |
| | **If the site was previously temporarily added:**<br>Copy of the previous approval<br>Copies of all studies & analysis approvals done for this site. |
| | **<u>For UL FPP</u>**<br>**Letter of Variation**<br>From product LH in COO<br>Stating the required variation<br>Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary |

| 12- Addition of a Manufacturing/Packaging site ( Local / UL Products ) | |
|---|---|
| | **Fees:**<br>2nd site: 5000 L.E<br>3rd site: 10000 L.E<br>4th site: 20000 L.E<br>**N.B: For addition the storage site refer to the fees of storage site addition** |
| | **Declaration Letter**<br>From Old Manufacturing/Packaging site.<br>The product trade name & reg. no. is mentioned.<br>Stating his approval of adding a new manufacturing site.<br>Authenticated from Bank & EDA Legal Affairs.<br>**<u>OR</u> Declaration Letter (Templet 4)**<br>From the LH<br>The product trade name & reg. no. is mentioned.<br>Stating: "The company takes the full legal responsibility for adding a new site without any responsibility on EDA, regarding to the obligations and duties imposed under the manufacturing contract with the old factory (factories)".<br>Name of old factories is mentioned. |

| | |
|---|---|
| | Authenticated from Bank & EDA Legal Affairs. |
| | **Manufacturing/Packaging contract**<br>Between LH/Applicant & New Manufacturer/Packager.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs.<br>In case of a foreign party signing the contract: Authentication from chamber of commerce or Notary& Egyptian embassy/consulate |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Manufacturing site license:**<br>Production line &/or area needed for manufacturing the product is present. |
| | **Last Updated Commercial Register**<br>Of the new manufacturing site |
| | **In case of Tentative registration license:**<br>AR approval of the 1st production batch from EDA Labs |
| | **If the site was previously temporarily added:**<br>Copy of the previous approval<br>Copies of all studies & analysis approvals done for this site. |
| | **For UL FPP**<br>**Letter of Variation**<br>From product LH in COO<br>Stating the required variation<br>Authenticated from chamber of commerce or Notary& Egyptian embassy/consulate |

| 13- Replacement or addition of a Storage Site | |
|---|---|
| | **Fees:**<br>1000 L.E |
| | **For Local FPP**<br>**Storage contract:**<br>Between LH & Storage site.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Storage site License** |
| | **For imported FPP**<br>**Importer record (**stating the name of storage site**)** |
| | **For UL FPP**<br>If the contract is between the applicant & Storage site: A letter from LH/MAH authorizing the applicant to sign contracts |

| 14- Replacement or addition of a Manufacturing/Packaging/Batch Releasing Site ( Imported/UL / Bulk Products ) | |
|---|---|
| | **Fees:**<br>1st site change: 3000 L.E<br>2nd site addition/change: 5000 L.E<br>3rd site addition/change: 10000 L.E<br>4th site addition/change: 20000 L.E |
| | **Letter of Variation**<br>From product LH in COO<br>Product name, reg.no. mentioned<br>Stating the required variation<br>Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary<br>****in case of the variation doesn't Mentioned in the CPP of the product (For 2ry Packaging/Batch Releasing Site)** |
| | **Certificate of Good Manufacturing Practice (GMP)**<br>For new site<br>Valid<br>Authenticated from Chamber of commerce & Egyptian consulate/embassy or Notary |
| | **If the New Site is located in a Non-reference country:**<br>**CPP from Reference country:**<br>Valid<br>Product registered & marketed<br>Where the proposed site in mentioned (For MFG/1ry Packaging site)<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |

| 15- Scaling up or down of FPP production batch size (Local/ UL / Imported Products) | |
|---|---|
| | **Fees:** 1000 L.E. |
| | **<u>For Local & UL Products</u>**<br>**EDA Inspection Report**<br>Stating the currently approved batch size & Mentioning the proposed batch size<br>Clarifying if this change will be accompanied by changes in the manufacturing process or equipment<br>Signed & stamped from EDA inspector |
| | **<u>For UL & Imported Products</u>**<br>**Letter of Variation**<br>From Product LH in COO<br>Stating the required variation |
| | **Declaration Letter** |

| | |
|---|---|
| | Stating that "This change is for marketing reasons only with NO change in quality, manufacture and stability of the product" |
| | **Declaration Letter**<br>Stating that "The company didn't get a previous approval for batch size change for this product"<br>In case presence of a previous approval, state number and date of the approval and attach it with the file |
| | **Declaration Letter**<br>Stating that "There is YES/No change in the manufacturing process"<br>**In Case of YES<br>Old & New Flow Chart of manufacturing process. |
| | **Declaration Letter**<br>Stating that "There is YES/No change in the manufacturing equipment except only those necessitated by the change in batch size (e.g. use of different sized equipment with same design & operating principle)<br>**In Case of YES<br>**Declaration Letter**<br>stating the comparison between the Old & New manufacturing equipment. |
| | **If New Registration license is registered according to 425 or 645 (in case of Change/Addition of Batch Size)**<br>(Please clarify if change is related to the first three production batches manufactured **or /No**) |

