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- Introduction

A variation application details a proposed change to approved documentation, providing a formal means by which the approved licence details held by the Competent Authorities for a given medicinal product can be updated.

2- Scope

Is to issue Post Authorized variations ensuring high quality, safe & effective human drugs in relation to time criticality & avoidance of drug shortage.

3- Definitions

***Types of variation approvals:**

Variation department approval (VDA): needs prior approval by the variation department (VDA) before implementation

Variation committee approval (VCA): needs prior approval by the variation committee (VCA) before implementation

Technical committee approval (TCA): needs to be approved by the technical committee (TCA) before implementation

***Requirements to be fulfilled according to the type of change in the guidelines:**

A) EDA LABS

1. Notification (N)

2. Analysis inspection Department (AI)
3. Analysis registration Department (AR)

B) Stability

1. None
2. Ongoing
3. Accelerated (6M)
4. 6M + long term stability

C) Dissolution

1. None (DN)
2. Comparative In-Vitro dissolution in most suitable medium (D1)
3. Comparative In-Vitro Dissolution at 3 different PH media (1.2/4.5/6.8) and most suitable medium (D3/4).
4. Bioequivalence study (BE).

D) Pricing (P)

N.B: In some cases, request within reporting category VDA can be issued to VCA if needed according to file case.

4-Procedures

***Types of Variations in Scope:**

- **Changes Related to Compositions, Finished Product Specifications, Active Ingredient Specifications, Physical Characters, Packs**
- **Changes Related to Raw Material Manufacturer**

- **Changes Related to Product License Holder/Manufacturer of Finished Product/Type of License and Modification of Registration license**

(Changes related to Compositions, Finished Product Specifications, Active Ingredient Specifications, Physical Characters, Packs)

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Composition: For Non- Sterile Products

	Immediate Release Oral Solid Dosage Forms & Modified release oral solid dosage forms – non- release controlling excipient:	**Requirements**			**Reporting Category**
		EDA LABS	**Stability**	**Dissolution/ Bioequivalence**	
1	Deletion or partial deletion of an ingredient intended to affect the color, taste or fragrance of the product or change in the ingredient of the printing ink to another approved ingredient.	N	None	DN	VDA
2	Addition or replacement of an ingredient intended to affect the color, taste or fragrance of the product.	AR	Ongoing	DN	VDA

3	A- Change in weight of capsule shells (excluding enteric coated) by NMT **5%.** B- The total additive effect of all excipient changes doesn't exceed **5%,** with individual changes within the limits specified. <u>Percent excipients (w/w) out of total target dosage form weight:</u> - Filler: ±5 - Disintegrant: Starch ±3 / Other ±1 - Binder: ±0.5 - Lubricant:(Ca)or(Mg)Stearate ±0.25/Other±1 - Glidant: Talc ±1 / Other ±0.1 - Film Coat ±1	N	Ongoing	DN Except For ODT (D1) only if change in Disintegrant	VCA

4	The total additive effect of all excipient changes is more than **5%** but less than **10%** with individual Changes within the limits specified. Percent excipients (w/w) out of total target dosage form weight: - Filler: ±10 - Disintegrant: Starch ±6 / Other ±2 - Binder: ±1 - Lubricant: Ca or Mg Stearate ±0.5/Other ±2 - Glidant: Talc ±2 /Other ±0.2 - Film Coat: ±2	N	6M	D1	VCA
5	Change in weight of capsule shell beyond 5% or change in coating weight more than 2% (where the coating is not a critical factor for release mechanism)	N	6M	D1	VCA
6	Replacement of an excipient with a comparable excipient. (e.g. Magnesium Stearate and Calcium Stearate).	AR	6M	D1	VCA
7	Any change in excipient percent beyond 10% with individual changes are more than the limits specified in 4.	AR	6M	D3/4	VCA
8	Addition, deletion or changing excipient to a non-comparable excipient.	AR	6M	D3/4	VCA

9	Any qualitative or quantitative change in Excipient beyond 5% to a narrow therapeutic drug and low solubility/low permeability drugs.	AR	6M	BE+ D3/4	VCA
10	Change in coating formulation excipient (composition) if the change does not alter release of the drug, specification, or stability	AR	6M	D1	VCA
11	Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses	N	Ongoing	DN	VDA
12	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	N	Ongoing	DN	VCA

Administrative documents:

- Common Administrative documents

In addition to

- Commitment that the change does not affect stability (For 1)
- Capsule shell composition on supplier paper (For 3, 5)
- Composition of coating blends e.g. Opadry on supplier paper (For 3, 4, 5, 10)
- Scientific justification (For 11, 12)

	Formulation changes: Modified release oral solid dosage forms – release controlling excipient	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution /Bioequivalence	
1	Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation less than or equal to **5%** w/w of total release controlling excipient content in the modified release solid oral dosage form.	N	Ongoing	D1	VCA
2	Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, is more than **5%** but less than **10% w/w** of total release controlling excipient content in the modified release solid oral dosage form.	N	6M	Non-narrow therapeutic range drugs D1 narrow therapeutic range drugs BE	VCA
3	Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer). **-a** b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for point 2	AR	6M	Non-narrow therapeutic range drugs D3/4	VCA

	change (i.e., **greater than 10% w/w** of total release controlling excipient content in the modified release solid oral dosage form). -Total weight of the dosage form may be within or outside the original approved application range.			narrow therapeutic range drugs	
				BE	

Administrative documents:

Common Administrative documents

In addition to

- Capsule shell composition on supplier paper

"In case of change or addition of capsule shell components in hard gelatin capsules"

- Composition of coating blends e.g. Opadry on supplier paper
- C.O.A &/or Composition of pellets/Premix on all supplier papers
- Calculations of pellets/Premix on company paper

Formulation changes: Non-Sterile Semisolid Dosage forms (Eg. Creams, Gels, lotions & ointments) intended for topical routes of administration		**Requirements**			**Reporting Category**
		EDA LABS	**Stability**	**Dissolution /Bioequivalence**	
1	Deletion or partial deletion of color.	AI	None	DN	VDA
2	Deletion of Fragrance or flavor.	N	None	DN	VDA
3	Up to **5%** change in approved amount of an excipient with the total additive effect of all excipient changes **≤ 5%** (except preservative or antioxidant)**.** The	N	Ongoing	DN	VCA

	amount of diluent is allowed to compensate change in composition.				
4	Change of **> 5% and ≤ 10%** of approved amount of an excipient with the total additive effect of all excipient changes **≤ 10%** or Change in particle size distribution of the drug substance, if the drug is in suspension. The amount of diluent is allowed to compensate change in composition.	AR	6M	DN	VCA
5	Any qualitative and quantitative changes in an excipient beyond the ranges noted in point 3 change or Change in crystalline form of the drug substance, if the drug is in suspension.	AR	6M	DN	VCA
6	Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses.	N	Ongoing	DN	VDA
7	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	N	Ongoing	DN	VCA

Administrative documents:

Common Administrative documents

In addition to

- Commitment that the change does not affect stability (For 1).
- Scientific justification (For 5, 6).
- C.O.A &/or Composition of supplier for active ingredient or premixes.

	Formulation Changes: Liquid dosage form (Solution)	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution /Bioequivalence	
1	Deletion or partial deletion of color.	AI	None	DN	VDA
2	Deletion of Fragrance or flavor	N	None	DN	VDA
3	Increase ,addition or replacement of one or more components of the coloring / flavoring systems	AR	Ongoing	DN	VDA
4	a. Replacement of an excipient with a comparable excipient.	AR	6M	DN	VCA
	b. Changing in percentage of the used excipients.	AR	6M	DN	VCA
	c. Addition, deletion of excipient to a non – comparable excipient	AR	6M	DN	VCA
5	Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses.	N	Ongoing	DN	VDA
6	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	N	Ongoing	DN	VCA

Administrative documents:

Common Administrative documents

In addition to

- Scientific justification (For 5, 6)

- C.O.A &/or Composition of supplier for active ingredient or premixes

	Formulation Changes: Liquid dosage form (Suspension)	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution/ Bioequivalence	
1	Reduction or deletion of one or more components of the coloring system	AR	None	DN	VDA
2	Reduction or deletion of one or more components of flavoring systems	N	None	DN	VDA
3	Increase ,addition or replacement of one or more components of the coloring / flavoring systems	AR	Ongoing	DN	VDA
4	a. Replacement of an excipient with a comparable excipient	AR	6M	DN	VCA
	b. Changing in percentage of the used excipients	AR	6M	Non release controlling excipient	VCA
				DN	
				release controlling excipient	
				D1	
	c. Addition, deletion of excipient to a non – comparable excipient	AR	6M	Non release controlling excipient	VCA
				DN	

				release controlling excipient D1	
5	Any change in the crystalline form of the drug substance	AR	6M	D3/4 or D1 according to the committee decision	VCA
6	Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses	N	Ongoing	DN	VDA
7	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	N	Ongoing	DN	VCA

Administrative documents:
Common Administrative documents
In addition to
- Scientific justification (For 5, 6)
- C.O.A &/or Composition of supplier for active ingredient or premixes
- Calculations of Premix on company paper

Composition: Sterile

	Sterile dosage forms	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution/ Bioequivalence	

1	**Replacement of an excipient with a comparable* excipient.** (Same functional characteristics of the excipient.)	AR	6 M	DN	VCA
2	**Replacement of an excipient with a non-comparable excipient.**	AR	6M	DN	VCA
3	**Increase or Decrease of quantity of any excipient.**	AR	6M	DN	VCA
4	**Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to Compensate for manufacturing losses.**	AR	Ongoing	DN	VCA
5	**Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)**	AR	Ongoing	DN	VCA

Administrative documents:
Common Administrative documents
In addition to
- Scientific justification (For 4, 5)
- C.O.A &/or Composition of supplier for active ingredient or premixes
- Calculations of pellets/Premix on company paper

	For Change of the following issue (In all dosage form):	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution/ Bioequivalence	
1	Clarification of salt equivalence and crystalline state (e.g hydrate, solvate, polymorph,.....)	AR	None	DN	VCA
2	Change in salt equivalence and crystalline state (e.g hydrate, solvate, polymorph,.....)	AR	6M	D3/4	VCA
3	Change in particle size for water Insoluble or sparingly soluble API (particle size must be stated in suppliers COA by D_{90} or mesh size)	AR	Ongoing or 6M if needed	D3/4	VCA
4	Addition or Change of solvents used in manufacturing process e.g ethanol, methanol.	AR including Residual solvent test if needed according to the class of the solvent	Ongoing	DN	VDA
5	Addition of capsule shell composition (not stated in any regulatory documents)	AR	6M	D1	VDA
6	Clarifying of capsule shell composition (Stated In any regulatory document)	N	None	DN	VDA

Administrative documents:

Common Administrative documents

In addition to

- Reference for Molecular weight of base and salt and calculation of salt equivalence on company paper **(For 1, 2)**
- Innovator reference stating the salt form. **(For 1, 2)**
- C.O.A of all suppliers for active ingredient **(For 3)**
- Capsule shell composition on supplier paper **(For 5, 6)**

Common Administrative Documents:	
Covering Letter from the applicant " on company paper signed and stamped"	Describing the reasons for the required change in details
Payment receipt.	1000 LE
Valid registration license	In case the registration license is not valid please submit an approval for renewal and in case of tentative registration license an extension for the license
Variation Notification form	According to template attached
EDA LABS composition	Recent edition with maximum two years ago
EDA LABS certificate of analysis	Recent edition with maximum two years ago
Calculations & scientific reference for molecular weight " on company paper signed and stamped"	In case of change or correcting or clarification of salt equivalence
Previous importation approvals	In case of clarification of salt equivalence / Premix
For composition change only:	
Old composition (3 copies)	Identical to EDA LABS composition
New composition (3 copies)	According to attached template
Comparison table between old and new composition " on company paper signed and stamped"	According to attached template
Copy of CPP (and see original one)	In case of imported / bulk / under license
Declaration letter from the license holder clarifying type of the change needed " Signed and stamped"	In case of imported / bulk / under license
Declaration Letter " on company paper signed and stamped"	According to template attached

Change in Finished Product Specification:

	Variation Item	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution/ Bioequivalence	
1	Tightening of specification limits	N	None	DN	VDA
2	Addition of a new test parameter to the specification	AR	None	DN	VDA
3	Widening of specification limits or deletion of a test parameter from the specification provided that the change is not the result of unexpected events arising during manufacture	AR	None or stability 6M according to the added test)	DN	VCA
4	Updating specifications to comply with an update of the relevant monograph of the Pharmacopoeia. "Within 5 years"	AR	None	DN	VDA
5	Change the Pharmacopeial product from one Pharmacopeia to another one	N	None	DN	VDA
6	Change the Pharmacopeial product from Pharmacopeial product to Non pharmacopeail one	AR	6M	D3/4	VCA

7	Chang the Pharmacopeial product e from Non pharmacopeial product to a Pharmacopeial one	N	None	D1	VDA

Administrative documents:

Common Administrative documents

In addition to

- Validation Process is needed (For 2, 3)
- Old & New Certificate of Analysis "on Company Paper" (2 Copies)
- Old & New Finished Product Specification "on Company Paper"(2 Copies)
- Pharmacopeia Monograph
- Reference for any change states in COA
- Scientific Justification for addition of new parameter (For 2)

Changing / Clarifying Active Ingredient Specification:

	Variation Item	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution/ Bioequivalence	
1	Change from One Pharmacopeia to another Pharmacopeial Specification.	N	None	DN	VDA
2	Change from Pharmacopeial Specification to In-house Specification. (if change is within pharmacopeial limits)	AR	6 M	D 3/4	VCA
3	Change from In-house Specification to Pharmacopeial Specification.	N	None	DN	VDA
4	Clarifying Specification for Active Ingredient (If API specs: In House)*	AR	6 M	D 3/4	VCA

5	Clarifying Specification for Active Ingredient (If API specs: Pharmacopoeial Specs) *	N	None	DN	VDA

Administrative documents:

Common Administrative documents

In addition to

Pharmacopeia Monograph

Certificate of analysis of supplier of active ingredient or pellets or premixes

Previous importation approvals

* Specification for Active Ingredient not stated in any regulatory documents.

