Notice to applicant

Central Administration of Pharmaceutical Products
General Administration For Stability

Guidance for File Content of Stability study dossier

Year 2024

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Table of Contents

• Scope:

This guidance is applied on submission data required for stability study dossier for local and imported pharmaceutical products. Ensuring that submissions are consistent, complete, and adhere to EDA standards, which ultimately facilitates quicker approvals and market access.

• Objective:

This guidance will help applicant company to prepare a well-organized dossier for submission to GA-Stab that eventually will benefit both the applicants and the regulatory evaluators. Using this standardized dossier format helps streamline the submission and evaluation process, ensuring that all essential information is presented clearly and efficiently, reducing misunderstandings and the need for additional clarifications, ultimately leading to a more efficient approval process for human pharmaceutical products.

Stability file Content for Human Pharmaceutical Products

Item	Document Name	Description and requirements (if applicable)	Under-Registration	Re-Registration	Variation	Registration License Requirements or post approval requirements
Regulatory Documents Folder						
	For Under-reg.: - Preliminary reg. (i.e. Box) approval - Naming approval - PV approval - Pricing approval - Extension approval (If needed) - CPP / free sale with its attached SmPC (Summary of product characteristics) / Insert		√	NA	NA	NA
	For Renewal / Re-reg. / Post approval: - Reg. license with its attached composition - Preliminary re-reg. approval and / or Transfer letter for expired license - Extension approval (If needed) - CPP / free sale with its attached SmPC (Summary of product characteristics) / Insert		NA	√	√	√
	EDA reports: - Previous stability approval(s) with its attachment(s) - Recent Variation approval(s) with its attachment(s) - CAO Report of primary batch(es) no. / type / order - CADC final report (must be for the submitted batch(es)) with its attachment(s) - Quality approval with its attached composition and FPS		If applicable √	√	√	√

	Stability study contract (if local st. performer ≠ applicant or FP manufacturer): - Annex for product name, strength and dosage form, and performed test(s) - Both contract and annex must be legalized (bank signatures and EDA legal affairs)		If applicable	If applicable	If applicable	If applicable
	- Payment code / Receipt copy: in case of variation (from last stability approval / reg. license) as shelf-life extension, storage conditions change, in-use storage conditions and / or shelf-life		NA	NA	In case of shelf-life extension/ storage condition variation/ In use addition (after opening/ after reconstitution/ after dilution)	NA
	Commitment for proposed storage conditions/ state shelf life	(Annex II) • Should be presented by Applicant company signed and stamped • Submit justification for proposed temperature as Egypt is located in climatic zone IV A with reference	√	If applicable	If applicable	If applicable
	COR	(Annex III) • Certificate of responsibility, signed from (Q.C. analyst, Q.C. Head &Q. A Head) • Should be presented by Stability testing site (signed and stamped)	√	√	√	√

	Declaration letter for API manufacturer	(Annex IV) • Should be presented by Applicant company (signed and/stamped) • Manufacturer of each Active ingredient entering in the manufacture of finished product Should be mentioned • Should mention finished Batch No. on which stability study is performed and country of origin • Batch Size/batch type should be mentioned • should be the same as stated in CTD Section3.2. S.2.1: Drug Substance Manufacturer(s) in case of products imported from reference countries or in products in quality module format is a requirement for registration)	√	√	√	√
Technical Documents Folder						
	Composition	-Refer to Annex I for full details	√	√	√	√
	Brand leaflet (i.e., Generic reference product SmPC (Summary of product characteristics)	Brand leaflet / SmPC in English with highlighted shelf life, storage conditions, in- use (after opening/after dilution/after reconstitution) shelf life and storage conditions, solvents used and their volume (if applicable), diluents used and their volume (if applicable)/package	√	√	√	√
	Post approval stability protocol and stability commitment	(Annex X) • Commitment for continuing stability studies of: 1. Production batches+ proposed protocol 2. Long term on same batches submitted for accelerated studies + proposed protocol On-going stability studies+ proposed protocol	√	√	√	√