| 16- Change Reg. Type from Imported Finished to Imported Bulk | |
|---|---|
| | **Fees:**<br>Packaging site change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of Packaging site of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Packaging contract**<br>Between LH/Applicant & New Packager.<br>A letter from LH/MAH authorizing the applicant to sign contracts<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce or Notary& Egyptian embassy/consulate is needed in case that the LH/MAH signing the contract. |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Packaging site license**<br>Area needed for packaging the product is present |

| | |
|---|---|
| | **Last Updated Commercial Register**<br>Of the new packaging site |
| | **Storage contract**<br>Between LH/Applicant & Storage site.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce or Notary& Egyptian embassy/consulate is needed in case that the LH/MAH signing the contract. |
| | **Storage Site License** |

| 17- Change Reg. Type from Imported Finished to UL | |
|---|---|
| | **Fees:**<br>Bulk Manufacturing Site Change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of Bulk Manufacturing Site of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Manufacturing Contract:**<br>Between LH/Applicant & New manufacturer.<br>A letter from LH/MAH authorizing the applicant to sign contracts<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce or Notary& Egyptian embassy/consulate is needed in case that the LH/MAH signing the contract. |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Manufacturing site license:**<br>Production line &/or area needed for manufacturing the product is present. |
| | **Last Updated Commercial Register** (New Manufacturer) |
| | **Storage contract**<br>Between LH/Applicant & Storage site.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce or Notary& Egyptian embassy/consulate is needed in case that the LH/MAH signing the contract. |
| | **Submission of API supplier addition request.** |

| | |
|---|---|
| | Refer to API supplier addition checklist |

| 18- Change Reg. Type from Imported Finished to Local | |
|---|---|
| | **Fees:**<br>Ownership Transfer: 5000 L.E<br>Bulk Manufacturing site change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of ownership of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **In case of Toll Manufacturing:**<br>**Manufacturing contract:**<br>Between New LH & New manufacturer/packager.<br>Authenticated from Bank & EDA Legal Affairs. |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Manufacturing site license**<br>Production line &/or area needed for manufacturing the product is present. |
| | **Last Updated Commercial Register** (New Manufacturer) |
| | **Storage contract:**<br>Between New LH & Storage site.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs. |
| | **Storage Site License** |
| | **3 Copies Composition declaration:**<br>On New LH Paper<br>Signed & stamped<br>Identical to the one attached with the registration license or to the latest finally approved composition |
| | **Submission of API supplier addition request.**<br>Refer to API supplier addition checklist |

| 19- Change Reg. Type from UL to Imported Finished | |
|---|---|
| | **Fees:**<br>Bulk Manufacturing Site Change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of Bulk MFG Site of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Certificate of Good Manufacturing Practice (GMP)**<br>For New Manufacturing site<br>Valid & Authenticated from Chamber of Commerce or Notary & Egyptian Consulate/Embassy |
| | **Manufacturing Waiver**<br>From old manufacturer<br>The product trade name & reg. no. is mentioned<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Importer Record** |

| 20- Change Reg. Type from UL to Imported Bulk | |
|---|---|
| | **Fees:**<br>Bulk Manufacturing Site Change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of Bulk Manufacturing Site of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Certificate of Good Manufacturing Practice (GMP)**<br>For new Manufacturing site<br>Valid<br>Authenticated from Chamber of Commerce or Notary & Egyptian Consulate/Embassy |
| | **Manufacturing Waiver**<br>From old manufacturer<br>The product trade name & reg. no. is mentioned<br>Authenticated from Bank & EDA Legal Affairs |
| | **Packaging contract (In Case of Changing Packaging Site)**<br>Between LH/Applicant & New Packager. |

| | |
|---|---|
| | A letter from LH/MAH authorizing the applicant to sign contracts<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce or Notary& Egyptian embassy/consulate is needed in case that the LH/MAH signing the contract. |
| | **Last Updated Importer Record** |

| 21- Change Reg. Type from UL to Local | |
|---|---|
| | **Fees:**<br>Ownership Transfer: 5000 L.E<br>Bulk Manufacturing Site Change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of ownership of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Manufacturing Waiver**<br>From old manufacturer (In case of changing MFG site)<br>The product trade name & reg. no. is mentioned<br>Authenticated from Bank & EDA Legal Affairs |
| | **In case of Toll Manufacturing:**<br>**Manufacturing contract:**<br>Between LH & New manufacturer/packager.<br>Authenticated from Bank & EDA Legal Affairs. |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Manufacturing site license**<br>Production line &/or area needed for manufacturing the product is present. |
| | **Storage contract:**<br>Between LH/Applicant & Storage site.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs. |
| | **Storage Site License** |
| | **3 Copies Composition declaration:**<br>On New LH Letterhead<br>Signed & stamped<br>Identical to the one attached with the registration license or to the latest finally approved composition |

