Egyptian Variation Guidelines

Variation Definition:

A variation application basically 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.

Types of variation:

Types	*Notification (N)*	*Variation department approval (VDA)*	*Variation committee approval (VCA)*	*Technical committee approval (TCA)*
Definition	They are variations, which don't require approval before implementation; however they require to be notified "$\mathcal{N}$" to be submitted by license holder	They need to be approved by the variation department (VDA)	They need to be approved by the the variation committee (VCA)	They need to be approved by the the technical committee (TCA).

Requirements to be fulfilled according to the type of change in the guideline:

A) Nodcar

1. Notification (N)
2. Analysis inspection (AI)
3. Analysis registration (AR)

B) Stability

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

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).
5. Comparative In-Vitro Release in most suitable medium (D Release)

Composition: For Non- Sterile Products

Serial	Immediate Release Oral Solid Dosage Forms & Modified release oral solid dosage forms – non- release controlling excipient:	Test Documents			Administrative documents	Reporting Category
		Nodcar	Stability	Disssolution/Bioequivalenc		
1	Deletion or partial deletion of an ingredient intended to affect the colour, taste or fragrance of the product or change in the ingredient of the printing ink to another approved ingredient.	N	N	Dn	1,2,3,4,5,6,7,8,17,18,22,23,24 Commitment that the change doesn't affect stability	N
2	Addition or replacement of an ingredient intended to affect the colour, taste or fragrance of the product.	N	Ongoing	Dn	1,2,3,4,5,6,7,8,17,18,22,23,24	VDA
3	A-Change in weight of capsule shells by NMT 5%. B-The total additive effect of all excipient changes doesn't exceed **5%,** with individual changes within the limits specified. Percent excipients (w/w) out of total target dosage form weight: 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	1,2,3,4,5,6,7,8,9,12,17,18,22,23,24	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	AI	6M	D1	1,2,3,4,5,6,7,8,9,12,17,18,22,23,24	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)	AI	6M	D1	1,2,3,4,5,6,7,8,9,10,12,17,18,22,23,24	VDA
6	Replacement of an excipient with a comparable excipient. (e.g. Magnesium Stearate and Calcium Stearate).	AI	6M	D1	1,2,3,4,5,6,7,8,17,18,22,23,24	VCA

7	Any change in excipient percent beyond 10% with individual changes are more than the limits specified in 4.	AR	6M	D3/4	1,2,3,4,5,6,7,8, 17,18,22,23,24	VCA
8	Addition, deletion or changing excipient to a non-comparable excipient.	AR	6M	D3/4	1,2,3,4,5,6,7,8, 17,18,22,23,24	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	1,2,3,4,5,6,7,8, 17,18,22,23,24	VCA
10	Change in coating formulation excipient (composition) if the change does not alter release of the drug, specification, or stability	AR	6M	D1	1,2,3,4,5,6,7,8, 17,18,22,23,24 ,10	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	1,2,3,4,5,6,7,8, 11, 17,18,22,23,24	VDA
12	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	AR	Ongoing	Dn	1,2,3,4,5,6,7,8, 11, 17,18,22,23,24	VCA

Serial	**Formulation changes : Modified release oral solid dosage forms – release controlling excipient**	**Test Documents**			**Administrative documents**	**Reporting Category**
		Nodcar	**Stability**	**Disssolution/ Bioequivalenc**		
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.	AI	ongoing	D_1	1,2,3,4,5,6, 7,8,9,10, ,15,16,17,1 8,22,23,24	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.	AI	6M	Non-narrow therapeutic range drugs D_1 narrow therapeutic range drugs BE	1,2,3,4,5,6, 7,8,9,10, ,15,16,17,1 8,22,23,24	VCA
3	**a-** Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer).	AR	6M	Non-narrow therapeutic range drugs	1,2,3,4,5,6, 7,8,9,10, ,15, 16,17,18,22 ,23,24	VCA

	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** 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.			D3/4 narrow therapeutic range drugs BE		