Change in Physical Character of Finished Product:

	Variation Item	Requirements			Reporting Category
		EDA LABS	Stability	Dissolution/ Bioequivalence	
1	Change or addition of imprints, embossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking (provided that the change in finished product specification is only in appearance)	N	None	DN	VDA
2	Change or addition of scoring/break lines on tablets (is not applicable when the coat is intended to control release or mask taste (Scoring Stated in Sc. Reference)	Subdivision test	None	DN	VDA
3	Change or addition of scoring/break lines on tablets (is not applicable when the coat is intended to control release or mask taste (Functional Scoring but Not Stated in Sc. Reference)	Subdivision test	In use Stability for the tablet after division	DN	VCA
4	Deletion of scoring/break lines on tablets:	N	None	DN	VDA
5.	Addition of Non-Functional Scoring / break lines as a mark and not intended for breakage.	N	None	DN	VDA
6.	a. Change in Range of color without any qualitative or quantitative change in excipients or	N	None	DN	VDA

	active ingredients (To be as the stated color in EDA Labs COA)				
	b. Change in Range of color without any qualitative or quantitative change in excipients or active ingredients (The Color Range differs from what is stated in EDA Labs COA)	AR	None or stability 6M if Needed	D1 If Needed	VCA
7	Change in shape of dosage form or capsule size without change in total weight of dosage form	AI	Ongoing	D1	VCA

Administrative documents:

Common Administrative documents

In addition to

- Sample
- Old & New Certificate of Analysis "on Company Paper" (2 Copies)
- Old & New Finished Product Specification "on Company Paper"(2 Copies)
- Safety data Sheet for Ink including composition of ink (For 1)
- Reference for scoring (For 2)
- Commitment to be written in pamphlet and pack (For 5)
- Pharmacopeia Monograph (For 6)
- Certificate of analysis of supplier of active ingredient or pellets or premixes (For 6)
- Declaration states that change doesn't affect stability for (1 to 7)
- Justification for change
- Manufacturer Factory License

Common Administrative Documents:	
Covering Letter from the applicant " on company paper signed and stamped"	Describing the reasons for the required change in details
Payment receipt.	1000 LE
Valid registration license	In case the registration license is not valid please submit an approval for renewal and in case of tentative registration license an extension for the license
Variation Notification form	According to the Attached Template
EDA LABS composition	Recent edition with maximum two years ago
EDA LABS certificate of analysis	Recent edition with maximum two years ago
Copy of CPP (and see original one)	In case of imported / bulk / under license
Declaration letter from the license holder clarifying type of the change needed " Signed and stamped"	In case of imported / bulk / under license
Declaration Letter " on company paper signed and stamped"	According to the Attached Template

Pack: Non-Sterile

	Type of change and Examples		Condition	Requirements			Reporting Category
				EDA LABS	Stability	Pricing	
1	**Changes that Have minimal potential to have adverse effects on the product**	- Adding or changing child resistant features of the closure Or Change from a metal to plastic screw cap or plastic to metal screw cap Or Change of Seal while the inner Liner remains unchanged. - Change in or addition of any accessory that is not in direct contact with the drug (eg. Spoon, measuring cup, Dropper .etc).	The Change is not in Direct Contact with the product.	N	None	N	VDA

		- Addition of a desiccant with solid dosage form. -Addition of Aluminum Pouch - Addition of an outer carton box.					

***Administrative documents:**

Common Pack Administrative documents

In addition to

Certificate of Analysis of new accessory or Cap Liner from supplier

Sample For the Old & New Pack

Type of added new accessory or Cap Liner must be mentioned in the declaration letter

2	**Changes That have moderate potential to have an adverse effect on the product.**	**1-Change in the size & Volume of container for non-sterile drug product.**	**-Liquid dosage form.** **-Same or less head/space or contact area ratio.** -Same primary packaging material	N	None	N	VDA
		***Administrative documents:** Common Pack Administrative documents **In addition to** Declaration Letter on Company paper states the old and New Capacity of the Bottle					
		2-Change in size and/or shape & Volume of a container for non-	**- Liquid or semi Solid dosage form.** **- Increase in the head/space or**	N	6M	N	VDA

		sterile drug product.	**Contact area ratio. - Same primary packaging material**					
		***Administrative documents:** Common Pack Administrative documents **In addition to** Scientific Reference states New Volume which you need to add Sample For the Old & New Pack Declaration Letter on Company paper states the old and New Capacity of the Bottle						
		3. Deletion of a desiccant OR an Aluminum Pouch	- Solid dosage form - Liquid dosage form	N	6M	D1*	N	VCA
		4.Addition of a desiccant	- In Direct Contact with the drug.	N	None		N	VDA
		***Administrative documents:** Common Pack Administrative documents						

		Certificate of Analysis of Desiccant (In case Liquid Dosage form Which is in Direct contact with the drug) D1* In case of Solid Dosage Form only. Sample For the Old & New Pack					
		4-Change to a new container closure system within Same Category of Packaging material	-In case of solid dosage form. -The new container closure system provide same or better protective properties than the approved system	N	None	N	VDA
		5- Change to a new container closure system within Same Category of Packaging material	-In case of Liquid dosage form. -The new container closure system provide same or better protective	N	None	N	VDA

			properties than the approved system				
		***Administrative documents:** Common Pack Administrative documents **In addition to** Certificate of Analysis of new accessory or Cap Liner from supplier Sample For the Old & New Pack					
3	**Changes that have a substantial potential to have an adverse effect on the product**	**1. A change to a new container closure system within same Category of Packaging material.**	-In case of solid dosage form. -The new container closure system does not provide the same or better protective properties than	N	6M	N	VDA

			the approved system.				
		2. A change to a new container closure system within same Category of Packaging material.	-In case of Liquid dosage form. - The new container closure system does not provide the same or better protective properties than the approved system.	AR	6M	N	VDA
		2. Change to a new container closure system within different Categories of Packaging material.	-In case of Liquid & Solid dosage form.	AR	6M	N	VDA

		***Administrative documents:** Common Pack Administrative documents **In addition to** Certificate of Analysis for Cap Liner from supplier Sample For the Old & New Pack Justification in case of new container closure system does not provide the same protective properties					
4	**Adding / Deletion of a pack size of the container of finished product.**	**1. For solid dosage forms: added or Change in the number of units (ex: tab, cap)**	-Same primary packaging material. -The new pack size should be consistent with the dosage regimen & treatment duration as approved in any Scientific Reference (**exception: Tender & Export Packs**).	N	None	P	VDA
		2. For liquid or semisolid: addition of	-Same primary packaging material	N	6M	P	VDA

		a new pack size (ex: 30 gm , 50gm cream).	-The new pack size should be consistent with the dosage regimen & treatment duration as approved in any Scientific Reference (**exception: Tender & Export Packs).**				
		***Administrative documents:** Common Pack Administrative documents **In addition to** Scientific Reference or Justification in case of no reference states Dose Regimen Pricing certificate (original to be seen) Sample for the Old & New Pack Declaration Letter on Company paper states the old and New Capacity of the Bottle Capacity and type of container must be stated					

Pack: Sterile

	Change in Container / Closure System	Condition	Requirements			Reporting Category
			EDA LABS	Stability	Pricing	
1	**Change in any part of the Primary packaging Material in Direct Contact with the finished Product formulation.**	• Not affecting delivery، use، safety of drug product • No change in drug product specification	AR	6M	N	VDA
	***Administrative documents:** Common Pack Administrative documents **In addition to** Sample for the Old & New Pack Capacity and type of container must be stated					
2	**Change in any part of the Primary packaging material NOT in Direct Contact with the finished product formulation (such as color of the flip-off caps, change of needle-shield/ different plastic used)** **- Addition of Outer carton box.**	The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety of the finished product.	N	None	N	VDA

	***Administrative documents:** Common Pack Administrative documents					
3	**Change in Primary Container/Closure shape in case there is a change in the headspace or change in the surface/ volume ratio.**	*No change in the quantitative or qualitative composition of the container. *The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety of the finished product	N	6M	N	VDA
	***Administrative documents:** Common Pack Administrative documents **In addition to** Sample for the Old & New Pack Declaration Letter on Company paper states the Old and New Capacity of the Bottle					
4	**Adding/ Deletion of pack size (number of the unites)**	*New pack size should be consistent with the posology and treatment duration as approved in the summary of product characteristics (**exception: Tender & Export Packs**).	N	None	P	VDA

		*The primary packaging material remains the same.				
5	**Adding of New pack size. (Not for Single Unit Dose Drugs)**		N	6 M	P	VDA
6	**Change in type of Solvent Packaging**		AR	6 M – In Use Stability		VDA
7	**Changing / Adding of New pack size for solvents**		AR	6 M (for solvent) – In Use Stability (product to be reconstituted with the solvents)		VDA
	<u>*Administrative documents:</u> Common Pack Administrative documents **<u>In addition to</u>** Scientific Reference (for 7) Pricing certificate (original to be seen) Declaration Letter on Company paper states the old and New type of the Vial or Ampoule or Cartage, etc.					

Common Pack Administrative Documents:	
Covering Letter from the applicant " on company paper signed and stamped"	Describing the reasons for the required change in details
Payment receipt.	1000 LE
Manufacturer Factory License	
Valid registration license	In case the registration license is not valid please submit an approval for renewal and in case of tentative registration license an extension for the license
Variation Notification form	According to the attached Template
EDA LABS certificate of analysis	In case of Appeals if you need to prove a pack that is not mentioned in Registration License
Leaflet of the Product	In case if we need to clarify the old approved pack or we need to know the dose Regimen
Copy of CPP (and see original one)	In case of imported / bulk / under license
Declaration letter from the license holder clarifying type of the change needed " Signed and stamped"	In case of imported / bulk / under license
Declaration Letter " on company paper signed and stamped"	According to the attached Template

Attachments

Appendix I:	Declaration Letter.
Appendix II:	Variation Notification form.
Appendix III:	Composition Form.
Appendix IV:	Comparison Composition Form.

Appendix I: Declaration Letter.

السيد الدكتور / رئيس الإدارة المركزية للمستحضرات الصيدلية.

تحية طيبة وبعد،،،،،

بخصوص المستحضر الاتي:

Trade Name:	
Generic Name:	
Strength:	
Dosage Form:	
Applicant Company :	
License Holder :	
Manufacturer:	
Reg. No.:	

١-نفيد سيادتكم علماً بأن السيد الدكتور/..... وبياناته كالآتي:

رقم إثبات الشخصية:	
بريده الإلكتروني:	
فاكس:	
رقم موبيل:	

هو المفوض من قبل الشركة لتقديم، متابعة وإنهاء طلبات المتغيرات الخاصة.

٢-نتعهد نحن شركة ..... بأن:

- الإخطار المقدم هو أخر إخطار صادر للمستحضر وهذا تعهد منا بذلك.
- جميع المستندات المقدمة بالملف صحيحة وعلى مسئولية الشركة وأنه مرفق جميع موافقات المتغيرات السابقة الخاصة به وهذا تعهد منا بذلك.

مرفق:

-١

-٢

- لم يتم إنتاج/استيراد أو تداول المستحضر بالسوق المحلي

* تم إنتاج/ استيراد المستحضر ومرفق جميع الدراسات التي تم إجراءها.

مرفق الدراسات (في حالة أن تم إنتاجه):

-١
-٢

وتفضلوا بقبول فائق التحية والتقدير.

رئيس مجلس ادارة الشركة ختم الشركة

Appendix II: Variation Notification form.

Trade Name:	
Generic Name/ strength:	
Dosage Form:	
Applicant:	
License Holder:	
Manufacturer:	
Reg. No.	
BCS Class of the drug:	
Class of solvent:	In case of addition solvents use during manufacturing
Type of Change (As Mentioned in Guidelines)	
Current Situation	
Proposed Change	

❖ **Category of the change:**

☐ *Notification Approval (N)*
Details of the change

☐ *Variation Department Approval (VDA)*
Details of the change

☐ *Variation Committee Approval (VCA)*
Details of the change

❖ **I declare that there are no other changes except mentioned above.**

رئيس مجلس ادارة الشركة ختم الشركة

Appendix III: Composition Form

1. **Submit composition certificate on the company letter head signed and stamped**
2. **Check spelling of trade name and active ingredient(s) according to Registration license, It's (their) hydrate(s) and salt form(s) with its (their) quantity (ies) per unit dose is (are) specified.**
3. **Separate active and inactive ingredients in composition**
4. **Arrange the item of composition as the following**

Ingredients	Quantity	Specifications	Function
Total Weight	Must be Mentioned		

5. **Unify the units of the ingredient's amount in the composition.**
6. **Specify the adjusted PH in case of presence of alkalinizer or any other PH adjuster.**
7. **Write the ingredients without abbreviations.**
8. **Write the coloring index of any coloring ingredient and determine the grade of the following ingredients :**

- Povidone
- Powdered Cellulose
- Hydroxy propyl methyl cellulose (HPMC)(Hypromellose)
- Methacrylic acid
- Methy cellulose
- Hydroxy ethyl cellulose
- Microcrystalline cellulose (MCC)

- Polyethylene glycol
- Poly vinyl pyrrolidine (PVP)
- Lactose (monohydrate – anhydrous)
- Colloidal silicon dioxide

9. **In Case of Coated tablets**: write the core and coat separated, mention the weight of tablet.
10. **Hard gelatin capsules**: *write the body and cap. Separated, mention the color and size of capsule.
    *Composition of the capsule shell on the supplier head letter.
    * In case of pellets- granules or premix, composition on supplier letterhead should be Attached & attach the calculation of pellets weight /capsule on company letterhead

11-N. B: * Please write the Composition Per:

1gm	1ml	5ml	Dosage Form
A. Cream B. Ointment C. Powder for external use D. Gel E. Paste	A. Drops B. Vial (if multiple dose) C. Ampoule (if multiple dose)	A. Syrup B. Suspension (After Re-constitution) C. Emulsion D. Elixir	A. Tablet B. Capsule C. Patch D. Sachet[4] E. Suppository F. Vial contains powder[5](if single dose) G. Ampoule (if single dose) H. Prefilled Syringe I. Cartridge J. Lotion K. Topical Solution

11. In case of powder for reconstitution write the amount of water used to reconstitute the powder & the final volume reached.
12. In case that the composition contains any type of parabens, please calculate it according to the technical committee decision in 18/2/2016:

١٣. بالنسبة لمادة الـ Methylparaben : يتم استخدامها بتركيز يتراوح من ٠,٠١٥% الى ٠,٢% بحيث لا تتخطى الجرعة اليومية (١٠ مجم/كجم/يوم) فى المستحضرات التي تعطى عن طريق الفم دون التقيد بفئة عمرية محددة.

١٤. بالنسبة لمادة الـ Propylparaben : يتم استخدامها بتركيز من ٠,٠٢% الى ٠,٠٦% فى المستحضرات التي تعطى عن طريق الفم بحيث لا تتخطى الجرعة اليومية (٢ مجم/كجم/يوم) وذلك للأطفال والكبار على حد سواء.
بالنسبة لـ Combination of Methyl & Propyl parabens يجب الا تزيد الجرعة من هذه المواد مجتمعة عن ١٠مجم/كجم/يوم مع الالتزام بألا يتم تجاوز الجرعة اليومية المسموح بها لكل منهما على حدة

14. In case of addition of solvents used in manufacturing process: write the state of theses solvent (e.g. evaporating during manufacturer)
15. In case of addition of overage: write this overage loss during manufacturer process.

Appendix IV: Comparison Composition Form

Trade Name:
Generic Name/Strength:
Dosage Form:

Ingredients	Old formula	New formula	Function	[%change]*	%change allowance**
Total					

* % change should be in absolute value

The change%= $\frac{New-Old}{Old*100}$

* *From Guidelines

(Changes related to Raw Material Manufacturers)

Table of Contents:

Requirements						
Serial	Variation issue	Test documents			Administrative documents	Reporting Category
		EDA Labs	Stability	Dissolution / Bioequivalence		
1	Addition / Change of raw material manufacturers having the same specification	AI	Accelerated (6m)	D1	1,2,3,4,5,6,9,10, 11, 12,13,14,15,17, 18,19,20,24,25, 26,27,29	VDA
2	Addition / Change of raw material manufacturers (In	AI	Accelerated (6m)	D1	1,2,3,4,5,6,9,10, 11,	TCA

	case of ISO is: food grade) having the same specification				12,13,14,15,17, 18,19,20,24,25, 26,27,29	
3	Name change of raw material manufacturer	None	None	None	1,2,3,4,21,22,23,24,25,26,28,29	VDA
4	Clarification of raw material manufacturers (in case not mentioned) in registration license	AR	Accelerated (6m)	D3 / 4	1,2,3,4,5,6,9,10, 11,12,13,14,15, 16,17,18,19,20, 24,25,26,29	VDA

Administrative Documents:	
1. Covering Letter from the applicant on company paper signed & stamped.	Showing product name, registration no., API, dosage form with describing the required change in details. Template 1.
2. Payment Receipt.	1000 L.E. for each issue.