	Declaration letter	Declaration letter from License Holder stating the shelf life, storage conditions, pack and in use in case of missing information in CPP	√	√	√	√
	Finished product specifications (P.5.1)	**(Annex V) • should be presented by stability testing site signed and stamped • Should clearly include product name, dosage form, concentration (if applicable) • Should include list of tests, acceptance criteria and reference for both analytical procedures and acceptance criteria • Should include method of analysis for each mentioned test • <u>Should include the following:</u> ✓Physical analysis (Color, shape, size. Scoring, justification for mottling is required) for solid dosage form ✓(clarity, homogeneity, opalescence, color for liquid dosage form ✓<u>Chemical analysis;</u> Should include assay of active ingredient(s), quantitation of impurities and related substances,and assay of preservative(s) and/or antioxidant(s) (when applicable) antibiotics Microbiological analysis (when applicable) ✓Biological analysis (when applicable) e.g.: enzymes /Biocides. ✓Performance test: dissolution viscosity, antiseptic effectiveness test (antiseptic and disinfectant test) <u>Notes:</u> • Any skip test should be mentioned as a footnote • Limit for any test should be specified as release and /or shelf specs (only) • Residual solvents should be included (if present in product formula) (release specifications) *(it should be the same as stated in CTD Section 3.2.P.5.1: Drug Product Specification(s) in case of products imported from reference countries or in products in which the CTD format is a requirement for registration)	√	√	√	√

N.B:
The required tests for each dosage form should
*Comply with the "EDA Guidelines for technical assessment of finished pharmaceutical products for human use files".
Comply with TRS1010 Annex 10 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products".
ICHQ6A specifications: Test procedures and acceptance criteria for new drug substances and new drug products Chemical substances-scientific guidelines

- **Required stability Sections in quality module**

(required in case of products imported from reference countries or in products in which the CTD format is a requirement for registration)

Stability Study Results Folder	P-Part	• Section 3.2.S.2.1: Drug Substance Manufacturer(s) • Section 3.2.P.1: Description and Composition of the Drug Product • Section 3.2.P.3: Drug Product Manufacturer(s) • Section 3.2.P.5.1: Drug Product Specification(s) • Section 3.2.P.5.2 Analytical procedure • Section 3.2.P.5.3 Validation of analytical procedure • Section 3.2.P.5.4: Batch Analyses • Section 3.2.P.5.5: Characteristics of impurities • Section 3.2.P.5.6: Justification of Specification(s) • Section 3.2.P.7: Container Closure System • Section 3.2.P.8.1: Stability Summary and Conclusion • Section 3.2.P.8.2: Post-approval Stability Protocol and Stability Commitment • Section 3.2.P.8.3: Stability Data	√	√	√	√

	S-Part	• **<u>Required DMF Sections or submit valid CEP containing retest period and container closure system</u>**: • Section 3.2.S.2.1: Manufacturer(s) • Section 3.2.S.3.2 Impurities • Section 3.2.S.4.1: Specifications • Section 3.2.S.4.2: Analytical procedure • Section3.2.S.4.3: Validation of analytical procedure • Section 3.2.S.4.4: Batch analysis • Section 3.2. S.4.5Justification of Specifications • Section 3.2. S.6: Container closure system • Section 3.2. S.7.1: Stability Summary and Conclusions • Section 3.2. S.7.2: Post-approval Stability Protocol and Commitment • Section 3.2. S.7.3: Stability Data	√	NA	NA	NA
	Certificate of analysis of stability batches for API	• Should be presented by stability testing site signed and stamped for the batch of finished product on which stability study is done • Should include product name, batch number,manufacturing and expiry date, batch type / batch size. • Should include results within release specifications • <u>It should include the following:</u> ✓ Physical analysis ✓ <u>Chemical analysis;</u> Should include identification & assay of activeingredient(s), impurities and related substances, and content of preservative(s) and/or antioxidant(s) (when applicable) ✓ Microbiological analysis ✓ Biological analysis (when applicable) ✓ Performance test (dissolution, disintegration, viscosity	√	√	√	√

	2-Method of analysis (P.5.2) For both finished product Specification and /or API	• Should be presented by stability testing site signed and stamped • Should include stability-indicating analytical-procedures used for physical, chemical and microbiological analysis • Should follow analytical procedurefound in a pharmacopoeia (if having pharmacopeial reference) **Notes:** ✓ Please attach and fill Annex (VI) in related analysis procedure if there's no pharmacopeial reference for product and ICH guidelines is being followed or CTD part characterization of impurities (P.5.5 and/or S.3.2) ✓ Justification should be submitted to clarify any deviation from the ICH limits. ✓ Procedure for test done in stability studies only should be submitted in full details	√	√	√	√