Serial	Formulation changes: Non-Sterile Semisolid Dosage forms (Eg. Creams, Gels, lotions & ointments) intended for topical routes of administration	Test Documents			Administrative documents	Reporting Category
		Nod car	Stability	Disssolution/Bioequivalenc		
1	Deletion or partial deletion of color. Fragrance or flavor.	N	None	DN	1,2,3,4,5,6,7,8, 11,12,13,17,18, 22,23,24 Commitment it doesn't affect stability	N
2	Up to 5% change in approved amount of an excipient with the total additive effect of all excipient changes ≤ 5%. A change in diluent (q.s. excipient) due to component and composition changes in excipient may be made and is excluded from the 5% change limit.	N	Ongoing	DN	1,2,3,4,5,6,7,8, 11,12,13,17,18, 22,23,24	VCA
3	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. Changes in diluent (q.s. excipient) due to component and composition changes in excipients are acceptable and are excluded from the 10% change limit.	AI	6 M	DN	1,2,3,4,5,6,7,8, 11,12,13,17,18, 22,23,24	VCA
4	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	6 M	DN	1,2,3,4,5,6,7,8, 11,12,13,17,18, 22,23,24	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	1,2,3,4,5,6,7,8, 11,12,13,17,18, 22,23,24	VDA
6	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	AR	Ongoing	Dn	1,2,3,4,5,6,7,8, 11,12,13,17,18, 22,23,24	VCA

Serial	Formulation Changes : Liquid dosage form (Solution)	Test Documents			Administrative documents	Reporting Category
		Nodcar	Stability	Disssolution/Bioequivalenc		
1	Reduction or deletion of one or more components of the coloring / flavoring systems	N	None	DN	1,2,3,4,5,6,7,8, 11, 12,13,17,18,22, 23,24 Commitment it doesn't affect stability	N
2	Increase ,addition or replacement of one or more components of the coloring / flavoring systems	AI	ongoing	DN	1,2,3,4,5,6,7,8, 11, 12,13,17,18,22, 23,24	VDA
3	a. Replacement of an excipient with a comparable excipient	AR	6 M	DN	1,2,3,4,5,6,7,8, 11, 12,13,17,18,22, 23,24	VCA
	b. Changing in percentage of the used excipients.	AR	6 M	DN	1,2,3,4,5,6,7,8, 11, 12,13,17,18,22, 23,24	VCA
	c. Addition, deletion of excipient to a non – comparable excepient	AR	6 M	DN	1,2,3,4,5,6,7,8, 11, 12,13,17,18,22, 23,24	VCA
4	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	1,2,3,4,5,6,7,8, 11, 12,13,17,18,22, 23,24	VDA
5	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	AR	Ongoing	Dn	1,2,3,4,5,6,7,8, 11, 12,13,17,18,22, 23,24	VCA

Serial	Formulation Changes : Liquid dosage form (Suspension)	Test Documents			Administrative documents	Reporting Category
		Nodcar	Stability	Disssolution /Bioequivalenc		
1	Reduction or deletion of one or more components of the coloring / flavoring systems	N	None	DN	1,2,3,4,5,6,7,8, 11, 12,13,14,15,16 17,18,22,23,24 Commitment it doesn't affect stability	N

2	Increase ,addition or replacement of one or more components of the coloring / flavoring systems	AI	ongoing	DN	1,2,3,4,5,6,7,8, 11,12,13,14,15, 16,17,18,22,23, 24	VDA
3	a. Replacement of an excipient with a comparable excipient	AR	6 M	DN	1,2,3,4,5,6,7,8, 11,12,13,14,15, 16,17,18,22,23, 24	VCA
	b. Changing in percentage of the used excipients	AR	6 M	Non release controlling excipient DN release controlling excipient D1	1,2,3,4,5,6,7,8, 11,12,13,14,15, 16,17,18,22,23, 24	VCA
	c. Addition, deletion of excipient to a non – comparable excipient	AR	6 M	Non release controlling excipient DN release controlling excipient D1	1,2,3,4,5,6,7,8, 11,12,13,14,15, 16,17,18,22,23, 24	VCA
4	Any change in the crystalline form of the drug substance	AR	6M	D3/4 or D1 according to the committee decision	1,2,3,4,5,6,7,8, 11,12,13,14,15, 16,17,18,22,23, 24	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	1,2,3,4,5,6,7,8, 11,12,13,14,15, 16,17,18,22,23, 24	VDA
6	Addition of overage to the drug product manufacturing batch formula to compensate manufacturing losses (for active ingredients or preservatives only)	AR	Ongoing	Dn	1,2,3,4,5,6,7,8, 11,12,13,14,15, 16,17,18,22,23, 24	VCA