| 22- Change Reg. Type from Imported Bulk to Imported Finished | |
|---|---|
| | **Fees:**<br>Packaging site change: 3000 L.E. |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of Packaging site of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **Waiver**<br>From old packager<br>The product trade name & reg. no. is mentioned<br>Authenticated from Bank & EDA Legal Affairs |
| | **Certificate of Good Manufacturing Practice (GMP)**<br>For new packaging site<br>Valid<br>Authenticated from Chamber of Commerce & Egyptian Consulate/Embassy |

| 23- Change Reg. Type from Imported Bulk to UL | |
|---|---|
| | **Fees:**<br>Bulk Manufacturing site change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of Bulk MFG site of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce or Notary & Egyptian consulate/embassy |
| | **In case of Toll Manufacturing:**<br>**Manufacturing contract**<br>Between LH/Applicant & New Manufacturer.<br>Valid.<br>A letter from LH/MAH authorizing the applicant to sign contracts<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract. |
| | **Attached Annex of the contract** |

| | |
|---|---|
| | The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Last Updated Manufacturing site license**<br>Production line &/or area needed for manufacturing the product is present. |
| | **Last Updated Commercial Register** ( New Manufacturer) |
| | **Packaging Waiver**<br>From old packager (In case of changing packaging site)<br>The product trade name & reg. no. is mentioned<br>Authenticated from Bank & EDA Legal Affairs |
| | **Storage contract**<br>Between LH/Applicant & Storage site.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract. |
| | **Storage Site License** |
| | **Submission of API supplier addition request.**<br>Refer to API supplier addition checklist |

| 24- Change Reg. Type from Imported Bulk to Local | |
|---|---|
| | **Fees:**<br>Ownership Transfer: 5000 L.E<br>Bulk Manufacturing site change: 3000 L.E |
| | **Letter of Variation**<br>From LH/MAH<br>Stating the transfer of ownership of the product with clarification of the consequential changes and justification for this change<br>The product trade name & reg. no. is mentioned<br>Authenticated by the Chamber of commerce & Egyptian consulate/embassy |
| | **In case of Toll Manufacturing:**<br>**Manufacturing contract**<br>Between New LH & New Manufacturer.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs. |
| | **Attached Annex of the contract**<br>The product trade name & reg. no. is mentioned.<br>Authenticated from Bank & EDA Legal Affairs |
| | **Latest Updated Manufacturing site license** |

| | |
|---|---|
| | Production line &/or area needed for manufacturing the product is present. |
| | **Last Updated Commercial Register**<br>Of the new manufacturing site |
| | **Packaging Waiver <u>(In case of Changing Packaging Site)</u>**<br>From old packager<br>The product trade name & reg. no. is mentioned<br>Authenticated from Bank & EDA Legal Affairs |
| | **Storage contract**<br>Between New LH & Storage site.<br>Valid.<br>Authenticated from Bank & EDA Legal Affairs.<br>Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract. |
| | **Storage Site License** |
| | **3 Copies of Composition declaration**<br>On New LH Letterhead<br>Signed & stamped<br>Identical to the one attached with the registration license or to the latest finally approved composition |
| | **Submission of API supplier addition request.**<br>Refer to API supplier addition checklist |

| 25- Updating Analysis File | |
|---|---|
| | **Fees:** 1000 L.E. |
| | * **150 EDA Chairman Renewal Approval**<br>* CADC Labs Analysis Certificate **<u>OR</u>** A "Not Found" Letter from CADC |

## III- Relevant Documents According the Variation Type for Composition & Specification Variations (Section 5) :

**(It should be noted that the required Fees is 1000 LE / each Variation)**

| 1- Change in name of the active substance or of an excipient | |
|---|---|
| **1** | Old composition "signed and stamped". |
| **2** | New composition "signed and stamped". |
| **3** | Comparison table between old and new composition. |
| **4** | C.O.A of all suppliers of Active / inactive Ingredients. |
| **5** | Pharmacopeia Monograph active ingredient or reference for the name of inactive ingredient. |

| 2- Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration | |
|---|---|
| **1** | Old composition "signed and stamped". (If needed) |
| **2** | New composition "signed and stamped". (If needed) |
| **3** | Safety Data Sheet for Ink including composition of ink (In case of change or addition of imprints). |
| **4** | Reference for scoring (In case of Change or addition of scoring/break lines on tablets). |
| **5** | Commitment to be written in pamphlet and on outer pack, reference of Innovator and its leaflet (In case of Addition of Non-Functional Scoring / break lines). |
| **6** | Commitment that change doesn't affect on stability of the product. |

| 3- Change in the shape or dimensions of the pharmaceutical form | |
|---|---|
| **1** | Sample (IF Needed). |
| **2** | Old & New Certificate of Analysis. |
| **3** | Old & New finished Pharmaceutical product specifications. |
| **4** | Commitment that change doesn't affect on stability of the product. |