	Stability study table(s)	• Should be presented by stability testing site signed and stamped • Should clearly state product name, dosage form, concentration (if applicable), batch numberon which stability study was done, manufacturing and expiry date, date of starting stability study in case of being different than manufacturing date, study conditions, testing intervals and product pack in details batch size and batch type. • Should include results within shelf-life specifications • <u>Should include the following</u>: ✓ Physical analysis ✓ Chemical analysis: ✓ Microbiological analysis ✓ Biological analysis (when applicable) • <u>May include (when applicable):</u> In case of **<u>In-use stability study</u>** (A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the batches should be chosen towards the end of its shelf life.) • **<u>Antimicrobial preservative effectiveness</u>** test in case of presence of preservatives. • Bulk stability studies (if present): Consideration should also be given to hold-time studies of bulk products,e.g. coated tablets prior to final packaging. For example, when the bulk product may be stored for a period exceeding 30 days before being packaged and/or shipped from a manufacturing site to a packaging site, the stability of the bulk product in the intended bulk container should be evaluated and studied. • Long term stability studies including holding time (if present). • Statistical analysis data should be submitted if applicable • Justification of any significant should be submitted if applicable • Multi container volume (Packaging Material)	√	√	√	√

		• In case of applying matrixing or bracketing; the design table, justification of the design, the design table data/ statistical analysis and data if applicable. (Annex IX) • Summary of study should be submitted according to annex VIII **Notes** • Dissolution results should be expressed as (average and range of individual results) for each individual time interval • Any out of specifications results should be scientifically justified • Any out of trend should be scientifically justified- * Data should be presented either in tables, graphs or both. • Any significant change should be justified • Any skipped test Should be scientifically justified				
	3-Method References + commitments	• Most updated monograph for finished product should be submitted. **In case of Combination Products:** If there's no pharmacopeia reference for combination finished product, finished monograph for each active ingredient should be submitted /impurities limits should comply with ICH guidelines for each API only if impurities are as a result of API interaction, it should be calculated according to least API amount (worst case) TRS 929 annex 5 • Commitment from stability testing site that method of analysis submitted for assay/ related/anti-oxidant/preservative is the same method of analysis submitted and validated in CADC (last updated guidelines for file assessment for pharmaceutical products for human use). • If a test is done in stability only, all documents should be submitted (procedure/validation and results), and justification of adopting new methods.	√	√	√	√

Assay &Validation protocol & Charts Folder for both locally manufactured products & imported from non-reference countries	4-Assay chromatograms	• Should include product name, batch number and injection date/time • Should include chromatograms of assay of active ingredient(s), quantitation of impurities and related substances, and content of preservative(s) and/or antioxidant(s) (when applicable)/ dissolution • Should include 3 injections for standard and test at each time interval • System suitability charts should be included. • Should be stamped by stability testing site **Notes**: • Each time interval should be in a separate pdf	√	√	√	√

	5-Validation of analytical procedure	• Should include validation of analytical procedures for assay of active ingredient(s), quantitation of impurities and related substances, and content ofpreservative(s) and/or antioxidant(s) (when applicable) • Validation data in section P.5.3 in CTD /similar to that presented and approved by CADC • In case of new method applied in stability dossier differs than that in section p.5.3, complete method validation data should be submitted • In case of variation of composition (additional of excipients /change of amount of excipients /grade s) complete validation required) • In case of site transfer in variation (apply method transfer requirements according to USP 1224) **In Case of Full Validation Data** • Complete validation of analytical procedures Should be conducted • the following validation characteristics should be submitted: specificity, precision, linearity, accuracy, ruggedness and robustness • Results for each validation parameter should be summarized in a tabulated form • In case of analytical procedure used, found in a pharmacopoeia, verification of analytical procedures Should be conducted in which the following validation characteristics should be considered including: specificity, precision and Accuracy (as required in USP 1226) • Verification is not necessary for compendial API assay method in S.4.3 (S-Part) • For Quantitative test (e.g.: individual and total degradation products) it should be ensured that the actual numerical results are provided rather than range statement such as within the limit or conform.	√	√	√	√