3. Valid registration license	In case of that, the registration license is not valid please, submit an approval for renewal & an extension in case of tentative registration license.
4. Registration license Composition	For the product signed & submitted from central administration of pharmaceutical affairs.
5. EDA LABS composition	Recent edition with maximum two years ago.
6. EDA LABS certificate of analysis	Recent edition with maximum two years ago.
7.Old composition / Specs (2 copies)	According to EDA LABS composition.
8. New composition / Specs (2 copies)	According to attached template.
9. Valid GMP for raw material manufacturer with annex including API.	For old & new raw material manufacturer.
10. Valid ISO 9001, ISO22000	For: extracts, minerals, salts … (Pharmaceutical grade, Food grade).
11. Valid raw material manufacturer complete license	In case of GMP annex is not including API.
12. Valid CPP for raw material manufacturer including API.	In case of raw material manufacturer dose not issue GMP.

13. Certificate of analysis of the manufacturer for API.	For old & new raw material manufacturer.
14. Comparison between all added / Changed manufacturers COAs	In case of manufacturer addition / Change.
15. Updated Pharmacopeia Monograph	For API specs.
16. Importation approvals & Invoices for API	For the last 5 years.
17. CPP copy & Check the original one	In case of under license products.
18. Declaration letter from the product license holder approving the API manufacturer addition / change	In case of under license products.
19. Original signed, stamped Letter of access	In case of HCV products.
20. S. part (Quality file) of API (Substance)	In case of HCV products.

21. COA with manufacturer old name + COA with manufacturer new name	In case of name change.
22. GMP / ISO with manufacturer old name & annex including API + Valid GMP / ISO with manufacturer new name including API / complete valid API manufacturer license in case of GMP annex not including API	In case of name change.
23. Signed & stamped declaration from the manufacturer submits the name change	In case of name change.
24. Declaration Letter From Company that States: - Attached License is the last updated, issued one from the central administration for pharmaceutical affairs signed and stamped. - The file including all changes & issued approvals for the product - All documents within the file are correct & on the responsibility of the company - All tentative registration license conditions will be done on the main manufacturer	Template 2.

25. Declaration from the company states that: Name & address of API manufacturer & manufacturer	Template 3.
26. Declaration letter from the Company States that: The company will bring for EGYPTIAN DRUG AUTHORITY GMPs & COAs for all APIs when importation of API.	Template 4.
27. Declaration letter From Company states that: no production	In case of no production (Template 5).
28. Declaration letter From Company states that: Specification of the API is the same	In case of name change (Template 6).
29. Declaration letter states that……is the commissioner by the company to deal with central administration for pharmaceutical affairs.	In each file (Template 7).

Important Notifications

1- Clarifying Old manufacturer (applied only in case of Old License format).
2- In case of sparingly soluble API. Particle size clarification, COA should including: solubility& PSD (D90 or sieve size) in all manufacturers COAs.
3- In certain cases, some additional documents may be needed to ensure the APIs quality & efficacy.

4- In case of HCV Products: It is allowed to add up to 5 API manufacturers.

Covering letter (Template 1):

الساده / رئيس الإدارة المركزية للمستحضرات الصيدلية
الإداره العامه للتسجيل
إدارة المتغيرات

اسم المستحضر:	
المادة الفعالة/التركيز:	
المصنع:	
رقم تسجيل:	
الرجاء من سيادتكم التكرم بالموافقه على الاتى :	
(إضافة / تغيير) (مصدر/ مصدرين / مصادر) (الماده الخام الفعاله) وهى :	
(وهو/ وهما/ وهم / من):	
(إلى المصدرالمضاف / المصدرين المضافيين):	
وحذف المصدر:	
والإبقاء على:	
ليصبح (مصادر / مصدري) الماده الخام الفعاله) (هم / هما):	1- 2- 3-

مدير إدارة التسجيل
د/

Declarations (Template 2):

تعهد

اسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

نتعهد نحن شركة..... أن الإخطار المقدم هو آخر إخطار صادر من رئيس الإدارة المركزية للمستحضرات الصيدلية حتى تاريخه وأن الملف يشمل كافة المتغيرات والموافقات الصادرة للمستحضر وأن جميع المستندات المقدمة بالملف صحيحة وعلى مسئولية الشركة و تلتزم الشركه بجميع البيانات المذكورة في التعهد .

وتتعهد الشركه بعمل جميع دراسات الإخطار المبدئي على مصدر الماده الخام الفعاله الأساسي.(في حالة الإخطارات المبدئيه)

مدير إدارة التسجيل
د/

Suppliers declaration (template 3):

تعهد

اسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة أن إسم المصنع وعنوانه كالآتى:

1. **……**
   Address:-
2. **……**
   Address:-
3. **……**
   Address:-

كما نتعهد بتقديم شهادات ال GMP وشهادات التحليل الخاصة بالمادة الخام وذلك عند التقدم لإستيراد المادة الخام بالإدارة المركزية للمستحضرات الصيدلية.

مدير إدارة التسجيل

د/

GMP declaration (template 4):

تعهد

إسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركه بتقديم شهادات ال GMP وشهادات التحليل الخاصة بالمادة الخام وذلك عند التقدم
لإستيراد المادة الخام بالإدارة المركزية للمستحضرات الصيدلية.

مدير إدارة التسجيل
د/

Production Declaration (Template 5):
تعهد

إسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة بأنه لم يتم إنتاج المستحضر حتى تاريخه.

مدير إدارة التسجيل
د/

API Declaration (Template 6):

تعهد

إسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة بأنه لا يوجد أى تغييرأوتعديل فى المواصفات الخاصة بالمادة الفعالة.
(Specification of API is the Same)

مدير إدارة التسجيل
د/

Delegation Declaration (Template 7):
تعهد

إسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تعهد الشركة بأن المفوض الرسمى للشركه للتعامل مع الإدارة المركزية للمستحضرات الصيدلية فى

الإجراءات اللازمه هو:.....
رقم قومى :.....

مدير إدارة التسجيل
د/

(Changes related to Product License Holder/Manufacturer of Finished Product/Type of License and Modification of Registration License)

Tablet of Contents:

B.1	For imported products
	B.1.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product
B.2	For local products
	B.2.1 Replacement of a manufacturing site for part or all of the manufacturing process of the finished product
	B.2.2 Addition of a manufacturing site for Export only
C	Change Type of License
	C.1 Change type of license from imported
	C.2 Change type of license from under license
	C.3 Change type of license from Bulk
D	General administrative documents
	Attachments

A. *Administrative Changes*

A.1 Change in Name and/or Address of Product License Holder or Marketing Authorization Holder	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
a) For local products	**1**	**1, 4**	**1**	**VDA**
b) For Imported Products	**1**	**2, 3, 4**	**1**	

Conditions

1. Product License Holder and/or Marketing Authorization Holder shall remain the same legal entity.

Documents

1. Copy of modified official documents (Tax card, Commercial register and Toll card) in which the new name is mentioned.
2. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin in which the new name and/or address is mentioned.
3. Declaration from the product license holder and/or marketing authorization holder states the new name and/or address and that there is no change in the legal entity of product license holder and/or marketing authorization holder.
4. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

A.2 Change in Name and/or Address of Manufacturing sites (including bulk manufacturer, packager & batch releaser)	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
a) For local products	**1**	**1, 7**	**1**	**VDA**
b) For Imported Products	**1**	**2, 3, 4, 5, 6, 7**	**1**	

Conditions

1. The location of the manufacturing site and all manufacturing operations shall remain the same.

Documents

1. Copy of modified official documents (Tax card, Commercial register and Manufacturing authorization) in which the new name is mentioned.
2. GMP certificate in which the new name and/or address is mentioned.
3. GMP certificate in which the old name and/or address is mentioned.
4. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin in which the new name and/or address is mentioned.
5. Declaration from the product license holder or marketing authorization holder states the new name and/or address and that there is no change in the manufacturing site location, operations, quality & composition of finished product.
6. A formal document from a relevant official body justifies the change of address, if available.
7. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

A.3 Change in Applicant	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
	–	1, 2, 3, 4, 5	–	VDA

Documents

1. Authorization letter from the product license holder states the authorized company name (with its full address) that has the right to register the product in Egypt with Arabic translation from approved translation center.
2. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin.
3. Waiver from the old applicant of the product **or** termination letter from the product license holder states that the old applicant doesn't have the right to register the product in Egypt with Arabic translation from approved translation center.
4. Commercial register **or** scientific office license for old and new applicant.
5. General administrative documents.

A.4 Modification of Registration license (including but not limited to trade name, shelf life, storage conditions, price, storage site)	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
	1	1, 2	1	VDA

Conditions

1. Approval of EGYPTIAN DRUG AUTHORITY relevant department(s).

Documents

1. Letter of acceptance from EGYPTIAN DRUG AUTHORITY relevant department(s) in which the new status of the product is mentioned.

2. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

A.5 Change in Product License Holder or Marketing Authorization Holder	**Conditions to be fulfilled**	**Documents to be applied**	**Post-approval Requirements**	**Reporting Category**
a) For local products	**1**	**1, 2, 3, 7, 8**	**1**	**VDA**
b) For Bulk or Under license Products	**1**	**2, 4, 5, 6, 7, 8**	**1**	
c) For Imported Products	**1**	**4, 5, 6, 7, 8**	**1**	

Conditions

1. The new Product License Holder or Marketing Authorization Holder is a different legal entity.

Documents

1. Waiver from the old product license holder with the product name, concentration and registration number.
2. Manufacturing/packaging contract between the new license holder and the manufacturer/packager, attaching annex with the product name, concentration and registration number.
3. Copy of official documents (Tax card, Commercial register, Toll card and Manufacturing authorization) of the new and old product license holders and manufacturer.
4. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin in which the new license holder is mentioned.
5. Declaration from the old license holder states the ownership transfer with Arabic translation from approved translation center.

6. Authorization letter from the new product license holder states the authorized company name (with its full address) that has the right to register the product in Egypt with Arabic translation from approved translation center.
7. Declaration letter from the new license holder ensuring that there is no change in product composition, specification, manufacturing process and container/closure system.
8. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

A.6 Addition of Product License Holder or Marketing Authorization Holder in Egypt	**Conditions to be fulfilled**	**Documents to be applied**	**Post-approval Requirements**	**Reporting Category**
For Imported Products	**1**	**1, 2, 3, 4, 5**	**1**	**VDA**

Conditions

1. Product License Holder and/or Marketing Authorization Holder **in Egypt** must comply with all product specifications, composition and manufacturer stated in the Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin.

Documents

1. Declaration from license holder and/or Marketing Authorization Holder in the country of origin states the ownership transfer of the product **in Egypt only** with Arabic translation from approved translation center.
2. Declaration from license holder and/or Marketing Authorization Holder in the country of origin clarifies the full responsibilities of the product License Holder and/or Marketing Authorization Holder in Egypt including but not limited to the right to sell the product **in Egypt** with Arabic translation from approved translation center.

3. Authorization letter from the new product license holder and/or Marketing Authorization Holder **in Egypt** states the name of the company (with its full address) that has the right to register the product in Egypt with Arabic translation from approved translation center.
4. Certificate of a Pharmaceutical product (CPP) from health authority in the country of origin (in which License Holder and/or Marketing Authorization Holder **in Egypt** is mentioned, if available).
5. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

A.7 Change in the country of origin of Product License Holder or Marketing Authorization Holder	**Conditions to be fulfilled**	**Documents to be applied**	**Post-approval Requirements**	**Reporting Category**
For Imported, Bulk & Under license Products	**1, 2**	**1, 2, 3**	**1**	**VDA**

Conditions

1. Product License Holder and/or Marketing Authorization Holder shall remain the same legal entity.
2. Product composition, specifications and manufacturer shall remain the same.

Documents

1. Certificate of a Pharmaceutical Product (CPP) from health authority in the new country of origin.
2. Declaration from the product license holder and/or marketing authorization holder in which the current and the proposed status of the product are mentioned.
3. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

A.8 Change or addition of supplier of solvent (water for injection)	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
For local products	**1, 2**	**1, 2, 3**	**–**	**VDA**

Conditions

1. Solvent must be registered.
2. The shelf life of solvent shall comply with the shelf life of the product.

Documents

1. Copy of valid registration license of solvent.
2. Copy of official documents (Tax card, Commercial register, and manufacturing authorization) of the solvent manufacturer.
3. General administrative documents.

B. *Quality Changes Concerning Manufacturing Sites*

B.1 For imported products

B.1.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
a) Manufacturer	**1, 2**	**1, 2, 3, 4**	**1, 2, 3**	**VDA**
b) Primary packager	**1, 2, 3**	**1, 2, 3, 4**	**1, 2, 3**	**VDA**
c) Secondary packager	**1, 2**	**1, 2, 4**	**1**	**VDA**
d) Batch releaser	**–**	**1, 2, 4**	**–**	**VDA**

Conditions

1. Satisfactory inspection in the last three years by an inspection service of a country where an operational Good Manufacturing Practice (GMP) exists.
2. The proposed site appropriately authorized to manufacture product concerned.

3. Product concerned is not a sterile product.

Documents

1. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin in which the new bulk manufacturer and/or primary packager is mentioned.
2. GMP certificate of the new site.
3. Declaration from the product license holder and/or marketing authorization holder in which the current and the proposed status of the product are mentioned.
4. General administrative documents.

Notes

- In case of replacement/ addition of a manufacturer from non-reference countries, a Certificate of a Pharmaceutical Product (CPP) from a reference country of origin with the non-reference site name is needed.
- In case the new secondary packager and/or batch releaser is not mentioned in the Certificate of a Pharmaceutical Product (CPP), a Legalized declaration from the product license holder and/or marketing authorization holder with the current and the proposed status of the product is needed.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.
2. Analysis of three consecutive production batches produced/packed at the new site at EDA LABS.
   - In inspection department (in case the product has EDA LABS conformity).
   - The first batch in registration department, the second and third batches in inspection department (in case the product doesn't have EDA LABS conformity).
3. Accelerated stability study for 6 Months on three consecutive production batches produced/packed at the new site.

B.2 For local products

B.2.1 Replacement of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
a) Manufacturer & primary packager	**1, 2**	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**VDA**
b) Secondary packager	**1, 2**	**1, 2, 4, 5**	**–**	**VDA**

Conditions

1. The proposed site appropriately authorized to manufacture product concerned.
2. The new manufacturer name is mentioned in Toll card of the license holder.

Documents

1. Waiver from the old manufacturer/packager, with the product name, concentration and registration number.
2. Manufacturing contract between the license holder and the new manufacturer, attaching annex with the product name, concentration and registration number.
3. A storage contract of the product between the license holder and the new storage site (in case of storing at a third party).
4. Copy of official documents (Tax card, Commercial register, and manufacturing authorization) of the new and old manufacturer and product license holder, in addition to storage site license.
5. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.
2. Analysis of three consecutive production batches produced/packed at the new site at EDA LABS
   - In inspection department (in case the product has EDA LABS conformity).

- The first batch in registration department, the second and third batches in inspection department (in case the product doesn't have EDA LABS conformity).