| 4- Changes in the composition (excipients) of the finished pharmaceutical product | |
|---|---|
| **1** | Old composition "signed and stamped". |
| **2** | New composition "signed and stamped". |
| **3** | Comparison table between old and new composition. |

| | |
|---|---|
| **4** | In case of hard gelatin capsule: submit capsule shell composition on supplier paper. |
| **5** | In case of clarification of capsule shell composition: A report from Inspection Department stating the Capsule shell composition including batch record if not documented in any previous approvals. |
| **6** | In case of Coating blends (e.g. Opadry / Eudragit / Kollicoat / Flavors on supplier paper/ Ink), submit composition and COA of supplier. |
| **7** | Scientific justification & Reference and write in composition the cause of Addition (e.g. for Manufacturing loss) (In case of Elimination, Reduction or Addition of an overage). |
| **8** | C.O.A & Composition of all suppliers of Active Ingredient or Premixes. |
| **9** | Calculations of pellets/Premix on company paper head. |
| **10** | In Case of Change of salt equivalence and/or crystalline state of the drug substance (refer to section 5). |
| **11** | Scientific Reference for Finished Pharmaceutical Product PH (In Case of Change PH Range). |
| **12** | Calculation of approved limit (In case of presence of Methyl paraben and propyl paraben in oral liquid dosage forms 'suspension and syrup'). |

| 5- Change in coating weight of oral dosage forms or change in weight of capsule shell | |
|---|---|
| **1** | Old composition "signed and stamped". |
| **2** | New composition "signed and stamped". |
| **3** | Comparison table between old and new composition. |
| **4** | In case of hard gelatin capsule: submit capsule shell composition on supplier paper. |
| **5** | In case of Coating blends (e.g. Opadry / Eudragit / Kollicoat / Flavors on supplier paper/ Ink), submit composition and COA of supplier. |
| **6** | Scientific justification & Reference and write in composition the cause of Addition (e.g. for Manufacturing loss) (In case of Elimination, Reduction or Addition of an overage). |
| **7** | Commitment that Finished Pharmaceutical product specification has only been updated in respect of weight and dimensions. |

| 6- Change in the specification parameters and/or limits of the Finished Pharmaceutical product | |
|---|---|
| **1** | Old Finished Pharmaceutical product specifications "signed and stamped". |
| **2** | New Finished Pharmaceutical product specifications "signed and stamped". |
| **3** | Comparison table between old and new Finished Pharmaceutical product specifications |
| **4** | Scientific justification & Reference for the requested change |
| **5** | Pharmacopeia Monograph |

| 7- Change in the shelf-life or storage conditions of the Finished Pharmaceutical product<br>Reduction of the shelf life | |
|---|---|
| **1** | Reference of Innovator. |

| | |
|---|---|
| **2** | Scientific Justification for this Reduction. |
| **3** | Any Stability studies or documents for new shelf life that clarifying the need of reduction of shelf life must be submitted. |
| **4** | **In Case of Imported or Under license Files:** Declaration Letter from LH/MAH in COO signed and stamped: Stating reasons of reduction. |

| 8- Change in the shelf-life or storage conditions of the Finished Pharmaceutical product Extension of the shelf life | |
|---|---|
| **1** | Stability study approval |

| 9- Change in storage conditions of the Finished Pharmaceutical product or the diluted/reconstituted product | |
|---|---|
| **1** | Stability study approval |

| 10- Change in test procedure for the Finished Pharmaceutical product | |
|---|---|
| **1** | Approved CoA from CADC with proposed change |

| 11- Clarification / Change of salt equivalence and/or crystalline state (E.g. hydrate, solvate, polymorph) | |
|---|---|
| **1** | Old composition "signed and stamped". |
| **2** | New composition "signed and stamped". |
| **3** | Comparison table between old and new composition. |
| **4** | Scientific Reference for Molecular weight of base and salt. (e.g. Pharmacopeia). |
| **5** | Calculations of salt equivalence on company paper signed and stamped. |
| **6** | Innovator Reference stating the salt form and its quantity. |
| **7** | C.O.A & Composition of all suppliers of Active Ingredient or Premixes. |
| **8** | In case of clarification: a report from Inspection Department stating the form of used materials including batch record and any previous studies on the same batch. |
| **9** | In case of clarification: Import plans or approvals, Customs releases, invoices and supplier certificates, have the same batch numbers that were imported for three years. |

| 12- Clarification /Change of particle size for water Insoluble or sparingly soluble API |
|---|

| | (Particle size must be stated in suppliers COA by D90 or mesh size) |
|---|---|
| **1** | Old composition "signed and stamped" |
| **2** | New composition "signed and stamped" |
| **3** | Comparison table between old and new composition |
| **4** | C.O.A of all suppliers for active ingredient stated D 90 or mesh size |
| **5** | Stating Range of D90 in New Composition. |
| **6** | A report from Inspection Department stating the Range of D90 of used materials (In case of Clarifying Particle Size). |
| **7** | Import plans or approvals, Customs releases, invoices and supplier certificates, have the same batch numbers that were imported for three years (In case of Clarifying Particle Size). |