		Notes: • Regarding stress conditions stability study, please apply conditions drastic enough to yield 10-30% degradation and fill Annex VII (TRS 929 annex 5) • Reference and scientific evidence should be submitted for products found to be stable in stress conditions stability study • If an officially recognized compendial method is used to control related substance that are not specified in the monograph, full validation of the method is expected with respect to those related substances. • If an officially recognized compendial standard is claimed and an in house method is used in lieu of the compendial method e.g.: for assay or related compounds), equivalency of in house and compendial method should demonstrated this could be accomplished by performing duplicated analysis one sample by both methods and providing the results for the study. • In case of stability method change or addition of new sections; method equivalency should be provided				

	Validation chromatograms (P.5.3)	• Should include chromatograms of validation of analytical procedures for assay of active ingredient(s), quantitation of impurities and related substances, and content of preservative(s)and/or antioxidant(s) (when applicable)/dissolution • Should be stamped by stability testing site • <u>Should include the following:</u> ✓ For specificity: injections for samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis and oxidationare required in addition to placebo and blank injections ✓ Minimum number of injections required for precision: 6 injections are required ✓ Minimum number of injections required for linearity: 5 concentrations are recommended with 1 injection required for each concentration ✓ Minimum number of injections required for accuracy: 3 concentrations are recommended with 3 injections requiredfor each concentration ✓ Minimum number of injections required for ruggedness: 3 injections are required for each random variation ✓ For robustness: 3 injections are required for each small variation in methodparameters **<u>Notes</u>**: • Each tested validation parameter should be in a separate pdf • Charts for stress conditions stability study (Should be for each API separately) should be with acceptable resolution showing peaks of active and degradation products • Chromatograms required for verification • Chromatograms required for method transfer	√	√	√	√
	Reference standard certificate	• Certificate of RS used in method of analysis (primary or secondary standard) As required in TRS 986/Annex 6 Or as CTD assessment is sections S.5/P.6	√	√	√	√

Stability File Content for Veterinary, Herbal and Biocides Pharmaceutical Products

Folder name	Description and requirements (if applicable)	Veterinary	Herbal	Biocides
		Under-Registration Renewal / Re-registration Post approval (Var., License req., Stability approval)		
Regulatory documents				
Preliminary approval for Registration with attached composition "if applicable"		NA in case of variation / re-registration		
Naming Approval "if applicable"	(i.e. Herbal)	NA in case of variation / re-registration		
Approval for Re-registration and/ or transfer letter		--NA in case of under- reg. -Applicable in case of re-registration - Applicable in case of variation if reg. license is non- valid		
Registration License and attached composition		NA in case of under-registration		
- Extension approval	(If needed)	Required in all cases (If needed)		
- CPP / free sale	with its attached SmPC (Summary of product characteristics) / Insert	Required in imported products		
EDA reports:	- Previous stability approval(s) with its attachment(s) - Recent Variation approval(s) with its attachment(s) - CAO Report of primary batch(es) no. / type / order - CADC final report (must be for the submitted batch(es)) with its attachment(s) - Quality approval with its attached composition and FPS	all available reports		
Payment code / Receipt copy	Copy for payment receipt should be submitted If the file is submitted for the one of the following purposes: 1. shelf life extension 2. storage condition change 3. change in in-use of the product	Required in-case of change of: In-use / Storage conditions / Shelf life extension of the finished product from last stability approval /registration license		
Stability study contract	- Annex for product name, strength and dosage form, and performed test(s)	Required when stability testing site is different from applicant company or manufacturer of finished product		

	- Both contract and annex must be legalized (bank signatures and EDA legal affairs)	
Commitment for storage conditions	(Annex II) Submitted in case of proposed storage conditions at temperature (different storage form 30°C) Should be presented by Applicant company signed and stamped Submit justification for proposed temperature as Egypt is located in climatic zone IVA with reference	Applicable only in case of Herbal or veterinary
COR	(Annex III)	Required
Declaration letter for API manufacturer	(Annex IV) Should be presented by Applicant company (signed and stamped) Should mention manufacturer of each Active ingredient entering in the manufacture of finished product Should mention finished Batch No. on which stability study is performed and country of origin Should state batch type (e.g.: R&D, pilot, production…),	Required
Technical Documents		
Composition	Annex I	NA in case of biocides Herbal API: must to be written in details as the approved herbal registration) refer to annex I for more Details
Finished product specifications*	**(Annex V)	Required • (In case of Vet: should comply with VICH GL39 specifications, test procedures and acceptance criteria for new veterinary drug substance and new medicinal products; chemical substances. • In Case of herbal: 1- It should comply with EDA guidelines for Registration of herbal pharmaceuticals 2- EMA Guidelines of specifications test procedures and acceptance criteria for herbal substances, herbal preparations, and herbal medicinal products/ traditional herbal medicinal