Composition : Sterile

Serial	Sterile dosage forms	Test Documents			Administrative documents	Reporting Category
		Nod car	Stability	Disssolution/Bio equival enc		
1	**Replacement of an excipient with a comparable* excipient.** (Same functional characteristics of the excipient.)	AR	ongoing		1,2,3,4,5,6,7,8,11,12, 13, 14, 15 , 16,17,18,22,23, 24	VCA
2	**Replacement of an excipient with a non comparable* excipient.**	AR	6 M		1,2,3,4,5,6,7,8,11,12, 13, 14, 15 , 16,17,18,22,23, 24	VCA
3	**Increase or Decrease of quantity of any excipient**	AR	6 M			VCA

Change in Finished Product Specification:

Serial	Type of Variation	Test Documents			Administrative documents	Reporting Category
		Nodcar	Stability	Disssolution/Bio equival enc		
1	Tightening of specification limits	N	None	DN	1,2,3,4,5,17,18 ,19,20, 21	VCA
2	Addition of a new test parameter to the specification or deletion of a test parameters	N	None	DN	1,2,3,4,5,17,18 ,19,20, 21 Validation Process is needed	VCA
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	N	None (or stability 6M according to the added test)	DN	1,2,3,4,5,17,18 ,19,20,21,22,23,24 Validation Process is needed	VCA
4	Updating specifications to comply with an update of the relevant monograph of the Pharmacopoeia.	N	None	DN	1,2,3,4,5,17,18 ,19,20,21,22,23,24 Copy of Monograph is needed	VCA

Change in Physical Character of Finished Product :

Serial	Type of Variation: Change in Physical Character	Test Documents			Administrative documents	Reporting Category
		Nodcar	Stability	Disssolution /Bioequivalenc		
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	1,2,3,4,5,17,18,19,20,22,23,24 Safety data Sheet for Ink	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)	Subdivision test	None	DN	1,2,3,4,5,17,18,19,20,22,23,24 Reference for scoring	VDA
3	Deletion of scoring/break lines on tablets :	N	None	DN	1,2,3,4,5,17,18,19,20,22,23,24	VDA
4	Addition of Scoring / break lines as a mark and not intended for breakage.	N	None	DN	1,2,3,4,5,17,18,19,20,22,23,24 Commitment to be written in pamphlet or pack	VDA
5.	Addition limit range of color without any qualitative or quantitative change in excipients or active ingredients	N	None or stability 6M	DN* If Needed	1,2,3,4,5,17,13,18,19,21,22,23,24	VCA
6.	Change in shape of dosage form or capsule size without change in total weight of dosage form	N	none	D1	1,2,3,4,5,17,18,19,21,22,23,24	VCA

Changing / Clarifying Active Ingredient Specification:

Serial	Type of Variation	Test Documents			Administrative documents	Reporting Category
		Nod car	Stability	Disssolution/Bioequivalenc		
1	Change from One Pharmacopeia to another Pharmacopeial Specification.	N	None	DN	1,2,3,4,5,13,14,,17,18,21,22,23,24	VDA
2	Change From Pharmacopeial Specification to In-house Specification. (if change is within pharmacopeial limits	AR	None	D1	1,2,3,4,5,13,14,,17,18,21,22,23,24	VCA
3	Change From In-house Specification to Pharmacopeial Specification.	N	None	DN	1,2,3,4,5,13,14,,17,18,21,22,23,24	VDA
4	Clarifying Specification (For Both Active and Inactive Ingredients)	N	None	DN	1,2,3,4,5,6,7,13,14,,17,18,21,22,23,24	VDA

Administrative Documents:	
1. Covering Letter from the applicant.	Describing the reasons for the required change in details (signed and stamped by the applicant)
2. Payment Receipt.	1000 LE
3. 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
4. Nodcar composition	Recent edition with maximum two years ago
5. Nodcar certificate of analysis	
6.old composition (3 copies)	Identical to nodcar composition
7. new composition (3 copies)	According to attached template
8. comparison table between old and new composition	According to attached template
9. capsule shell composition on supplier paper	In case of change or addition of capsule shell components in hard gelatin capsules
10.composition of coating blends e.g opadry on supplier paper	In case of addition or change of coating blends
11.scientific reference	In case of overage (According to attached template)
12. calculations on company paper & scientific reference for molecular weight	In case of change or correcting or clarification of salt equivalence
13. certificate of analysis of supplier of active ingredient or pellets or premixes	In case of change or correcting or clarification of salt equivalence
14. previous importation approvals	In case of clarification of salt equivalence / Premix
15. composition of pellets/Premix on all supplier papers	The composition must be identical in all suppliers
16. calculations of pellets/Premix on company paper	