| | 13- Clarification /Change or Addition of the solvents used in manufacturing process (e.g. ethanol, methanol) |
|---|---|
| **1** | Old composition "signed and stamped" |
| **2** | New composition "signed and stamped" |
| **3** | Comparison table between old and new composition |
| **4** | Declaration Letter States class of the solvent according to USP Classification. |
| **5** | In New Composition; write the solvent used & that it is totally evaporated during manufacturing process. |
| **6** | In case of Clarification: inspection report including Batch Record for old production batches clarifying that the solvent was used before |

| | 14- Clarification /Change of Active / Inactive Ingredient Specification |
|---|---|
| **1** | Pharmacopeia Monograph (Last Edition) |
| **2** | C.O.A of all suppliers of Active Ingredient or Premixes. |
| **3** | Comparison between Old & New Finished Pharmaceutical product Specification signed and stamped. |
| **4** | Import plans or approvals, Customs releases, invoices and supplier certificates, have the same batch numbers that were imported for three consecutive years. (In case of clarifying Specifications of Active Ingredient or in case of suppliers are not stated in registration license) |
| **5** | Old composition "signed and stamped" |
| **6** | New composition "signed and stamped" |
| **7** | Comparison table between old and new composition. |

| 15- Change in Color of Finished Pharmaceutical product | |
|---|---|
| **1** | Sample (IF Needed). |
| **2** | Old & New Certificate of Analysis. |
| **3** | Pharmacopeia Monograph & Certificate of analysis of supplier of active ingredient or pellets or premixes (In Case of Change in Range of color without any qualitative or quantitative change in composition). |
| **4** | Scientific Justification for color change with scientific reference. |
| **5** | Manufacturing process flow chart (In case of the Change in physical character is due to change in Manufacturing process). |
| **6** | Composition of capsule shell on supplier paper (In case of Change color of capsule shell). |

| 16- Correcting Dosage Form | |
|---|---|
| **1** | Innovator reference and it's leaflet. |
| **2** | Any studies issued previously for New Dosage form. |

| 17- Change / Addition of Route of Administration | |
|---|---|
| **1** | Reference for Innovator and its leaflet. |
| **2** | Any Studies issued previously for New Route of Administration. |
| **3** | In case of Infusion: Submit declaration letter stating the used solvent for infusion. |

| 18- Change in primary packaging of the finished pharmaceutical product | |
|---|---|
| **1** | COAs of Old Packs containing full detailed description for type of pack, its capacity and liner. |
| **2** | COAs of New Packs from suppliers containing full detailed description for type of pack, its capacity and liner. |
| **3** | Sample. |

| 19- Change in shape of the container | |
|---|---|
| **1** | COAs of Old Packs containing full detailed description for type of pack, its capacity and liner. |
| **2** | COAs of New Packs from suppliers containing full detailed description for type of pack, its capacity and liner. |
| **3** | Sample. |
| **4** | Reference for new shape. |

| | 20- Change in pack size of the finished product |
|---|---|
| **1** | COAs of Old Packs containing full detailed description for type of pack, its capacity and liner. |
| **2** | COAs of New Packs from suppliers containing full detailed description for type of pack, its capacity and liner. |
| **3** | Sample. |
| **4** | Reference for new pack size. |

| | 21- Change in any part of the primary packaging not in direct contact with the finished product formulation |
|---|---|
| **1** | COAs of Old Packs containing full detailed description for type of pack, its capacity and liner. |
| **2** | COAs of New Packs from suppliers containing full detailed description for type of pack, its capacity and liner. |
| **3** | Sample. |
| **4** | Reference for new pack (Related to change / addition accessory). |

| | 22- Change in supplier of packaging components / devices |
|---|---|
| **1** | COAs of Old Packs containing full detailed description for type of pack, its capacity and liner. |
| **2** | COAs of New Packs from suppliers containing full detailed description for type of pack, its capacity and liner. |
| **3** | Sample. |
| **4** | Certificate of device. |

| | 23-Final Approval Variation for composition change |
|---|---|
| **1** | Approved Composition "on company paper signed and stamped". |
| **2** | All Studies issued on primary approval for the product and its original copies (to be seen):<br>a) EDA LABS COA & Composition<br>b) Stability Approval<br>c)In Vivo or In Vitro study approval |
| **3** | Copy of receiving receipt from stability & BE administrations |
| **4** | A copy of the Inspection sampling report, stating the batch number and the date of its production |

| 24-Final Approval Variation for pack change | |
|---|---|
| **1** | All Studies issued on primary approval for the product and its original copies (to be seen):<br>a. EDA LABS COA / Composition.<br>b. Stability Approval. |
| **2** | Copy for receiving receipt from stability administration. |
| **3** | A copy of the Inspection sampling report, stating the batch number and the date of its production. |