3. Accelerated stability study for 6 Months on three consecutive production batches produced/packed at the new site.
4. Process validation is performed at the new site and is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

Notes

- For tentative registration licenses: Long term stability is required to be performed at the new site (in case it hasn't been performed at the old site).

B.2.2 Addition of a manufacturing site for Export only	**Conditions to be fulfilled**	**Documents to be applied**	**Post-approval Requirements**	**Reporting Category**
	1, 2	**1, 2, 3**	**1**	**VDA**

Conditions

1. The proposed site appropriately authorized to manufacture product concerned.
2. The new manufacturer name is mentioned in Toll card of the license holder.

Documents

1. Manufacturing contract between the license holder and the new manufacturer, attaching annex with the product name, concentration and registration number.
2. Copy of official documents (Tax card, Commercial register, and manufacturing authorization) of the new manufacturer.
3. General administrative documents.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

C. *Change Type of License*

C.1 Change type of license from imported to:	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
a) Bulk *(for primary packaging in Egypt)*	1, 2	1, 2, 3, 4, 5	1, 2, 3, 5	TCA
b) Bulk *(for secondary packaging in Egypt)*	1	1, 2, 3, 4, 5	1	TCA
c) Under license	1	1, 2, 3, 4, 5	1, 2, 3, 5	TCA
d) Local	1, 3, 4	2, 3, 4, 5	1, 2, 3, 4, 5	TCA

Conditions

1. The proposed site appropriately authorized to manufacture product concerned.
2. Product concerned is not a sterile product.
3. The new manufacturer name is mentioned in Toll card of the license holder.
4. The physical and the chemical specifications must remain the same as the imported product.

Documents

1. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin.
2. Declaration from the product license holder and/or marketing authorization holder, with the full data (name, concentration and registration number) of the product, in which the current and the proposed status of the product are mentioned. The letter must include justification of the change.
3. Manufacturing/Packaging contract between the license holder and the new manufacturer, attaching annex with the product name, concentration and registration number.
4. Copy of official documents (Tax card, Commercial register, and manufacturing authorization) of the new manufacturer/packager.
5. General administrative documents.

Notes

1. In case of Toll companies, toll card is needed.

2. In case of under license and local products, submission of a separate file for addition of suppliers is needed.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.
2. Analysis of three consecutive production batches produced/packed at the new site at EDA LABS
   - In inspection department (in case the product has EDA LABS conformity)
   - The first batch in registration department, the second and third batches in inspection department (in case the product doesn't have EDA LABS conformity).
3. Accelerated stability study for 6 Months on three consecutive production batches produced/packed at the new site.
4. Comparative In-Vitro dissolution at 3 different PH media (1.2 / 4.5 / 6.8) and the most suitable medium (D3/4) on the first production batch, the study must be performed at one of the approved bioequivalence centers.
5. Process validation is performed at the new site and is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

C.2 Change type of license from under license to:	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
a) Imported finished	**1, 2**	**1, 2, 3, 4, 7**	**1, 2, 4**	**TCA**
b) Bulk *(for primary packaging in Egypt)*	**1, 2, 3**	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 4, 8**	**TCA**
c) Bulk *(for secondary packaging in Egypt)*	**1, 2**	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 4**	**TCA**
d) Local *(at the same manufacturing site)*	**4, 5**	**2, 6, 7**	**1, 3, 5, 6**	**TCA**
e) Local *(transfer to different manufacturing site)*	**2, 4, 5**	**2, 4, 5, 6, 7**	**1, 2, 4, 7, 8**	**TCA**

Conditions

1. Satisfactory inspection in the last three years by an inspection service of a country where an operational Good Manufacturing Practice (GMP) exists.
2. The proposed site appropriately authorized to manufacture product concerned.
3. Product concerned is not a sterile product.
4. The new manufacturer name is mentioned in Toll card of the license holder.
5. The physical and the chemical specifications must remain the same as the under license product.

Documents

1. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin in which the new data is mentioned.
2. Declaration from the product license holder and/or marketing authorization holder, with the full data (name, concentration and registration number) of the product, in which the current and the proposed status of the product are mentioned. The letter must include justification of the change.
3. GMP certificate of the new site.

4. Waiver from the old manufacturer/packager with the product name, concentration and registration number.
5. Copy of official documents (Tax card, Commercial register, and manufacturing authorization) of the new manufacturer/packager.
6. Manufacturing/packaging contract between the license holder and the new manufacturer/packager, attaching annex with the product name, concentration and registration number.
7. General administrative documents.

Notes

1.In case of Toll companies, toll card is needed.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.
2. Analysis of three consecutive batches produced/packed at the new site at EDA LABS
   - In inspection department (in case the product has EDA LABS conformity)
   - The first batch in registration department the, second and third batches in inspection department (in case the product doesn't have EDA LABS conformity).
3. EDA LABS Notification.
4. Accelerated stability study for 6 Months on three consecutive batches produced/packed at the new site.
5. Ongoing stability study on production batches submitted upon request.
6. Comparative In-Vitro dissolution in the most suitable medium (D1) on the first production batch. The study can be performed at the manufacturing site.
7. Comparative In-Vitro dissolution at 3 different PH media (1.2/4.5/6.8) and most suitable medium (D3/4) on the first production batch. The study must be performed at one of the approved bioequivalence centers.

8. Process validation is performed at the new site and is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

C.3 Change type of license from Bulk to:	Conditions to be fulfilled	Documents to be applied	Post-approval Requirements	Reporting Category
a) Imported finished	**1, 2**	**1, 2, 3, 4, 7**	**1, 2, 3**	**TCA**
b) Under License	**2**	**1, 2, 4, 5, 6, 7**	**1, 2, 3, 5**	**TCA**
c) Local	**2, 3, 4**	**2, 4, 5, 6, 7**	**1, 2, 3, 4, 5**	**TCA**

Conditions

1. Satisfactory inspection in the last three years by an inspection service of a country where an operational Good Manufacturing Practice (GMP) exists.
2. The proposed site appropriately authorized to manufacture product concerned.
3. The new manufacturer name is mentioned in Toll card of the license holder.
4. The physical and the chemical specifications must remain the same as the imported bulk product.

Documents

1. Certificate of a Pharmaceutical Product (CPP) from health authority in the country of origin in which the new data is mentioned.
2. Declaration from the product license holder and/or marketing authorization holder, with the full data (name, concentration and registration number) of the product, in which the current and the proposed status of the product are mentioned. The letter must include justification of the change.
3. GMP certificate of the new site.
4. Waiver from the old packager with the product name, concentration and registration number.
5. Manufacturing/Packaging contract between the license holder and the new manufacturer, attaching annex with the product name, concentration and registration number.
6. Copy of official documents (Tax card, Commercial register, and manufacturing authorization) of the new manufacturer/packager.

7. General administrative documents.

Notes:

1. In case of Toll companies, toll card is needed.
2. In case of under license and local products, submission of a separate file for addition of suppliers is needed.

Post-approval Requirements

1. Amendment of product information (i.e. Inner leaflet and Mock up) that is followed up by EGYPTIAN DRUG AUTHORITY inspection department.
2. Analysis of three consecutive batches produced/packed at the new site at EDA LABS
   - In inspection department (in case the product has EDA LABS conformity).
   - The first batch in registration department and the second and third batches in inspection department (in case the product doesn't have EDA LABS conformity).
3. Accelerated stability study for 6 Months on three consecutive production batches produced/packed at the new site.
4. Comparative In-Vitro dissolution at 3 different PH media (1.2 / 4.5 / 6.8) and the most suitable medium (D3/4) on the first production batch, the study must be performed at one of the approved bioequivalence centers.
5. Process validation is performed at the new site and is followed up by EGYPTIAN DRUG AUTHORITY inspection department.

*Some of supplied documents may need: • Authentication/legalization from chamber of commerce and the embassy of Egypt in the country of origin of the license holder. • Approval from EGYPTIAN DRUG AUTHORITY Legal consultant, for more details please refer to the **checklist** for each type of variation**.**

- ***General administrative documents***

1. Covering letter (Template (1))	On company (license holder or applicant) original letterhead dated, stamped and signed by qualified person and clarifies the following: - All product data - Status of the product (valid or re-registration) - A table of the current status and the proposed status of the product mentioning the reason and the results of this change. - The latest variations that haven't been added to the last registration license of the product. - All attached documents.
2. Commitments (Template (2))	On company (license holder or applicant) original letterhead dated, stamped and signed by qualified person and clarifies the following - The registration license is the latest one of the product. - All data and all documents submitted with the file are correct and are on the responsibility of the company. - The file contains all variations and approvals of the product since its registration to date. - Storage site of the product. - Status of the product regarding the date of production/importation and marketing of the last production batch. - The attached pricing approval of the product is the latest one to date.

3. Commitments (Template (3))	On company (license holder or applicant) original letterhead dated, stamped and signed by qualified person clarifies the supplier (s) of raw material (s). **(In case of local and under license products).**
4. Commitment (Template (4))	On company (license holder or applicant) original letterhead dated, stamped and signed by qualified person states that the product doesn't have other concentrations or dosage forms. **(In case of change license holder for local products).**
5. Commitment (Template (5))	Using company head letter signed and stamped clarifies the number of registered and under-registered products owned by the company. **(In case of Toll products).**
6. Registration license of product/solvent	- 2 copies of the latest valid registration license of the product with all its attachments (with original to be checked). - In case of invalid final registration license: a copy of re-reg file receipt or approval is submitted. - In case of invalid tentative registration license: a copy of registration license validity extension is submitted.
7. Latest pricing certificate	A copy of the latest pricing certificate with the original to be checked.
8. Copy of all previous approvals for the product	With originals to be checked.
9. Copy of EDA LABS certificate	clarifies physical and chemical specifications of the product **(In case of valid old edition registration licenses)**
10. The first marketing report	In case of local products that are registered according to ministerial decree No. 425 in 2015.
11. Payment of fees	

(نموذج ١)

السيد الدكتور / رئيس قسم المتغيرات للمستحضرات الصيدلية المسجلة

تحية طيبة وبعد،،،

بخصوص المستحضر الآتى:

Trade Name:		
Dosage Form:		
Active Ingredients / Strength:		
Registration No.:		
Applicant Company:		
License Holder / MAH:		
Manufacturer / Packager:		
License Validity:	○ Valid	Re-Reg 296/2009 Re-Reg 425/2015
Current status:		
Proposed status:		

نرجوا من سيادتكم التكرم بالموافقة على إجراء التغيير الآتي على المستحضر:

- الوضع الحالي للمستحضر:
- الوضع المقترح:
- سبب التغيير (إن وجد):
- ما يترتب على التغيير (إن وجد):
- علماً بأنه تم عمل المتغيرات الآتية /(لم يتم عمل اى متغيرات) للمستحضر ولم يتم إضافتها بأخر إخطار تسجيل صادر للمستحضر:

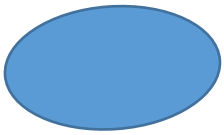
المستندات المرفقة بالملف كالآتي:

نوع التغيير	من	إلى

و تفضلوا بقبول وافر الإحترام والتقدير،،،

رئيس مجلس ادارة الشركة

ختم الشركة



(نموذج ٢)

السيد الدكتور / رئيس قسم المتغيرات للمستحضرات الصيدلية المسجلة

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	Re-Reg 296/2009 Re-Reg 425/2015
Current status:		
Proposed status:		

أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بالآتي:

- إخطار تسجيل المستحضر المرفق بالملف هو أخر إخطار صادر للمستحضر حتى تاريخه.
- جميع المستندات والبيانات المقدمة بالملف صحيحة وعلى مسؤلية الشركة.
- الملف المقدم يشمل كافة المتغيرات والموافقات الصادرة للمستحضر منذ تاريخ تسجيله وحتى تاريخه.
- مكان تخزين المستحضر هو:
- رقم أخر تشغيلة من المستحضر تم إنتاجها/إستيرادها وتداولها بالسوق المحلي هو ..... و تاريخ إنتاجها/إستيرادها هو .....

أو (لم يتم إنتاج/إستيراد وتداول المستحضر منذ تسجيله وحتى تاريخه)

- التسعيرة المقدمة بالملف (المذكورة بالإخطار) وهي ..... هي أخر تسعيرة صادرة للمستحضر حتى تاريخه.

و تفضلوا بقبول وافر الإحترام والتقدير،،،،

رئيس مجلس ادارة الشركة **ختم الشركة**

(نموذج ٣)

السيد الدكتور / رئيس قسم المتغيرات للمستحضرات الصيدلية المسجلة

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	Re-Reg 296/2009 Re-Reg 425/2015
Current status:		
Proposed status:		

أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بأن مصادر المواد الخام الفعالة هي كالآتي:

Name of API:	**Name of Manufacturer:** **Address of Manufacturer:** *As stated in GMP*
	Name of Supplier: **Address of Supplier:**

كما أتعهد بتقديم شهادة الGMP وشهادة التحليل الخاصة بالمادة الخام ,وذلك عند التقدم لإستيراد المادة الخام بالإدارة المركزية للشئون الصيدلية.

و تفضلوا بقبول وافر الإحترام والتقدير ،،،،

رئيس مجلس ادارة الشركة **ختم الشركة**

(نموذج ٤)

السيد الدكتور / رئيس قسم المتغيرات للمستحضرات الصيدلية المسجلة

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	Re-Reg 296/2009 Re-Reg 425/2015
Current status:		
Proposed status:		

أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بالآتي:

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**

(نموذج ٥)

السيد الدكتور / رئيس قسم المتغيرات للمستحضرات الصيدلية المسجلة

تحية طيبة وبعد،،،،،

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

المستحضرات المسجلة	المستحضرات تحت التسجيل

و تفضلوا بقبول وافر الإحترام والتقدير،،،،

رئيس مجلس ادارة الشركة **ختم الشركة**

5-References

- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01) (EMA)

- The GCC for Variations Requirements

6-Annexes

- **Dosage Form List**

  * Please write the product's dosage form as mentioned in the below table

Oral Dosage Forms	
Tablet	أقراص
Film coated tablet	أقراص مغلفة
Sugar coated tablet	أقراص ذات كسوة سكرية
Enteric coated tablet	أقراص ذات كسوة معوية
Extended release tablet	أقراص ممتدة المفعول
Effervescent tablet	أقراص فوارة
Dispersible tablet	أقراص قابلة للإنتشار
Orodispersible tablet	أقراص قابلة للذوبان بالفم
Orally Disintegrating Tablet	أقراص للذوبان بالفم
Hard gelatin capsule	كبسولات صلبه
Hard gelatin capsules containing enteric coated pellets	كبسولات تحتوى على حبيبات ذات كسوة معوية
Hard gelatin capsules containing enteric coated granules	كبسولات تحتوى على حبيبات ذات كسوة معوية
Hard gelatin capsules containing enteric coated minitablets	كبسولات تحتوى على أقراص ذات كسوة معوية
Soft gelatin capsule	كبسولات جيلاتنية رخوة
Enteric coated soft gelatin capsule	كبسولات جيلاتنية رخوة ذات كسوة معوية
Powder in sachets for oral solution	بودرة فى أكياس لعمل محلول للتناول بالفم