17. copy of cpp (and see original one)	In case of imported / bulk / under license
18. signed and stamped declaration letter from the license holder clarifying type of the change needed	In case of imported / bulk / under license
19.Old & New Certificate of Analysis On company Paper	2 copies
20. Old & New Finished Product Specification On company Paper	2 copies
21. Pharmacopeial Monograph	Updated
22. Letter of attorney for a person(s) authorized for communication on behalf of the applicant company. On company letter head signed & stamped.	According to Declarations template
23. Declaration Letter From Company States all previous variation approvals on company paper signed and stamped.	According to Declarations template
24. Declaration Letter From Company States that attached License is the last updated one on company paper signed and stamped.	According to Declarations template

Guidelines for composition change concerning tentative regisrtation license

أولاً : في حالة **عدم** قيام الشركة بالإنتاج ببيان التركيب القديم

Thus,will be according to **Significance of Changes**

Non-Significant Change

Changes that are unlikely to have an detectable impact on formulation quality and performance

-

يتم الإلتزام بمتطلبات إخطار التسجيل المبدئي ، وذلك علي بيان التركيب الجديد ، **و خلال فترة صلاحية الإخطار المبدئي** .

Significant Change

Changes that have a significant impact on formulation quality and performance

- يتم الإلتزام بمتطلبات إخطار التسجيل المبدئي علي بيان التركيب الجديد ، **و ذلك خلال فترة صلاحية الإخطار المبدئي**

- ولا يتم الإفراج من التفتيش عن التشغيلات المنتجة إلا بعد صدور المطابقة بالتحليل (شعبة تسجيل) و إعتماد دراسة التكافؤ الحيوي (أو الدراسة المطلوبة كشرط إفراج في إخطار التسجيل المبدئي) و **إعتماد دراسة الثبات المعجلة لمدة ٣ أشهرمن لجنة الثبات للتشغيلة الإنتاجية الأولى** بعد التعديل .

- بشرط أن تستكمل الشركة باقى ال ٦ أشهر لدراسة الثبات المعجلة **على ال ٣ تشغيلات** بعد الإفراج و يتم تقديمهم معاً الي لجنة الثبات ، و **ذلك خلال فترة صلاحية الإخطار المبدئي** ، وعلي أن يتم متابعة ذلك من قبل إدارة التفتيش الصيدلي.

ثانياً: في حالة قيام الشركة بالإنتاج ببيان التركيب القديم

في حالة إستيفاء **جميع** متطلبات إخطار التسجيل المبدئي **و إعتمادها** من قبل الجهات المعنية **ماعدا دراسة الثبات طويلة المدى**

Non-Significant Change

- الموافقة علي طلب الشركة مع إخطار **Nodcar**.

مع تعهد الشركة بتقديم **دراسة الثبات طويلة المدى** ذلك عند تحويل الإخطار من مبدئي الي نهائي .

Significant Change

١- تحليل (شعبة تسجيل)

٢- إجراء دراسة معدل الذوبان (أو إعادة إجراء دراسة التكافؤ و ذلك في الحالات التي تراها لجنة المتغيرات او في حالة ال Narrow therapeutic index drugs)

٣- دراسة ثبات معجلة ٦ شهور

وذلك علي **نفس التشغيلة الانتاجية الأولى ببيان التركيب الجديد** ، ولا يتم الإفراج عن هذه التشغيلة إلا بعد **إعتماد ال ٣ دراسات السابقة** .

، و ذلك **خلال فترة صلاحية الإخطار المبدئي** و يتم متابعته من قبل إدارة التفتيش الصيدلي .

- مع تعهد الشركة بتقديم **دراسة الثبات طويلة المدى** علي بيان التركيب الجديد علي ٣ تشغيلات و ذلك عند تحويل الإخطار من مبدئي الي نهائي .

في حالة إستيفاء **جزء** من متطلبات إخطار التسجيل المبدئي

Non-Significant Change

- الموافقة علي طلب الشركة مع إخطار **Nodcar**.