# Variation Application Form of Post Marketed Human Products

| | |
|---|---|
| **Name of the product/s:** | **Applicant:** |
| | |
| **Active substance(s):** | **Manufacturer of Finished Pharmaceutical product:** |
| | |
| **Concentration:** | **Manufacturer of solvent:** |
| | |
| **Dosage form:** | **Name of contact:** |
| | |
| **Registration Decree:** | **Telephone number:** |
| | |
| **Registration number:** | **E-mail:** |
| | |

| **Classification of the Submitted Variation**<br>**According to Variation Guidelines** | |
|---|---|
| **PAC-N** | |
| **PAC-A** | |
| **PAC-B** | |
| **PAC-II** | |
| **Relevant part according to Variation Guidelines:** | |
| **Not Reportable in Guidelines:** | |
| **Evaluation Route:** | ☐ **Full Evaluation Route**<br>☐ **Reliance Evaluation Route** |

| **Variation changes (Tick the appropriate change required)**<br>**Please Tick all the variations submitted in case of multiple variations** | **Change** | **Addition** | **Clarify** |
|---|---|---|---|
| **A) Composition & Specification Changes As:** | | | |
| Name of active substance | | | |
| Name of an Excipient | | | |
| Imprints / Embossing / other marking | | | |
| Scoring | | | |
| Shape of pharmaceutical finished product | | | |
| Dimensions of pharmaceutical finished product | | | |
| Excipient | | | |
| Coating weight / weight of capsule shell | | | |
| Color of (coat / capsule shell, etc ….) | | | |
| Specification of Finished Pharmaceutical product | | | |
| Shelf life | | | |

| | Change | Addition | Clarify |
|---|---|---|---|
| Storage Conditions | | | |
| API form as salt equivalence and/or crystalline state | | | |
| Test procedure | | | |
| The particle size of API (state D90) | | | |
| Solvents | | | |
| Specification of Active ingredient | | | |
| Specification of Inactive ingredients | | | |
| Route of Administration | | | |
| Dosage Form | | | |
| **B) Container Closure System Changes As:** | | | |
| Primary packaging of finished pharmaceutical product | | | |
| Shape of container | | | |
| Pack size of finished pharmaceutical product | | | |
| Part of primary packaging material not in contact with the finished product formulation | | | |
| Supplier of packaging components / Devices | | | |
| Clarify the change concerning which type of packs: Local/Tender/Export/Hospital use | | | |
| **C) Ownership / Manufacturing Changes As:** | | | |
| Name of License holder | | | |
| Address of License holder | | | |
| Name of Manufacturer site | | | |
| Address of Manufacturer site | | | |
| Applicant for imported FPPs | | | |
| Modification of Registration License | | | |
| License Holder Transfer | | | |
| Marketing Authorization holder Transfer | | | |
| Marketing Authorization holder in **Egypt** | | | |
| Solvent Manufacturer | | | |
| Manufacture site | | | |
| Primary Packager | | | |
| Secondary Packager | | | |
| Storage Site | | | |
| Batch Releaser | | | |
| Batch size factor of 10 X | | | |
| Batch size over 10 X | | | |
| Change Registration Type | | | |
| Updating Analysis File | | | |
| Addition of Manufacturer for Export only | | | |

| | Change | Addition | Clarify |
|---|---|---|---|
| **D) API Manufacturer changes as:** | | | |
| Name of API Manufacturer | | | |
| Address of API Manufacturer | | | |
| Deletion of API Manufacturer | | | |
| API Manufacturer | | | |
| Manufacturing process of API | | | |
| Batch size of API | | | |
| In process tests during the manufacture of API | | | |
| Specification parameters &/or limits of API | | | |
| Test Procedures during the manufacture of API | | | |
| Primary packaging of API | | | |
| Retest period/storage period of API | | | |
| Storage condition of API | | | |
| CEP | | | |
| **E) Miscellaneous** | | | **Tick for required Issue** |
| Final Approval Composition/Specification | | | |
| Final Approval for container closure system | | | |
| Final Approval for API Manufacturer | | | |
| Appeal | | | |
| Cancelling previous variation approvals | | | |

| **BACKGROUND & JUSTIFICATION FOR REQUIRED CHANGE/ S**<br>**(Please give brief background explanation for the proposed changes)** | |
|---|---|
| **Current** | **Proposed** |
| | |

**In case of Appeal / Final Approvals:** **(Please Clarify exactly the issue required)**

**In Case of Reliance Evaluation Route:**
Please Identify the Climatic Zone on which the stability study in country of origin was approved.