Powder in sachets for oral suspension	بودرة فى أكياس لعمل معلق للشرب
Powder for oral suspension	بودرة لعمل معلق للشرب
Oral suspension	معلق للشرب (عن طريق الفم)
Syrup	شراب
Oral liquid	محلول للشرب(عن طريق الفم)
Oral solution	محلول للشرب(عن طريق الفم)
Oral Emulsion	مستحلب للشرب(عن طريق الفم)
Granules in sachets	حبيبات فى أكياس
Granules in sachets for oral solution	حبيبات فى أكياس لعمل محلول للشرب (عن طريق الفم)
Granules in sachets for oral suspension	حبيبات فى أكياس لعمل معلق للشرب(عن طريق الفم)
Oral gel	جل للفم
Lozenges	أقراص للإستحلاب
Elixir	ألكسير
Linctus	دواء للكحه
Gargles	غرغرة
Mouth Wash	مضمضة
Gums	علكة
Pill	أقراص
Pilules Microspheres	حبيبات
Sublingual tablets	أقراص تحت اللسان
Caplets	أقراص
Melt tablets	أقراص تنصهر
Quick tablets	

Flash tablets	أقراص سريعة الذوبان
Dragees	أقراص سريعة الذوبان جداً
Lactab	لاكتاب
Sustained release tablet	أقراص ممتدة المفعول
Controlled release tablet	أقراص ممتدة المفعول
Modified release tablet	أقراص ممتدة المفعول
Extended release tablet	أقراص ممتدة المفعول
Retard tablet	أقراص ممتدة المفعول
Enteric Coated capsule	كبسولات ممتدة المفعول ذو كسوه معدية
Sustained release capsule	كبسولات ممتدة المفعول
Controlled release capsule	كبسولات ممتدة المفعول
Modified release capsule	كبسولات ممتدة المفعول
Extended release capsule	كبسولات ممتدة المفعول
Retard Capsule	كبسولات ممتدة المفعول
Depotabs.	أقراص ذو طبقة مختزنة
Oral Pastes	معجون للفم
Extended Release Film Coated tablet	أقراص مغلفة ممتدة المفعول
Extended Release Granule For oral Suspension	حبيبات ممتدة المفعول لعمل معلق للشرب
Irrigant	
Pastille	بستلية
Extended Release Coated Pellets	حبيبات ممتدة المفعول
Delayed Release	متأخرة الأنطلاق
Chewable tablet	أقراص للمضغ

Topical Dosage Forms	
Topical cream	كريم موضعي
Topical ointment	مرهم موضعي
Topical lotion	لوسيون موضعي
Topical solution	محلول موضعي
Topical suspension	معلق موضعي
Topical spray	سبراي موضعي
Topical powder	بودرة موضعية
Topical gel	جل موضعي
Transdermal patchs	لاصقات جلدية لها تأثير عضوي
Topical Foam	محلول رغوي موضعي
Topical Emulsion	مستحلب موضعي
Liniment	لبخة
Medicated dressings	ضمادات طبية
Tulles	ضمادات طبية
Emulgel	ايملجل
Shampoo	شامبو
Massage cream	كريم مساج
Poultices	كمادات لبخة
Rectal preparations	
Rectal cream	كريم شرجي
Rectal ointment	مرهم شرجي
Rectal suppositories	أقماع شرجية

Rectal foam	محلول رغوي شرجي
Enema	حقنة شرجية
Vaginal preparations	
Vaginal suppositories	أقماع مهبلية
Vaginal cream	كريم مهبلي
Intravaginal cream	كريم مهبلي
Vaginal ovules	بويضات مهبلية
Vaginal pessaries	أقماع مهبلية
Vaginal tablets	أقراص مهبلية
Injections	
Sterile Water for injection	ماء معقم للحقن
Solution for intramuscular injection	محلول للحقن العضلي
Solution for intravenous injection	محلول للحقن الوريدي
Solution for subcutenous injection	محلول للحقن تحت الجلد
Solution for intravenous infusion	محلول للتنقيط الوريدي
Solution for I.M./I.V. injection	محلول للحقن العضلي والوريدي
Solution for I.M./I.V./S.C. injection	محلول للحقن العضلي أوالوريدي أوتحت الجلد
Concentrate for intramuscular injection	محلول مركز للحقن العضلي
Concentrate for intravenous injection	محلول مركز للحقن الوريدي
Concentrate for subcutenous injection	محلول مركز للحقن تحت الجلد
Concentrate for intravenous infusion	محلول مركز للتنقيط الوريدي
Concentrate for I.M./I.V. injection	محلول مركز للحقن العضلي والوريدي
Concentrate for I.M./I.V./S.C. injection	محلول مركز للحقن العضلي أوالوريدي أوتحت الجلد

Implantable Pellet	أقراص توضع تحت الجلد
Inhalations	
Dry powder for inhalation	بودرة جافة للإستنشاق
Turbohaler (= dry powder inhaler)	
Aerosol inhalation	
Accuhaler (dry powder for inhalation)	
Powder in sachets for solution for inhalation	

- **Narrow Therapeutic Range Drugs.**

A narrow Therapeutic Index:

Is defined medically as the ratio between the average effective dose and the average lethal dose. It is an extremely close margin between an effective concentration of a therapeutic drug circulating in the blood and a fatal concentration.

- Aminophylline Tablets, ER Tablets
- Carbamazepine Tablets, Oral Suspension
- Clindamycin Hydrochloride Capsules
- Clonidine Hydrochloride Tablets
- Clonidine Transdermal Patches
- Dyphylline Tablets
- Disopyramide Phosphate Capsules, ER Capsules
- Ethinyl Estradiol/Progestin Oral Contraceptive Tablets
- Guanethidine Sulfate Tablets
- Isoetharine Mesylate Inhalation Aerosol
- Isoproterenol Sulfate Tablets
- Lithium Carbonate Capsules, Tablets, ER Tablets
- Metaproterenol Sulfate Tablets
- Minoxidil Tablets
- Oxtriphylline Tablets, DR Tablets, ER Tablets
- Phenytoin, Sodium Capsules (Prompt or Extended), Oral Suspension
- Prazosin Hydrochloride Capsules

- Primidone Tablets, Oral Suspension
- Procainamide Hydrochloride, Capsules, Tablets, ER Tablets
- Quinidine Sulfate Capsules, Tablets, ER Tablets
- Quinidine Gluconate Tablets, ER Tablets
- Theophylline Capsules, ER Capsules, Tablets, ER Tablets
- Valproic Acid Capsules, Syrup
- Divalproex, Sodium DR Capsules, DR Tablets
- Warfarin, Sodium Tablets
- Cyclosporine
- Digitoxin
- Digoxin
- Aprindine
- Clonazepam
- Ethosuximide
- Flecainide
- Isoprenaline
- Levoxyine
- Methotrexate
- Phenobarbital
- Sirolimus
- Sulfonylurea Antidiabetic Drugs Compounds
- Tacrolimus
- Zonisamide
- Glybuzole
- Clonazepam

- Others (Specify & submit reference document from EMA or US FDA))

- **Abbreviations.**

EDA LABS: the labs of the Egyptian drug authority
VDA: Variation Department Approval
VCA: Variation Committee Approval
TCA: Technical Committee Approval
CPP: Certificate of pharmaceutical products
COA: Certificate of Analysis
BE: Bioequivalence
MAH: Market Authorization Holder
P: Pricing

▪ General Notifications

- **In some cases, request within reporting category VDA can be issued to VCA if needed according to file case.**
- **In cases of multiple requests submitted from a company the variation committee decision may differ from what stated in guidelines according to the case of the file.**
- **In cases of company's request to change composition where EDA LABS C.O.A or EDA LABS Composition aren't available or couldn't be submitted from EDA LABS, Analysis Registration (AR) will be required in variation approval.**
- **In cases of any change in composition which requires EDA LABS Notification Only, the company must submit a commitment that the total weight of the product & its specifications is not different from that stated in EDA LABS COA. If there is any change Analysis Inspection (AI) will be required.**
- **In some cases, variation department may issue the company's request to TCA to take their decision.**
- **For all variation approvals with No Requirements there is a maximum one-year permission (as a grace period) for implementation to be started with the proposed status (current status is allowed to be used within this grace period).**

▪ Reference List.

Reference Country	The Website
FDA	http://www.accessdata.fda.gov/scripts/cder/daf/?source=govdelivery&utm_medium=email&utm_source=govdelivery
Spain -AEMPS	https://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm
France (ANSM)	http://agence-prd.ansm.sante.fr/php/ecodex/index.php
Belgium	http://www.fagg-afmps.be/fr/items/banque_donnees
Australia (TGA)	https://www.ebs.tga.gov.au
Canada	https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
UK (MHRA)	http://www.mhra.gov.uk/spc-pil/?prodName=DO-DO%20CHESTEZE&subsName=&pageID=ThirdLevel&searchTerm=theophylline#retainDisplay
Germany	https://www.pharmnet-bund.de/dynamic/en/drug-information-system/index.html
Swissmedic	http://ch.oddb.org

The Netherland	http://db.cbg-meb.nl/ords/f?p=111:1:0:::SESSION:P0_DOMAIN,P0_LANG:H,EN
Denmark	http://www.produktresume.dk/docushare/dsweb/helpdesk
Italy	https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/cerca-per-principio-attivo
Ireland (HPRA)	https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine
Sweden	https://lakemedelsverket.se/english/
Portugal	http://app7.infarmed.pt/infomed/inicio.php
New Zealand	http://www.medsafe.govt.nz/regulatory/DbSearch.asp
Norway	https://legemiddelverket.no/English
Finland	http://www.fimea.fi/web/en/databases_and_registeries/spcs/human_medicinal_products
Japan	http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html
Austria	https://aspregister.basg.gv.at/aspregister/faces/aspregister.jspx?_afrLoop=45028630015782264&_afrWindowMode=0&_adf.ctrl-state=1b7ups43h2_4
Iceland	https://www.serlyfjaskra.is

EMA	http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=WC0b01ac058001ce7e
PDR	http://www.pdr.net/browse-by-drug-name
Eudra Inspection	http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPCompliance.do
FDA Inspection	https://www.accessdata.fda.gov/scripts/inspsearch/

Submission Guidance of Variation Administration of Human Pharmaceutical Products

Submission Guidance for Evaluation Unit of API Manufacturer Variations for Human Pharmaceuticals

The APIs manufacturer's soft file should be arranged as follows:

I) Common Administrative documents:

Section (1) **Cover letter + Declaration letters & Payment receipt (Signed and Stamped)**	
Required Documents	
1	Covering Letter: From the applicant on company's letterhead showing product name, registration no., APIs, dosage form with describing in details the required APIs manufacturers addition /change, deletion, name change, final approval, name clarification, appeal or APIs specification / Particle size changing / clarification & APIs manufacturers not to be deleted. **(Template 1)**
2	Declaration letter on company's letterhead states that: - Submitted Product registration license is the last updated, issued one from the central administration for pharmaceutical products (Egyptian Drug Authority). - The file including all variations & issued variation approvals for the product. - All documents within the file are correct & on the responsibility of the company. - The last produced batch (Batch number, Production Date & Expiry Date): In case of final registration license. - All tentative registration license requirements will be done on the main API manufacturer (for each API): In case of tentative registration licenses. **(Template 2**)
3	Declaration Letter on company's letterhead states that: Name & address of all API manufacturers. **(Template 3)**

4	Declaration Letter on company's letterhead that states: The company will submit GMPs & COAs of all APIs manufacturers for central administration for pharmaceutical products (Egyptian Drug Authority) when API importation. **(Template 4**)
5	Declaration letter on company's letterhead states that: … is the commissioner by the company to deal with central administration for pharmaceutical products (Egyptian Drug Authority). **(Template 7)**
6	Payment Receipt: 1000 L.E (Showing product name, Conc., registration no. & Type of variation).

Section (2) Product registration license & attachments (Signed & stamped)	
Required Documents	
1	Valid product registration license.
2	**In Case of Imported finished Human Pharmaceutical Product if the applicant is either scientific Office or Company the following documents to be submit:** ***Scientific Office:** **a) "Authorization letter for the Scientific Office to register finished Imported Human Pharmaceutical Products"** issued by Evaluation Unit of registration requests for human pharmaceuticals. **b) Declarations Letter** Clarifying the Company's profile Code signed & stamped ***Company:** **Declarations Letter** Clarifying the Company's profile Code describing its activity as "Company Authorized for Registration" And if not Available The company must apply to systems & information unit for creating a company profile to be able to submit variation requests **N.B.: If Applicant Change for the Imported finished Product is needed** kindly submit separate Fulfilled file (as check list) for the Applicant change**.**
3	Receipt or an approval for renewal: In case of the final registration license is not valid.
4	Validity extension or what declares that the tentative registration license has submitted for conversion to final registration license: In case of tentative registration license is not valid.

5	Registration license Composition For the product from central administration of pharmaceutical products (Egyptian Drug Authority).
6	Product CPP / E-CPP (Certificate of pharmaceutical product): In case of under license / imported products.
7	Minister decree 600 exception (If needed).

II) Relevant Documents According to the Variation Type:

Section (3) **1. Documents for APIs Manufacturer(s) addition / change (Signed & stamped / digitally signed)**	
Required Documents	
1	Complete & recent GMP certificate / (ISO 9001 – 2015 certificate in case of minerals, vitamins, extracts) / CPP / Written confirmation letter with manufacturer name including API for APIs manufacturer(s) to be added.
2	Complete API manufacturer license in case of GMP certificate annex is not including API for APIs manufacturer(s) to be added.
3	GMP certificate / (ISO 9001 – 2015 certificate in case of minerals, vitamins, extracts) / CPP / Written confirmation letter with manufacturer name including API for APIs manufacturer(s) not to be deleted.

4	API manufacturer data certificate with API production line in case of local manufacturer(s).
5	API manufacturer COA with the same specification of the product license composition.
6	Relationship Declaration Letter: In case of submitted COA on manufacturer letterhead different from the API manufacturer mentioned in GMP certificate.
7	Updated Pharmacopeia Monograph for API specification matching with product license composition.

Section (4) **2. Documents for APIs Manufacturers names change (Signed & stamped / digitally signed)**	
Required Documents	
1	Declaration on Company's letterhead states that: There is no change in Specification of the API. **(Template 6)**
2	Complete, recent GMP certificate / ISO 9001 – 2015 certificate in case of minerals, vitamins, extracts / CPP / Written confirmation letter with manufacturer new name including API (with the same address of old name certificate).
3	Complete recent API manufacturer license (with the same address of new name certificate) in case of new name certificate annex is not including API.
4	GMP certificate / ISO 9001 – 2015 certificate in case of minerals, vitamins, extracts / CPP / Written confirmation letter with manufacturer old name (with the same address of new name certificate).

5	Manufacturer new name COA with the same specification of the product license composition, matching with pharmacopeia, with expiry date / re-test date.
6	Relationship Declaration Letter: In case of submitted COA on manufacturer letterhead Different from the API manufacturer.
7	Declaration letter from the authority which is responsible for manufacturer inspection directed to the manufacturer with the manufacturer new named mentioned & approval of the change: In case of GMP / ISO 9001 – 2015 (In case of minerals, vitamins, extracts) / CPP / Written confirmation letter with manufacturer new name including API (with the same address of old name certificate) is not issued yet.

Section (5) 3. Documents for APIs manufacturers deletion (Signed & stamped / digitally signed)	
Required Documents	
1	Complete GMP / ISO 9001 – 2015 (In case of vitamins, extracts or minerals) / CPP / Written confirmation letter with manufacturer name: For API manufacturers not to be deleted.
2	Manufacturer COA with the same specification of the product license composition & (particle size test with the same specification limit range & solubility test in case of particle size clarify/change request): For API manufacturer not to be deleted.
3	API Manufacturer License issued from Egyptian Drug Authority or Data Certificate with API Manufacturer name issued from Egyptian Drug Authority + API manufacturer License issued from Ministry of Industry (In case of local API manufacturers): For API manufacturer not to be deleted.
4	Relationship Declaration Letter (In case of submitted COA on manufacturer letterhead different from the API manufacturer): For API manufacturer not to be deleted.
5	Declaration letter from the product license holder declares that the agreement to API manufacturer deletion: (In case of under license products).