مع أستكمال باقي متطلبات إخطار التسجيل المبدئي وذلك علي بيان التركيب الجديد ، **و ذلك خلال فترة صلاحية الإخطار المبدئي**.

Significant Change

- يتم الإلتزام بمتطلبات إخطار التسجيل المبدئي ، وذلك علي بيان التركيب الجديد ، و خلال فترة صلاحية الإخطار المبدئي .

- علي أن يتم الإكتفاء بإجراء دراسة معدل الذوبان في حالة إن سبق إجراء داسة التكافؤ.(إلا في الحالات التي تري فيها لجنة المتغيرات ضرورة إعادة إجراء دراسة التكافؤ أو في حالة ال Narrow therapeutic index drugs

ويتم ذلك علي أول تشغيلة انتاجية ببيان التركيب الجديد ، و ذلك **خلال فترة صلاحية الإخطار المبدئي** ، ولا يتم الإفراج عن هذه التشغيلة إلا بعد صدور المطابقة بالتحليل (شعبة تسجيل) وإعتماد دراسة التكافؤ الحيوى (أو دراسة معدل الذوبان في حالة الاعفاء من إعادة إجراء دراسة التكافؤ الحيوي) و كذلك إعتماد دراسة الثبات المعجلة **لمدة ٣ أشهر** ، علي أن تلتزم الشركة إستكمال باقى ال ٦ أشهر لدراسة الثبات المعجلة بعد الإفراج ، وعلي أن يتم متابعة ذلك من قبل إدارة التفتيش الصيدلي.

- بشرط أن تتعهد الشركة بتقديم **دراسة الثبات طويلة المدى** علي بيان التركيب الجديد و ذلك عند تحويل الإخطار من مبدئي الي نهائي

Administrative Documents For Tentative Composition:	
1. Covering Letter from the applicant.	Describing the reasons for the required change in details (signed and stamped by the applicant)
2. Payment Receipt.	1000 LE
3. Valid registration license	in case the registration license is not valid please submit an extension for the license
4. Nodcar composition	In case of production
5. Nodcar certificate of analysis	In case of production
6.old composition (3 copies)	Identical to registration license composition
7. new composition (3 copies)	According to attached template #1
8. comparison table between old and new composition	(as attached template #2)
9. capsule shell composition on supplier paper	In case of change or addition of capsule shell components in hard gelatin capsules
10.composition of coating blends e.g opadry on supplier paper	In case of addition or change of coating blends
11.scientific reference	In case of overage (#3 see attached accepted references)
12. calculations on company paper & scientific reference for molecular weight	In case of change or correcting or clarification of salt equivalence
13. certificate of analysis of supplier of active ingredient or pellets	In case of change or correcting or clarification of salt equivalence
14. previous importation approvals	In case of clarification of salt equivalence / Premix
15. composition of pellets/Premix on all supplier papers	The composition must be identical in all suppliers
16. calculations of pellets/Premix on company paper	

17. copy of cpp (and see original one)	In case of imported / bulk / under license
18. signed and stamped declaration letter from the license holder clarifying type of the change needed	In case of imported / bulk / under license
19.Old & New Certificate of Analysis On company Paper	2 copies
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21. Pharmacopeial Monograph	Updated
22. Letter of attorney for a person(s) authorized for communication on behalf of the applicant company.	According to Declarations template
23. Declaration Letter From Company States all previous variation approvals on company paper signed and stamped.	According to Declarations template
24. Declaration Letter From Company States that attached License is the last updated one on company paper signed	According to Declarations template
25. declaration letter stating product situation from production	(attach any studies approvals in case of production)

Attachments

- *Appendix I:* *Declarations.*
- *Appendix II:* *Composition* Form
- *Appendix III:* Comparison Composition Form
- *Appendix IV:* Dosage Form List
- *Appendix V:* *Narrow Therapeutic Range Drugs.*
- *Appendix VI:* *Reference List.*
- *Appendix VII:* *Variation Notification form.*
- *Appendix VIII:* *Abbreviations..*

Appendix I: Declarations.

السيد الدكتور / رئيس الإدارة المركزية للشئون الصيدلية.