| **kindly fulfill the following Amendments by Yes / NO** | **Yes** | **No** |
|---|---|---|
| 1- Is All documents & information submitted in the file are correct and on the responsibility of the company | | |
| 2- Is the submitted file contains all the approvals for the product that were not mentioned in the last released registration license | | |
| 3- Is the submitted file contains the latest issued registration license | | |

| | | |
|---|---|---|
| 4- Is the submitted file contains Valid registration license **(In case of Invalidation Please submit registration renewal or validity extension)** | | |
| 5- Is the submitted file contains Valid Pricing license | | |
| 6- Is the submitted EDA lab composition and its certificate of analysis is the last composition analyzed by CADC Labs. | | |
| 7- Is the submitted file contains all approvals, variations, decisions & exemptions issued for the product from different EDA departments | | |

**Kindly state the following data:**

1- In case of Any previous variations' approvals, variations, decisions & exemptions issued for the product from different EDA departments **(please arrange the with dates if available)**

1-
2-

2- Data of the last manufactured/imported production batch:

A- Batch No.:
B- Production date:
C- Expiry date:
Is a Ministerial decree 600/2018 exemption approval **(If needed)** is Attached: **Yes / No**

3- If New Registration license is registered according to 425 or 645 **(In case of Batch Size)**
(Please clarify if change is related to first three production batches manufactured or No) **Yes / No**

4- Status from submission to pharmacovigilance (In case of changing the Marketing Authorization data)

5- Payment receipt No: (Its Value according to Variation Request, must be directed to variation department and stamped with EDA Stamp with the Product Name, Concentration, Dosage Form, Type of variation.

6-Please clarify which conditions according to guideline concerning variation request are fulfilled (with evidence)
A-
B-
C-
D-

7- Name & address of Manufacturers of API of product as stated in GMP Name & address of suppliers of API of product

| |
|---|
| |
| 8- Please Clarify the Following<br>A- BCs Class of Active Substance: (Kindly attach Biopharmaceutics Classification System **Reference**)<br>☐ Class I<br>☐ Class II<br>☐ Class III<br>☐ Class IV<br><br>B- The Product Is Innovator:<br>☐ Yes<br>☐ No |
| |

| **Signature by the Authorized Person:** | **Company Stamp** |
|---|---|
| | |

## Template 1

**السيد / رئيس الإدارة المركزية للمستحضرات الصيدلية**
**الإدارة العامة لتسجيل المستحضرات البشرية**
**إدارة المتغيرات للمستحضرات البشرية**

**تحية طيبة وبعد،،،،،**

**بخصوص المستحضر الآتي:**

| | | |
|---|---|---|
| **Trade Name:** | | |
| **Dosage Form:** | | |
| **Active Ingredients / Strength:** | | |
| **Registration No.:** | | |
| **Applicant Company:** | | |
| **License Holder / MAH:** | | |
| **Manufacturer / Packager:** | | |
| **License Validity:** | ○ Valid<br>○ In-valid | Re-Reg 296/2009<br>Re-Reg 425/2015<br>Re-Reg 150/2022 |
| **Current status:** | | |
| **Proposed status:** | | |

أتعهد أنا ..... رئيس مجلس إدارة شركة .....(المالك القديم للمستحضر) ..... بأن المستحضر ليس له تركيزات أخرى من نفس الشكل الصيدلي أو أشكال صيدلية أخرى مسجلة أو تحت التسجيل مملوكة للشركة.

**و تفضلوا بقبول وافر الإحترام والتقدير،،،،،**

**رئيس مجلس ادارة الشركة** **ختم الشركة**

## Template 2

**السيد / رئيس الإدارة المركزية للمستحضرات الصيدلية**
**الإدارة العامة لتسجيل المستحضرات البشرية**
**إدارة المتغيرات للمستحضرات البشرية**

**تحية طيبة وبعد،،،،،**

**بخصوص المستحضر الآتي:**

| | | |
|---|---|---|
| **Trade Name:** | | |
| **Dosage Form:** | | |
| **Active Ingredients / Strength:** | | |
| **Registration No.:** | | |
| **Applicant Company:** | | |
| **License Holder / MAH:** | | |
| **Manufacturer / Packager:** | | |
| **License Validity:** | ○ Valid<br>○ In-valid | Re-Reg 296/2009<br>Re-Reg 425/2015<br>Re-Reg 150/2022 |
| **Current status:** | | |
| **Proposed status:** | | |

أتعهد أنا ..... رئيس مجلس إدارة شركة .....(المالك الجديد للمستحضر) ..... بأن المستحضر ليس له تركيزات أخرى من نفس الشكل الصيدلي أو أشكال صيدلية أخرى مسجلة أو تحت التسجيل مملوكة للشركة.