Section (6) 4. Documents for APIs Specification / Particle size change / clarification (Signed & stamped / digitally signed)	
Required Documents	
1	The more recent EDA labs Composition (In case of production).
2	Declaration letter on company's letterhead that states the submitted EDA labs composition is the last one has been analyzed (In case of production). **(Template 8)**
3	On company's letterhead: old composition + new composition with new specs / Particle Size.
4	API manufacturer COA with the same specification of the product license composition, with particle size test (same specification limit range) & solubility test: for API manufacturer not to be deleted.
5	On company's letterhead scientific justification: (In case of there is no need for Particle sizes change / clarify).
6	An inspection report stating that the used API is with particle size: (In case of particle size clarification).

7	Declaration letter from the product license holder declares that the agreement to API particle size / specification clarification / change: (In case of under license & imported products).

Section (7) **5. Documents for APIs manufacturers final approval (Signed & stamped)**	
Required Documents	
1	Copy of preliminary approval for API(s) manufacturer(s) addition.
2	Copy of 1st production batch withdrawal report for the API(s) manufacturer(s).
3	EDA labs. Certificate of analysis for 1st production batch.
4	EDA labs. Composition (in case of registration analysis).
5	Copy of accelerated stability study on the 1st production batch for API(s) manufacturer(s).
6	Copy of comparative in – vitro study on the 1st production batch for API(s) manufacturer(s).

Section (8) 6. Documents for API manufacturer(s) addition preliminary approval period extension 7. (Signed & stamped)	
Required Documents	
1	Copy of preliminary approval for API(s) manufacturer(s) addition in case of API manufacturer is not mentioned in product registration license.
2	Copy of 1st production batch withdrawal report for the API(s) manufacturer(s).
3	EDA labs. Certificate of analysis for 1st production batch.
4	EDA labs. Composition (in case of registration analysis).
5	Copy of accelerated stability study on the 1st production batch for API(s) manufacturer(s) if done.
6	Copy of comparative in – vitro study on the 1st production batch for API(s) manufacturer(s) if done.

Covering letters (Template 1):

السيد الدكتور / رئيس هيئة الدواء المصرية

الإداره العامه لتسجيل المستحضرات البشرية

إدارة المتغيرات للمستحضرات البشرية

اسم المستحضر:	
المادة الفعالة/التركيز:	
المصنع:	
رقم تسجيل:	
الرجاء من سيادتكم التكرم بالموافقه على الاتى:	
توضيح (مصدر/ مصدرين/ مصادر) (الماده/المواد الخام الفعاله) وهو/هما/هى:	
(وهو/ وهما/ وهى/من):	
(إلى المصدر المضاف/المصدرين المضافيين):	
وحذف المصدر:	
والإبقاء على:	
لتصبح (مصدر/مصدري/ مصادر) الماده الخام الفعاله (هم/ هما/هي):	1- 2- 3-

Declarations (Template 2):

تعهد

اسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

نتعهد نحن شركة.....

- **أن الإخطارالمقدم هو آخر إخطار صادر من هيئة الدواء المصرية حتى تاريخه.**
- **أن الملف يشمل كافة المتغيرات والموافقات الصادرة للمستحضر.**
- **أن جميع المستندات المقدمة بالملف صحيحة وعلى مسئولية الشركة .**
- **تلتزم الشركه بجميع البيانات المذكورة في التعهد .**
- **في حالة الإخطارات المبدئيه: تلتزم الشركه بعمل جميع دراسات الإخطار المبدئي على مصدر الماده الخام الفعاله الأساسي.**
- **في حالة الإخطارات النهائية: تتعهد الشركة بأن رقم أخر تشغيلة هو ..... وتاريخ إنتاجها هو...../...../.....**

وتاريخ إنتهائها هو...../...../.....

مدير إدارة التسجيل

د/

Suppliers' declaration (Template 3):

تعهد

اسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة أن اسم المصنع وعنوانه للمادة الخام الفعالة كالآتى:

1. **Manufacturer: ……..**
   Address: ……
2. **Manufacturer: ……..**
   Address: ……
3. **Manufacturer: ……..**
   Address: ……

مدير إدارة التسجيل

د/

GMPs & COAs Declaration (Template 4):

تعهد

اسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركه بتقديم شهادات ال GMP وشهادات التحليل الخاصة بالمادة الخام وذلك عند التقدم لإستيراد المادة الخام بهيئة الدواء المصرية.

مدير إدارة التسجيل

د/

Production Declaration (Template 5):

تعهد

اسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة بأنه لم يتم إنتاج المستحضر حتى تاريخه.

مدير إدارة التسجيل

د/

API Declaration (Template 6):

تعهد

اسم المستحضر:	
الماده الفعالة والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة بأنه لا يوجد أى تغيير أو تعديل فى المواصفات الخاصة بالمادة الفعالة.

(Specification of API is the same)

مدير إدارة التسجيل

د/

Delegation Declaration (Template 7):

تعهد

إسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة بأن المفوض الرسمى للشركه للتعامل مع هيئة الدواء المصرية فى الإجراءات اللازمه:

هو:.....

رقم قومى :.....

رقم موبايل:.....

عنوان البريد الالكتروني: .....

مدير إدارة التسجيل

د/

Analysis declaration (Template 8):

تعهد

إسم المستحضر:	
الماده الفعاله والتركيز:	
المصنع:	
رقم تسجيل:	

تتعهد الشركة أن بيان التركيب المرفق هو آخر بيان تركيب تم التحليل عليه

(في حالة التقدم لتوضيح / إثبات ال Particle size أو توضيح / تغييرالمرجعية الدستورية للمادة الخام الفعالة)

مدير إدارة التسجيل

د/

Submission Guidance for Composition & Specifications Variations for Human Pharmaceuticals Unit

A- Composition & Specification Variations file

The Composition & Specification Variations file should be arranged as the following:

I- Common Administrative Documents:

Section (1) Variation Notification form & Declaration letter & (Signed and Stamped) + Payment receipt	
Required Documents	
1	**Variation Notification form:** ▪ Clearly states the variation required (current and proposed status).
2	**Declaration Letter states:** ▪ Any other variations took place and had not been added to the registration license. ▪ All EDA approvals for the product. ▪ All Data Included in the file is correct and on Company's responsibility. ▪ The submitted EDA lab composition and its certificate of analysis (the last composition analyzed by EDA Labs). ▪ Last production batch (Batch number, Date of Production & Date of Expiration.
3	**Payment receipt 000 LE (Per each variation issue)** (With product name and type of variation mentioned)

Section (2) EDA License & Approvals	
Required Documents	
1	**EDA Valid Registration License** ▪ If Final & invalid: Valid Approval for registration renewal. ▪ If Tentative & invalid: License validity extension approval or approval for submission from Tent. to final.
2	**In Case of Imported finished Human Pharmaceutical Product if the applicant is either scientific Office or Company the following documents to be submit:** ***Scientific Office:** **a) "Authorization letter for the Scientific Office to register finished Imported Human Pharmaceutical Products"** issued by Evaluation Unit of registration requests for human pharmaceuticals. **b) Declarations Letter** Clarifying the Company's profile Code signed & stamped ***Company:** **Declarations Letter** Clarifying the Company's profile Code describing its activity as "Company Authorized for Registration" And if not Available The company must apply to systems & information unit for creating a company profile to be able to submit variation requests **N.B.: If Applicant Change for the Imported finished Product is needed** kindly submit separate Fulfilled file (as check list) for the Applicant change**.**
3	Any other EDA or Variation approvals.
4	Minister decree 600 exception (If needed).
5	Any Previous Stability Approvals (Accelerated Stability or Long-term Stability).

6	Leaflet of the product and innovator.
7	EDA labs certificate of analysis.
8	EDA labs composition certificate.
9	Manufacturing factory license.

Section (3) **Other Documents (In Case of Imported / UL Products)**	
Required Documents	
1	**Valid CPP/eCPP: (With All Attachment):** ▪ Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy.
2	**Declaration Letter from LH/MAH in COO:** ▪ Clarifies the change if not stated in CPP. ▪ Authenticated from Chamber of commerce & Egyptian consulate/embassy.
3	**Declaration Letter from LH/MAH in COO signed and stamped**: ▪ Stating the reasons of change.
4	**CTD:** ▪ Part related to required change.

II- <u>Relevant Documents According the Variation Type:</u>

Section (4) **Composition Change**
Required Documents

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 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').

Section (5) Clarification / Change of salt equivalence and/or crystalline state (E.g. hydrate, solvate, polymorph)	
Required Documents	
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.

Section (6) 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)	
Required Documents	
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).

Section (7) Clarification /Change or Addition of the solvents used in manufacturing process (e.g. ethanol, methanol)	
Required Documents	
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

Section (8) **Clarification /Change of Active / Inactive Ingredient Specification:**	
Required Documents	
1	Pharmacopeia Monograph (Last Edition)
2	C.O.A of all suppliers of Active Ingredient or Premixes.
3	Comparison between Old & New Finished 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" (In Case of Clarification)
6	New composition "signed and stamped" (In Case of Clarification)
7	Comparison table between old and new composition (In Case of Clarification)

Section (9) **Change in Physical Character of Finished Product**	
Required Documents	
1	Sample (IF Needed).

2	Old & New Certificate of Analysis.
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	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).
7	Scientific Justification for color change with scientific reference.
8	Manufacturer Factory License (In Case of change in dosage form with change in physical character).
9	Manufacturing process flow chart (In case of the Change in physical character is due to change in Manufacturing process).
10	Composition of capsule shell on supplier paper (In case of Change color of capsule shell).

Section (10) **Correcting Dosage Form**	
Required Documents	
1	Innovator reference and it's leaflet.
2	Any studies issued previously for New Dosage form.
3	EDA labs CoA / Composition.

Section (11) Shelf Life Reduction	
Required Documents	
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.

Section (12) Change / Addition of Route of Administration	
Required Documents	
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.

B- <u>Change / Addition of container Closure system Variations:</u>

The Change / Addition of container Closure system Variations file should be arranged as follows:

Section (1) Variation Notification form & Declaration letter & (Signed and Stamped) + Payment receipt	
Required Documents	
1	**Variation Notification form:**

	▪ Clearly states the variation required (current and proposed status).
2	**Declaration Letter states:** ▪ Any other variations took place and had not been added to the registration license. ▪ All EDA approvals for the product. ▪ All Data Included in the file is correct and on Company's responsibility. ▪ The submitted EDA lab composition and its certificate of analysis (the last composition analyzed by EDA Labs). ▪ Last production batch (Batch number, Date of Production & Date of Expiration.
3	▪ Payment receipt 1000 LE (Per each variation issue) showing product name and type of variation mentioned).

Section (2) **EDA License & Approvals**	
Required Documents	
1	**EDA Valid Registration License** ▪ If Final & invalid: Valid Approval for registration renewal. ▪ If Tentative & invalid: License validity extension approval or approval for submission from Tent. To final.
2	**In Case of Imported finished Human Pharmaceutical Product if the applicant is either scientific Office or Company the following documents to be submit:** ***Scientific Office:** **a) "Authorization letter for the Scientific Office to register finished Imported Human Pharmaceutical Products"** issued by Evaluation Unit of registration requests for human pharmaceuticals.

	b) Declarations Letter Clarifying the Company's profile Code signed & stamped ***Company:** **Declarations Letter** Clarifying the Company's profile Code describing its activity as "Company Authorized for Registration" And if not Available The company must apply to systems & information unit for creating a company profile to be able to submit variation requests **N.B.: If Applicant Change for the Imported finished Product is needed** kindly submit separate Fulfilled file (as check list) for the Applicant change**.**
3	Any other EDA or variation approvals.
4	Minister decree 600 Exception (If Needed).
5	Pricing Certificate.
6	Any Previous Stability Approvals (Accelerated Stability or Long-term Stability).
7	Leaflet of the product and innovator.
8	EDA labs certificate of analysis.

Section (3) **Other documents (In Case of Imported / UL Products)**	
Required Documents	
1	**Valid CPP/eCPP: (With All Attachment)** Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy.
2	**Declaration Letter from LH/MAH in COO:** ▪ Clarifies the change if not stated in CPP.

	▪ Authenticated from Chamber of commerce & Egyptian consulate/embassy.
3	**CTD:** ▪ Part related to packaging material.

Section (4)	
Required Documents	
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.
5	Certificate of Analysis of Desiccant.

C- Change / Addition of container Closure system Variations:

The Final Approval Variations file should be arranged as follows:

I- Common Administrative Documents:

Section (1) **Variation Notification form & Declaration letter & (Signed and Stamped) + Payment receipt**	
Required Documents	
1	**Variation Notification form:** ▪ Clearly states the variation required (current and proposed status).

2	**Declaration Letter states:** ▪ Any other variations took place and had not been added to the registration license. ▪ All EDA approvals for the product. ▪ All Data Included in the file is correct and on Company's responsibility. ▪ The submitted EDA lab composition and its certificate of analysis (the last composition analyzed by EDA Labs). ▪ Last production batch (Batch number, Date of Production & Date of Expiration.
3	**Payment receipt 1000 LE (Per each variation issue)** showing product name and type of variation mentioned.

Section (2) **EDA License & Approvals**	
Required Documents	
1	**EDA Valid Registration License** ▪ If Final & invalid: Valid Approval for registration renewal. ▪ If Tentative & invalid: License validity extension approval or approval for submission from Tent. to final.
2	**In Case of Imported finished Human Pharmaceutical Product if the applicant is either scientific Office or Company the following documents to be submit:** ***Scientific Office:** **a) "Authorization letter for the Scientific Office to register finished Imported Human Pharmaceutical Products"** issued by Evaluation Unit of registration requests for human pharmaceuticals.

	b) Declarations Letter Clarifying the Company's profile Code signed & stamped ***Company:** **Declarations Letter** Clarifying the Company's profile Code describing its activity as "Company Authorized for Registration" And if not Available The company must apply to systems & information unit for creating a company profile to be able to submit variation requests **N.B.: If Applicant Change for the Imported finished Product is needed** kindly submit separate Fulfilled file (as check list) for the Applicant change**.**
3	Primary Approval.
4	Any other EDA or Variation approvals.
5	Minister decree 600 Exception (if needed).

Section (3) **Other documents (In Case of Imported / UL Products)**	
Required Documents	
1	**Valid CPP/eCPP: (With All Attachment)** ▪ Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy.

II- Relevant Documents According the Variation Type:

Section (4) Other Documents (Relevant to Final Approval Composition)	
Required Documents	
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): EDA LABS COA & Composition Stability Approval 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**
5	Any Exemption from any study stated in primary approval.

Section (5) Other Documents (Relevant to Final Approval Pack)	
Required Documents	
1	All Studies issued on primary approval for the product and its original copies (to be seen): **a.** EDA LABS COA / Composition. **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.
4	Any Exemption from any study stated in primary approval.