تحية طيبة و بعد،،،،،

نفيد سيادتكم علماً بأن السيد الدكتور/..... و بياناتة كالأتى:

رقم إثبات الشخصية:	
بريدة الإلكترونى:	
فاكس:	
رقم موبيل:	

هو المفوض من قبل الشركة لتقديم، متابعة و إنهاء التغييرات الخاصة بالمستحضر الأتي:

Trade Name:	
Generic Name:	
Strength:	
Dosage Form:	
Applicant Company :	
License Holder :	
Manufacturer:	

و تفضلوا بقبول فائق التحية و التقدير.

رئيس مجلس ادارة الشركة **ختم الشركة**

السيد الدكتور / رئيس الإدارة المركزية للشئون الصيدلية.

تحية طيبة و بعد،،،،،

نتعهد نحن شركة ..... بأن جميع المستندات المقدمة بالملف صحيحة و علي مسئولية الشركة و أنه مرفق جميع موافقات المتغيرات السابقة الخاصة به و هذا تعهد منا بذلك .

مرفق :

١-

٢-

و تفضلوا بقبول فائق التحية و التقدير.

رئيس مجلس ادارة الشركة **ختم الشركة**

السيد الدكتور / رئيس الإدارة المركزية للشئون الصيدلية.

تحية طيبة و بعد،،،،،

نتعهد نحن شركة ..... بأن الإخطار المقدم هو أخر إخطار صادر للمستحضر و هذا تعهد منا بذلك .

و تفضلوا بقبول فائق التحية و التقدير.

رئيس مجلس ادارة الشركة **ختم الشركة**

السيد الدكتور / رئيس الإدارة المركزية للشئون الصيدلية.

تحية طيبة و بعد،،،،،

نتعهد نحن شـركة ..... بأنه لم يتم إنتاج أو تداول المسـتحضـر بالسـوق المحلي / تم إنتاج المستحضر و مرفق جميع الدراسات التي تم إجراءها .

مرفق الدراسات (في حالة أن تم إنتاجه) :

-١

-٢

و تفضلوا بقبول فائق التحية و التقدير.

رئيس مجلس ادارة الشركة **ختم الشركة**

• Appendix II: 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 box and naming approvals, It's (their) hydrate(s) and salt form(s)with its(their)quantity(ies) per unit dose is(are) specified.

   N.B: Attach the equivalence reference if present and the reference of the quantities of salt and base.
   * If quantities are not present in the reference (insert of the brand) , submit calculation on the company letter head signed and stamped and submit a reference for molecular weight
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 & If the ingredient(s) name differ (s) in the composition from that stated in the COA of the supplier or from the reference, bring synonyms.
8. In case of injectable powders, please submit the license of the used solvent.
9. 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
10. **In Case of Coated tablets**: write the core and coat separated, mention the weight of tablet.
11. **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 letter head should be attached & attach the calculation of pellets weight /capsule on company letter head

12. 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

13. In case of powder for reconstitution write the amount of water used to reconstitute the powder & the final volume reached.

14. In case that the composition contains any type of parabens, please calculate it according to the technical committee decision in 18/2/2016:

١- 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.

٢- 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.

٣- 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.

- **Appendix III: Comparison Composition Form**

Product name:_____
Active ingredient: _____
Dosage form:_____

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

* From Guidlines
*: % change should be in absolute value.
*: Signed & Stamped
*: On Company paper head letter

- **Appendix IV: 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
Controled 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
Controled 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	

- **Appendix V: 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
Others (Specify & submit reference document from EMA or US FDA)

- **Appendix VI: 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=450286300157822 64&_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/

• Appendix VII: Variation Notification form.

Product Name/ Active ingredient:	
Dosage Form/strength :	
Applicant:	
Manufacturer:	
Marketing Authorization Holder:	
Category(`s) of the Change: (Specify type of the variation Change) as mentioned in these guidelines	
Current Situation	• In Case of Notification Or VDA Approval
Proposed Change	• In Case of Notification Or VDA Approval

❖ **Category of the change:**

☐ *Notification Approval (N)*

Details of the change and document submitted[1]:

☐ *Variation Department Approval (VDA)*

Details of the change and document submitted[1]:

☐ *Variation Committee Approval (VCA)*

Details of the change and document submitted[1]

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

Name of responsible Pharmacist _____ _____

Signature:

Date _____

To be fulfilled in all submitted changes

- **Appendix VIII: Abbreviations.**

NODCAR: The National Organization for Drug Control & Research
N: Notification
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