**و تفضلوا بقبول وافر الإحترام والتقدير،،،،،**

**رئيس مجلس ادارة الشركة** **ختم الشركة**

## Template 3

**السيد / رئيس الإدارة المركزية للمستحضرات الصيدلية**
**الإدارة العامة لتسجيل المستحضرات البشرية**
**إدارة المتغيرات للمستحضرات البشرية**

**تحية طيبة وبعد،،،،،**

أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بأن المستحضرات المملوكة للشركة هم كالآتي:

| Registered Product | | | | Under-Registration Products | | | |
|---|---|---|---|---|---|---|---|
| | Trade Name / Dosage Form | API / Strength | Reg. Decree | | Trade Name / Dosage Form | API / Strength | Reg. Decree |
| 1 | | | | 1 | | | |

**و تفضلوا بقبول وافر الإحترام والتقدير،،،،**

**رئيس مجلس ادارة الشركة** **ختم الشركة**

## Template 4

**السيد / رئيس الإدارة المركزية للمستحضرات الصيدلية**
**الإدارة العامة لتسجيل المستحضرات البشرية**
**إدارة المتغيرات للمستحضرات البشرية**

**تحية طيبة وبعد،،،،،**

**بخصوص المستحضر الآتي:**

| | | |
|---|---|---|
| **Trade Name:** | | |
| **Dosage Form:** | | |
| **Active Ingredients / Strength:** | | |
| **Registration No.:** | | |
| **Applicant Company:** | | |
| **License Holder / MAH:** | | |
| **Manufacturer / Packager:** | | |
| **License Validity:** | ○ Valid<br>○ In-valid | Re-Reg 296/2009<br>Re-Reg 425/2015<br>Re-Reg 150/2022 |
| **Current status:** | | |
| **Proposed status:** | | |

أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بتحمل كافة المسؤولية القانونية لإضافة مكان التصنيع .....(اسم المصنع الجديد/المصانع الجديدة)..... دون أدنى مسؤولية على هيئة الدواء المصرية تجاه عقود التصنيع المبرمة بين شركة .....(اسم المالك للمستحضر)..... وشركة .....(اسم المصنع القديم/المصانع القديمة).....

**و تفضلوا بقبول وافر الإحترام والتقدير،،،،،**

**رئيس مجلس ادارة الشركة** **ختم الشركة**

## Template 5

**السيد / رئيس الإدارة المركزية للمستحضرات الصيدلية**
**الإدارة العامة لتسجيل المستحضرات البشرية**
**إدارة المتغيرات للمستحضرات البشرية**

**تحية طيبة وبعد،،،،،**

**بخصوص المستحضر الآتي:**

| | | |
|---|---|---|
| **Trade Name:** | | |
| **Dosage Form:** | | |
| **Active Ingredients / Strength:** | | |
| **Registration No.:** | | |
| **Applicant Company:** | | |
| **License Holder / MAH:** | | |
| **Manufacturer / Packager:** | | |
| **License Validity:** | ○ Valid<br>○ In-valid | Re-Reg 296/2009<br>Re-Reg 425/2015<br>Re-Reg 150/2022 |
| **Required Variation:** | | |

أتعهد أنا ..... رئيس مجلس إدارة شركة .....(أو الشخص المسؤول) ..... بالالتزام بالآتي في كلا من المصنعين:

Batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates or FPP Specifications.

كما اتعهد بالالتزام بالاتى:

Commitment to place the first production-scale batch of the FPP produced at the new site into the long-term stability program to be conducted and the applicant is responsible to notify the Pharmaceutical Products (Human/Veterinary, ….) Variation Administrations in EDA in case of any unfavorable out of specification that have negative impact on the quality of the finished pharmaceutical products.

**و تفضلوا بقبول وافر الإحترام والتقدير،،،**

**رئيس مجلس ادارة الشركة/ أو الشخص المسؤول** **ختم الشركة**

## Template For Commitment of fulfilling conditions

**السيد / رئيس الإدارة المركزية للمستحضرات الصيدلية**
**الإدارة العامة لتسجيل المستحضرات البشرية**
**إدارة المتغيرات للمستحضرات البشرية**

**تحية طيبة وبعد،،،،،**

**بخصوص المستحضر الآتي:**

| | | |
|---|---|---|
| **Trade Name:** | | |
| **Dosage Form:** | | |
| **Active Ingredients / Strength:** | | |
| **Registration No.:** | | |
| **Applicant Company:** | | |
| **License Holder / MAH:** | | |
| **Manufacturer / Packager:** | | |
| **License Validity:** | ○ Valid<br>○ In-valid | Re-Reg 296/2009<br>Re-Reg 425/2015<br>Re-Reg 150/2022 |
| **Required Variation:** | | |

أتعهد أنا ..... رئيس مجلس إدارة شركة .....(أو الشخص المسؤول) ..... بأن التغيير المطلوب يستوفي كافة الشروط (Fulfilling conditions) المنصوص عليها بالإصدار الثالث للقواعد الإرشادية الخاصة بإدارة المتغيرات للمستحضرات البشرية.

**و تفضلوا بقبول وافر الإحترام والتقدير،،،**

**رئيس مجلس ادارة الشركة/ أو الشخص المسؤول** **ختم الشركة**