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

تحية طيبة وبعد،،،،

بخصوص المستحضر الاتى:

Trade name:	
Generic name:	
Strength:	
Dosage form:	
Applicant company:	
License holder:	
Manufacturer:	
Reg. No.:	

- نفيد سيادتكم علماً بأن السيد الدكتور/..... وبياناته كالآتي:

رقم إثبات الشخصية:	
بريده الإلكتروني:	
فاكس:	
رقم موبيل:	

هو المفوض من قبل الشركة لتقديم، متابعة وإنهاء طلبات المتغيرات الخاصة.

٢- نتعهد نحن شركة ..... بأن:

- الإخطار المقدم هو أخر إخطار صادر للمستحضر وهذا تعهد منا بذلك.
- جميع المستندات المقدمة بالملف صحيحة وعلى مسئولية الشركة وأنه مرفق جميع موافقات المتغيرات السابقة الخاصة به وهذا تعهد منا بذلك.

مرفق:

١-

٢-

- لم يتم إنتاج/استيراد أو تداول المستحضر بالسوق المحلي
  * تم إنتاج/ استيراد المستحضر ومرفق جميع الدراسات التي تم إجراءها.

مرفق الدراسات (في حالة إن تم إنتاجه):

١-

٢-

- تتعهد الشركة بأن آخر تشغيلة إنتاجية تم إنتاجها من المستحضر المذكور أعلاه بياناتها كالتالي:

Batch No.: **Manufacturing Date:** **Expiry Date:**

وتفضلوا بقبول فائق التحية والتقدير،،،،

Appendix II: Variation Notification form.

Trade Name:	
Generic Name/ strength:	
Dosage Form:	
Applicant:	
License Holder:	
Manufacturer:	
Reg. No.:	
BCS Class of the drug:	
Class of solvent:	In case of addition solvents use during manufacturing
Current Situation	
Proposed Change	

- **I declare that there are no other changes except mentioned above.**

وتفضلوا بقبول فائق التحية والتقدير،،،،

رئيس مجلس ادارة الشركة **ختم الشركة**

Submission Guidance for Ownership & Manufacturing Variations Unit

The Ownership/MFG Variation file should be arranged as Follows:

III- Common Administrative Documents:

Section (1) Cover letter + Payment receipt + Declarations	
1	**Delegation of the company's representative (Template 1)**
2	**Covering Letter (Template 2)** Clearly states the variation required current and purposed status. Stating any approvals for the product that were not mentioned in the last released registration license. Signed & stamped.
3	**Payment receipt** According to Variation Request With the product name, type of variation and the name of the applicant written Directed to variation department Stamped with EDA Stamp
4	**Declarations Letter (Template 3)** Attached registration license is the latest issued one. All documents & information submitted in the file are correct and on the responsibility of the company Attached pricing certificate is the latest issued one.

	Proposed Storage site(s). Data of the last manufactured/imported production batch (Batch No., Production date & Expiry date) The submitted file contains all approvals, variations & decisions issued for the product from different EDA departments. Signed & stamped.
5	**Declaration Letter (Template 4)** Name & address of Manufacturers of API of product as stated in GMP Name & address of suppliers of API of product. Signed & stamped.

Section (2) **EDA License & Approvals**	
1	**EDA Valid Registration License** If Final & invalid: Valid Approval for registration renewal If Tentative & invalid: License validity extension approval or approval for submission from Tent. To final
2	**Certificate of Pharmaceutical Product (CPP)** For Imported & UL products Valid From Country of Origin of LH, mentioning the Product Trade Name in Egypt & all Data up to date Product registered & marketed Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy **OR:** Electronic Certificate of Pharmaceutical Product (E-CPP)

3	**Pricing Certificate** (Latest pricing certificate issued for the product)
4	**Ministerial decree 600/2018 exemption approval** (If needed)
5	All previous approvals, variations & decisions issued for the product from different EDA departments

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

IV- Relevant Documents According to Variation Type:

1- Ownership Transfer (Local FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 5000 L.E.
2	**Ownership Waiver** From Old LH To New LH Authenticated from Real Estate Registry at Ministry of Justice Authenticated from EDA Legal Affairs Product trade name, strength, dosage form & reg.no. is mentioned
3	**Manufacturing contract** Between LH & Manufacturing Site Valid Authenticated from Bank & EDA Legal Affairs
4	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
5	**3 Copies Composition declaration** On New LH head letter Identical to the one attached with the registration license or to the latest finally approved composition Signed & stamped
6	**Declaration Letter (Template 5)** From Old LH FPP does not have any other strengths of the same dosage form or other dosage forms either registered or under registered products. Signed & stamped.

7	**Declaration Letter (Template 5)** From New LH FPP does not have any other strengths of the same dosage form or other dosage forms either registered or under registered products. Signed & stamped.
8	**Declaration Letter (Template 6)** Stating all registered & under-registrations human FPP owned by the new owner company In case of Toll companies Signed & stamped.
9	**Declaration Letter** NO change in composition, specifications, manufacturing process, or container/closure system of the FPP. Signed & stamped.
10	**Declaration Letter** 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.
11	**1st Marketing Permission Report** For the products registered under the ministerial decree 425/2015

2- MFG Site Transfer (Local & UL FPP)	
Section (5) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:**

	1st site: 3000 L.E 2nd site: 5000 L.E 3rd site: 10000 L.E 4th site: 20000 L.E **N.B: For Transferring the storage site refer to the fees of storage site transfer**
2	**Manufacturing contract** Between LH/Applicant & New Manufacturer. Valid. Authenticated from Bank & EDA Legal Affairs. In case of a foreign party signing the contract: Authentication form chamber of commerce, Egyptian embassy/consulate or Notary
3	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
4	**Latest New Manufacturing site license:** Production line &/or area needed for manufacturing the product is present.
5	**Last Updated Commercial Register** Of the new manufacturing site
6	**If the site was previously temporarily added:** Copy of the previous approval Copies of all studies & analysis approvals done for this site.

7	**Waiver** From Old Manufacturing Site Mentioning the product name & reg. no. Stating his approval of transferring manufacturing of the product to a new manufacturing site Authenticated from Bank & EDA Legal Affairs **OR Termination letter** From LH to Old Manufacturing Site signed & Stamped With proof of delivery.
8	**Declaration Letter** NO change in composition, specifications, manufacturing process, or container/closure system of the FPP. *Signed & Stamped.
9	**Letter of Variation** For UL Products From product LH in COO Stating the required variation Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary

3- MFG Site Addition (Local & UL FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 2nd site: 5000 L.E 3rd site: 10000 L.E 4th site: 20000 L.E **N.B: For addition the storage site refers to the fees of storage site addition**
2	**Manufacturing contract** Between LH/Applicant & New Manufacturer. Valid. Authenticated from Bank & EDA Legal Affairs. In case of a foreign party signing the contract: Authentication form chamber of commerce, Egyptian embassy/consulate or Notary
3	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
4	**Latest New Manufacturing site license:** Production line &/or area needed for manufacturing the product is present.
5	**Last Updated Commercial Register** Of the new manufacturing site
6	**In case of Tentative registration license:** AR approval of the 1st production batch from EDA Labs
7	**If the site was previously temporarily added:** Copy of the previous approval Copies of all studies & analysis approvals done for this site.

8	**Declaration Letter** From Old Manufacturing site. The product trade name & reg. no. is mentioned. Stating his approval of adding a new manufacturing site. Authenticated from Bank & EDA Legal Affairs.
9	**<u>OR</u> Declaration Letter** From the LH The product trade name & reg. no. is mentioned. Stating: "The company takes the full legal responsibility against the main manufacturing site 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." Authenticated from Bank & EDA Legal Affairs
10	**Letter of Variation** For UL Products From product LH in COO Stating the required variation Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary

4- MFG site Addition for Export Only (Local & UL FPP)	
Separator (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 3000 L. E
2	**Manufacturing contract** Between LH & New Manufacturer.

	Valid. Authenticated from Bank & EDA Legal Affairs.
3	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
4	**Latest New Manufacturing site license:** Production line &/or area needed for manufacturing the product is present.
5	**Last Updated Commercial Register** Of the new manufacturing site

5- 2ry Packaging Site Addition/Change (Local & UL FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	1st site change: 3000 L.E 2nd site addition/change: 5000 L.E 3rd site addition/change: 10000 L.E 4th site addition/change: 20000 L. E
2	**In Case of Addition:** **Declaration Letter** From Old 2ry Packaging site. The product trade name & reg. no. is mentioned Stating his approval of adding a new 2ry packaging site. Authenticated from Bank & EDA Legal Affairs. **OR Declaration Letter** From the LH

	The product trade name & reg. no. is mentioned Stating: "The company takes the full legal responsibility against the main 2ry packaging site 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." Authenticated from Bank & EDA Legal Affairs
3	**In Case of Change:** **Waiver** From old 2ry packaging site The product trade name & reg. no. is mentioned Authenticated from Bank & EDA Legal Affairs **OR Termination letter** From LH to old 2ry packaging site The product trade name & reg. no. is mentioned With proof of delivery
4	**Manufacturing contract** Between LH/Applicant & New 2ry Packager. Valid. Authenticated from Bank & EDA Legal Affairs In case of a foreign party signing the contract: Authentication form chamber of commerce, Egyptian embassy/consulate or Notary
5	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
6	**Latest New 2ry Packager site license:** Production line &/or area needed for manufacturing the product is present.
7	**Last Updated Commercial Register**

	Of the new manufacturing site
8	**Letter of Variation** For UL Products From product LH in COO Stating the required variation Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary

6- Solvent MFG Addition/Change (Local & UL FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 1000 L.E.
2	**EDA Valid Registration License of solvent** If Final & invalid: Approval for registration renewal If Tentative & invalid: License validity extension approval or approval for submission from Tent. To final *Shelf Life of solvent MUST BE compatible with shelf life of product * Pack of solvents from all manufacturers MUST BE compatible with each other
3	**In Case of Lidocaine Addition/Change:** Composition of Lidocaine the old and new manufacturers Previously approved stability study and AR for the old lidocaine manufacturer
4	**Last Updated Commercial Register** of manufacturer of solvent
5	**Latest New Manufacturing site license** of manufacturer of solvent
6	Letter of Variation For UL Products From product LH in COO Stating the required variation

	Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary
7	Storage site License
8	**Importer record** For imported products

7- Batch Size Change (Local, UL & Imported FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 1000 L.E.
2	**EDA Inspection Report** For Local & UL Products In case of Scaling up/downs to a factor of less than or equal 10 folds Stating the currently approved batch size Mentioning the required batch size Clarifying if this change will be accompanied by changes in the manufacturing process or equipment Signed & stamped from EDA inspector
3	**Letter of Variation** For UL & Imported Products From product LH in COO Stating the required variation Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary
4	**Declaration Letter**

	Stating that "This change is for marketing reasons only with NO change in quality, manufacture and stability of the product"
5	**Declaration Letter** Stating that "The company didn't get a previous approval for batch size change for this product" In case presence of a previous approval, state number and date of the approval and attach it with the file
6	**Declaration Letter** Stating that "There is No change in the manufacturing process" In case of a change clarify the current approved & proposed process along with a justification for this change
7	**Declaration Letter** Stating that "There is No change in the manufacturing equipment except only those necessitated by the in batch size (e.g. use of different sized equipment with same design & operating principle) In case of a change clarify the current approved & proposed equipment along with a justification for this change
8	**Narrative Description for the Manufacturing Process and Equipment used <u>before and after separately</u> scaling** -Machine type -Machine Model -Machine Serial Number -Principle of the machine *Signed and stamped

8- Local Company Name Change	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 1000 L.E.
2	**Declaration Letter** With list of all products affected by this name change. Clarifying the role of the name-changed company whether it's a LH, Applicant or Manufacturing site *Signed & stamped.
3	**Declaration Letter** The proposed company trade name in English *Signed & stamped.

9- Updating Registration License	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 1000 L.E.
2	**EDA Approval** Of the required change to be updated in the registration license issued from relevant EDA department

10- Updating Analysis File	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 0000 L.E.

2	***Valid Renewal approval/Assessment report/150 EDA Chairman renewal approval** *CADC Labs Analysis Certificate + CADC Labs Composition **Or** A "Not Found" Letter from CADC

11- LH/MAH Transfer (Imported & UL FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 5000 L.E.
2	**Declaration Letter** From New LH/MAH Stating the ownership transfer Ensuring that there is **NO CHANGE** in product composition, specification, manufacturing process and container/closure system. Authenticated from chamber of commerce & the Egyptian consulate/embassy The product trade name & reg. no. is mentioned Authenticated from Chamber of commerce & Egyptian consulate/embassy + Original Arabic translation from a certified translation center.
3	**Authorization Letter** From New LH/MAH in Egypt to the current applicant. The product trade name & reg. no. is mentioned Name & address of applicant mentioned Clarifying its responsibilities for registration & all regulatory activities Authenticated from chamber of commerce & the Egyptian consulate/embassy
4	**Manufacturing contract** For UL FPP

	Between New LH/MAH & Manufacturer. Authenticated from Chamber of Commerce, Egyptian Consulate/Embassy, EDA Legal Affairs and Bank If the contract is between the applicant & manufacturer: A letter from LH/MAH authorizing the applicant to sign contracts
5	**Attached Annex** Mentioning the product name & reg. no. Authenticated from Bank & EDA Legal Affairs

12- Applicant Change (Imported & UL FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** In Case of Transfer from Scientific office to Company: 5000 L. E+ 1000 LE In Case of Transfer from Company to Scientific Office: 15000 LE +1000 LE In Case of Transfer from Scientific Office to Scientific Office: 10000 LE +1000 LE
2	**In Case of Imported finished Human Pharmaceutical Product if the applicant is either Scientific Office or Company the following documents to be submit:** ***Scientific Office:** **a) "Authorization letter for the Scientific Office to register finished Imported Human Pharmaceutical Products"** issued by Evaluation Unit of registration requests for human pharmaceuticals. **b) Declarations Letter** Clarifying the Company's profile Code signed & stamped ***Company:**

	Declarations Letter Clarifying the Company's profile Code describing its activity as "Company Authorized for Registration" And if not Available The company must apply to systems & information unit for creating a company profile to be able to submit variation requests **N.B.: If Applicant Change for the Imported finished Product is needed** kindly submit separate Fulfilled file (as check list) for the Applicant change
3	**Termination letter** From LH The product trade name & reg. no. is mentioned Name & address of old applicant mentioned Authenticated from chamber of commerce from country of origin & the Egyptian consulate/embassy + Original Arabic translation from a certified translation center **Or Waiver** From Old Applicant The product trade name & reg. no. is mentioned Authenticated from Bank
4	**Authorization Letter** From LH The product trade name & reg. no. is mentioned Name & address of new applicant mentioned Clarifying its responsibilities for registration, all regulatory activities & signing contracts. Authenticated from chamber of commerce from country of origin & the Egyptian consulate/embassy + Original Arabic translation from a certified translation center. OR **Agency Agreement between** LH **and New Applicant** The product trade name & reg. no. is mentioned Name & address of new applicant mentioned (as written in its commercial register)

	Clarifying its responsibilities for registration & all regulatory activities. Authenticated from chamber of commerce from country of origin & the Egyptian consulate/embassy + Original Arabic translation from a certified translation center
5	Last Updated Commercial Register For Old Applicant **OR Scientific office License** In case of scientific office
6	**Manufacturing contract** For UL FPP Between New Applicant & Manufacturer. Authenticated from Chamber of Commerce, Egyptian Consulate/Embassy, EDA Legal Affairs and Bank
7	**Attached Annex** Mentioning the product name & reg. no.

13- MAH in Egypt Addition/Change (Imported & UL FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees: 5**000 L.E.
2	**Declaration Letter** From LH in COO Product name, reg.no. mentioned Appointing the New MAH in Egypt clarifying its full responsibilities including but not limited to **the right to sell the product in Egypt** Authenticated from Chamber of commerce & Egyptian consulate/embassy
3	**Applicant Authorization Letter** From New MAH in Egypt

	Product name, reg.no. mentioned Name & address of applicant mentioned matching with Commercial Register Clarifying its responsibilities for registration & all regulatory activities Authenticated from chamber of commerce & the Egyptian consulate/embassy
4	**NO CHANGE Declaration Letter** From New MAH in Egypt Ensuring that there is **NO CHANGE** in product composition, specification, manufacturing process and container/closure system. Authenticated from chamber of commerce & the Egyptian consulate/embassy

14- MFG/Packaging/Batch Releasing Site Addition/Change (Imported FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 1st site change: 3000 L.E 2nd site addition/change: 5000 L.E 3rd site addition/change: 10000 L.E 4th site addition/change: 20000 L. E
2	**Letter of Variation** From product LH in COO Product name, reg.no. mentioned Stating the required variation Authenticated from chamber of commerce, Egyptian embassy/consulate or Notary
3	**Certificate of Good Manufacturing Practice (GMP)** For new site

	Valid Authenticated from Chamber of commerce & Egyptian consulate/embassy
4	**If the New Site is located in a Non-reference country:** **CPP from Reference country:** Valid Product registered & marketed Where the proposed site in mentioned (For MFG/1ry Packaging site) Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate

15- Site Name/Address Change (Imported FPP)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 1000 L.E.
2	**No Change Declaration Letter** From LH 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 & Egyptian consulate/embassy
3	**Certificate of Good Manufacturing Practice (GMP)** For the Site with the NEW Name/Address Valid Authenticated from Chamber of commerce & Egyptian consulate/embassy
4	**Certificate of Good Manufacturing Practice (GMP)** For the Site with the OLD Name/Address Authenticated from Chamber of commerce & Egyptian consulate/embassy

5	**Official document from a relevant official body** In case of changing address Justifying the change in address

16- LH/MAH Name/Address Change (Imported & UL FPP)	
Section (4) **Relevant Documents (Acc. To Variation Type)**	
1	**Fees**: 1000 L. E
2	**Declaration Letter** From LH/MAH Stating that it's the same legal entity with no change in LH/MAH, product specifications, quality, composition, manufacturing site & process. Authenticated from Chamber of commerce & Egyptian consulate/embassy
3	**Official document from a relevant official body** In case of changing address **Justifying the change in address**

17- Change Reg. Type from Imported Bulk to Imported Finished (i.e., 2ry Packaging Site Change With/Without 1ry Packaging Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 2ry packaging site change: 3000 L.E. 1ry packaging site change (If different): 3000 L.E.

	N.B: For adding more than one site refer to the fees of site addition
2	**Letter of Variation** From LH/MAH Stating the change in packaging site(s) of the product and justification for these changes The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy
3	**Waiver** From old packager The product trade name & reg. no. is mentioned Authenticated from Bank & EDA Legal Affairs
4	**Certificate of Good Manufacturing Practice (GMP)** For new packaging site Valid Authenticated from Chamber of Commerce & Egyptian Consulate/Embassy

18- Change Reg. Type from Imported Bulk to UL (i.e., Bulk MFG Site Change With/Without Packaging site change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** Bulk MFG site change: 3000 L.E 1ry packaging site change (If different): 3000 L.E. 2ry packaging site change (If different): 3000 L.E. **N.B: For adding more than one site refer to the fees of site addition**

2	**Letter of Variation** From LH/MAH Stating the change in MFG Site(s) of the product and justification for this change The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy
3	**In case of Toll Manufacturing:** **Manufacturing contract** Between LH/Applicant & New Manufacturer. Valid. A letter from LH/MAH authorizing the applicant to sign contracts Authenticated from Bank & EDA Legal Affairs. Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract.
4	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
5	**Latest New Manufacturing site license** Production line &/or area needed for manufacturing the product is present.
6	**Latest Update Commercial Register** (New Manufacturer)
7	**Packaging Waiver** From old packager (In case of changing packaging site) The product trade name & reg. no. is mentioned Authenticated from Bank & EDA Legal Affairs
8	**Storage contract** Between LH/Applicant & Storage site.

	Valid. Authenticated from Bank & EDA Legal Affairs. Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract.
9	**Storage Site License**
10	**Submission of API supplier addition request.** Refer to API supplier addition checklist

19- Change Reg. Type from Imported Bulk to Local (i.e., Ownership Transfer + Bulk MFG &/or Packaging Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** Ownership Transfer: 5000 L.E Bulk MFG site change: 3000 L.E 1ry packaging site change (If different): 3000 L.E. 2ry packaging site change (If different): 3000 L.E. **N.B: For adding more than one site refer to the fees of site addition**
2	**Letter of Variation** From LH/MAH Stating the transfer of ownership of the product with clarification of the consequential changes and justification for this change The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy

3	**In case of Toll Manufacturing:** **Manufacturing contract** Between LH & New Manufacturer. Valid. Authenticated from Bank & EDA Legal Affairs.
4	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
5	**Latest New Manufacturing site license** Production line &/or area needed for manufacturing the product is present.
6	**Last Updated Commercial Register** Of the new manufacturing site
7	**Packaging Waiver** From old packager (In case of changing packaging site) The product trade name & reg. no. is mentioned Authenticated from Bank & EDA Legal Affairs
8	**Storage contract** Between LH/Applicant & Storage site. Valid. Authenticated from Bank & EDA Legal Affairs. Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract.
9	**Storage Site License**
10	**Composition declaration** On New LH Paper Signed & stamped

	Identical to the one attached with the registration license or to the latest finally approved composition
11	**Submission of API supplier addition request.** Refer to API supplier addition checklist

20- Change Reg. Type from Imported Finished to Imported Bulk (i.e., 2ry Packaging Site Change With/Without 1ry Packaging Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** 2ry packaging site change: 3000 L.E. 1ry packaging site change (If different): 3000 L.E. **N.B: For adding more than one site refer to the fees of site addition**
2	**Letter of Variation** From LH/MAH

	Stating the change in packaging site(s) of the product and justification for these changes The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy
3	**Packaging contract** Between LH/Applicant & New Packager. A letter from LH/MAH authorizing the applicant to sign contracts Authenticated from Bank & EDA Legal Affairs. Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract.
4	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
5	**Latest New Packaging site license** Production line &/or area needed for manufacturing the product is present
6	**Last Updated Commercial Register** Of the new packaging site
7	**Storage contract** Between LH/Applicant & Storage site. Valid. Authenticated from Bank & EDA Legal Affairs. Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract.
8	**Storage Site License**

21- Change Reg. Type from Imported Finished to UL (i.e., Bulk MFG & Packaging Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** Bulk MFG Site Change: 3000 L.E Packaging Site Change (If different): 3000 L.E **N.B: For adding more than one site refer to the fees of site addition**
2	**Letter of Variation** From LH/MAH Stating the change in MFG site(s) of the product and justification for these changes The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy
3	**Manufacturing contract:** Between LH/Applicant & New manufacturer/packager. A letter from LH/MAH authorizing the applicant to sign contracts Authenticated from Bank & EDA Legal Affairs. Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract.
4	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
5	**Latest New Manufacturer site license:** Production line &/or area needed for manufacturing the product is present.
6	**Last Updated Commercial Register** (New Manufacturer)
7	**Storage contract**

	Between LH/Applicant & Storage site. Valid. Authenticated from Bank & EDA Legal Affairs. Authentication form chamber of commerce, Egyptian embassy/consulate or Notary is needed in case that the LH/MAH signing the contract.
8	**Submission of API supplier addition request.** Refer to API supplier addition checklist

22- Change Reg. Type from Imported Finished to Local (i.e., Ownership Transfer + Bulk MFG & Packaging Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** Ownership Transfer: 5000 L.E Bulk MFG site change: 3000 L.E 1ry packaging site change (If different): 3000 L.E. 2ry packaging site change (If different): 3000 L.E. **N.B: For adding more than one site refer to the fees of site addition**
2	**Letter of Variation** From LH/MAH Stating the transfer of ownership of the product with clarification of the consequential changes and justification for this change The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy
3	**In case of Toll Manufacturing:** **Manufacturing contract:** Between LH & New manufacturer/packager. Authenticated from Bank & EDA Legal Affairs.
4	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
5	**Latest New Manufacturing site license** Production line &/or area needed for manufacturing the product is present.
6	**Last Updated Commercial Register** (New Manufacturer)

7	**Storage contract:** Between LH/Applicant & Storage site. Valid. Authenticated from Bank & EDA Legal Affairs.
8	**Storage Site License**
9	**3 Copies Composition declaration:** On New LH Paper Signed & stamped Identical to the one attached with the registration license or to the latest finally approved composition
10	**Submission of API supplier addition request.** Refer to API supplier addition checklist

23- Change Reg. Type from UL to Imported Bulk (i.e., Bulk MFG Site Change With/Without Packaging Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** Bulk MFG Site Change: 3000 L.E 1ry Packaging Site Change (If different): 3000 L.E 2ry Packaging Site Change (If different): 3000 L.E **N.B: For adding more than one site refer to the fees of site addition**
2	**Letter of Variation** From LH/MAH Stating the change in MFG site(s) of the product and justification for these changes The product trade name & reg. no. is mentioned

	Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy
3	**Certificate of Good Manufacturing Practice (GMP)** For new MFG/Packaging site Valid Authenticated from Chamber of Commerce & Egyptian Consulate/Embassy
4	**Manufacturing Waiver** From old manufacturer The product trade name & reg. no. is mentioned Authenticated from Bank & EDA Legal Affairs
5	**Last Updated Importer Record**

24- Change Reg. Type from UL to Imported Finished (i.e., Bulk MFG & Packaging Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** Bulk MFG Site Change: 3000 L.E 1ry Packaging Site Change (If different): 3000 L.E 2ry Packaging Site Change (If different): 3000 L.E **N.B: For adding more than one site refer to the fees of site addition**
2	**Letter of Variation** From LH/MAH Stating the change in MFG site(s) of the product and justification for these changes The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy

3	**Certificate of Good Manufacturing Practice (GMP)** For New MFG/Packaging site Valid Authenticated from Chamber of Commerce & Egyptian Consulate/Embassy
4	**Manufacturing Waiver** From old manufacturer The product trade name & reg. no. is mentioned Authenticated from Bank & EDA Legal Affairs
5	**Last Updated Importer Record**

25- Change Reg. Type from UL to Local (i.e., Ownership Transfer With/Without MFG Site Change)	
Section (4) **Relevant Documents** (Acc. To Variation Type)	
1	**Fees:** Ownership Transfer: 5000 L.E Bulk MFG Site Change: 3000 L.E 1ry Packaging Site Change (If different): 3000 L.E 2ry Packaging Site Change (If different): 3000 L.E **N.B: For adding more than one site refer to the fees of site addition**
2	**Letter of Variation** From LH/MAH

	Stating the transfer of ownership of the product with clarification of the consequential changes and justification for this change The product trade name & reg. no. is mentioned Authenticated by the Health Authority in COO, Chamber of commerce & Egyptian consulate/embassy
3	**Manufacturing Waiver** From old manufacturer (In case of changing MFG site) The product trade name & reg. no. is mentioned Authenticated from Bank & EDA Legal Affairs
4	**In case of Toll Manufacturing:** **Manufacturing contract:** Between LH & New manufacturer/packager. Authenticated from Bank & EDA Legal Affairs.
5	**Attached Annex of the contract** The product trade name & reg. no. is mentioned. Authenticated from Bank & EDA Legal Affairs
6	**Latest New Manufacturing site license** Production line &/or area needed for manufacturing the product is present.
7	**Storage contract:** Between LH/Applicant & Storage site. Valid. Authenticated from Bank & EDA Legal Affairs.
8	**Storage Site License**
9	**3 Copies Composition declaration:** On New LH Paper Signed & stamped Identical to the one attached with the registration license or to the latest finally approved composition

V- Declarations Templates

Template 1: Delegation Letter
Template 2: Cover Letter
Template 3: Common Declarations
Template 4: API Suppliers Declaration
Template 5: Strengths & Dosage Forms of FPP
Template 6: All Registered & Under-registration FPP of a Toll company

Template 1

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

تحية طيبة وبعد،،،،،

بخصوص المستحضر الاتي:

Trade Name:	
Dosage Form:	
Active Ingredients / Strength:	
Reg. No.:	
Applicant Company:	
License Holder/MAH:	
Manufacturer/Packager:	

نفيد سيادتكم علماً بأن السيد الدكتور/..... وبياناته كالآتي:

رقم إثبات الشخصية:	
بريده الإلكترونى:	
فاكس:	
رقم موبيل:	

هو المفوض من قبل الشركة لتقديم، متابعة وإنهاء طلبات المتغيرات الخاصة.

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 الاتي:
نرجو من سيادتكم التكرم بالموافقة على إجراء التغيير الآتي على المستحضر:

- الوضع الحالي للمستحضر:
- الوضع المقترح:

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

- سبب التغيير (إن وجد):
- ما يترتب على التغيير (إن وجد):

- علماً بأنه تم عمل المتغيرات الآتية /(لم يتم عمل اى متغيرات) للمستحضر ولم يتم إضافتها بأخر إخطار تسجيل صادر للمستحضر:
المستندات المرفقة بالملف كالاتي:

و تفضلوا بقبول وافر الإحترام والتقدير،،،

نوع التغيير	من	إلى

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،،،،،

بخصوص المستحضر الاتي:

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

أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بالآتي:

- إخطار تسجيل المستحضر المرفق بالملف هو أخر إخطار صادر للمستحضر حتى تاريخه.
- جميع المستندات والبيانات المقدمة بالملف صحيحة وعلى مسؤلية الشركة.
- الملف المقدم يشمل كافة المتغيرات والموافقات الصادرة للمستحضر منذ تاريخ تسجيله وحتى تاريخه.
- مكان تخزين المستحضر هو:
- رقم أخر تشغيلة من المستحضر تم إنتاجها/إستيرادها وتداولها بالسوق المحلي هو ..... و تاريخ إنتاجها هو ..... وتاريخ انتهاء صلاحيتها هو .....
  أو (لم يتم إنتاج/إستيراد وتداول المستحضر منذ تسجيله وحتى تاريخه)
- التسعيرة المقدمة بالملف (أو المذكورة بالإخطار) وهي ..... هي أخر تسعيرة صادرة للمستحضر حتى تاريخه.

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،،،،

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

بخصوص المستحضر الاتي:

- أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بأن مصادر المواد الخام الفعالة هى كالآتي:

Name of API:	**Name of Manufacturer:** **Address of Manufacturer:** *As stated in GMP*	
	Name of Supplier: **Address of Supplier:**	

- كما أتعهد بتقديم شهادة الGMP وشهادة التحليل الخاصة بالمادة الخام ,وذلك عند التقدم لإستيراد المادة الخام بالإدارة المركزية للسياسات الدوائية ودعم الأسواق.

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 ○ In-valid	Re-Reg 296/2009 Re-Reg 425/2015 Re-Reg 150/2022
Current status:		
Proposed status:		

- أتعهد أنا ..... رئيس مجلس إدارة شركة ..... بالآتي:

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 6

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**