		products scientific guidelines In Case of Biocides: (Biocides -Antiseptics-Disinfectants) references
Certificate of analysis		Required Antiseptic effectiveness test is required in case of antiseptic
Method of analysis		Required
Stability study table(s)		Required
References + commitments	• Most updated monograph for finished product should be submitted "if present " • Pharmacopeia references with highlighted limits (if applicable)	Required If applicable
Assay chromatograms		Required if applicable
Validation of analytical procedure		Required if applicable -Declaration that these methods and their validations are the same submitted and approved by CADC if applicable
Validation chromatograms		Required if applicable
Reference standard certificate	• Certificate of RS used in method of analysis (primary or secondary standard) • Standard in case of herbal	Required
Calculation sheets	For all stability study intervals	Required in all cases

Annexes

Title	No.
Reviewing Composition	**I**
Commitment for Storage Conditions other than Zone IV in Storage Condition	**II**
Commitment for Responsibility/ "authenticity of data submitted"	**III**
Declaration of API	**IV**
Finished Product Specifications	**V**
Impurities ICH Calculations	**VI**
Stress Conditions Stability Study Results	**VII**
Stability Summary Table	**VIII**
Bracketing and Matrixing	**IX**
Stability Commitment	**X**

References TRS 986 annex 6

- Technical Report series 1010 Annex 10,2018
- Note for guidance on in-use stability testing of human medicinal products- EMA
- Guidelines for technical assessment of finished pharmaceutical products for human use files-EDA.
- ICH Q6A Specifications
- References (ICH HARMONISED TRIPARTITE GUIDELINE STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2) ICH Q1D)

Annex I

Composition Certificate

Trade Name & Dosage form	This section to be filled by the Applicant company

The description of the finished product included a physical description, the proposed strength and dosage form is submitted.

Composition of the dosage form: (p.3.1)

Ingredient(s)	Amount/ Unit	Percentage % w/w or % w/v	Function	Reference (Compendial or In-house)
API				
Excipient				
Total weight / Volume				

Applicant Company Signature, Date & Stamp:

Notes:

1- *This template should be copied and submitted on Applicant Company letterhead.*
2- *API (s), it's (their) hydrate(s) and salt form(s) with its (their) quantity (ies) per unit dose is (are) specified.*
3- *Grades of excipient should be mentioned beside excipient name.*
4- *Coat or Capsule Shell should be mentioned separate from the core or capsule content.*
5- *Weight of core tablet or content of capsule should be mentioned separately from total weight.*
6- *Solvents and Nitrogen Gas(its grade) used during manufacturing process: should be declared.*
7- *Composition of all components used as mixtures should be mentioned in details and submitted on supplier's Letterhead (e.g. Pellets, premixes, colorants, coatings, capsule shells and imprinting inks).*
8- *The Overage should be mentioned, and justification should be submitted on a separate document.*
9- *Reconstitution Solvents should be mentioned if present. (Not applicable for solvents with registration license).*
10- *In case of Pellets & Premix: composition on supplier letterhead should be attached. (template 4)*
11- *In case of presence of iso-tonicity agent, calculation for osmolality should be submitted*
12- *In Case of API equivalence (calculation of equivalence should be submitted)*
13- *In case of varying amount of API according to potency (equation for calculation should be stated in the footnote and the component which compensate change should be mentioned (template 4)*

- **Declaration states reference drug product used in developmental studies / BE approval**

Applicant Company:	This section to be filled by the Applicant company
Trade Name:	This section to be filled by the Applicant company
Generic Name(s) + Strength(s):	This section to be filled by the Applicant company
Dosage Form:	This section to be filled by the Applicant company

Reference Product Details:

Reference Drug Product	
Name, strength and dosage form of reference Product	This section to be filled by the Applicant company
Name of MAH,Manufacturer and Country of origin	This section to be filled by the Applicant company

Applicant Company Signature, Date & Stamp:

- **Calculation of Equivalent base of API/ Semi-Finished or Intermediate product -Quantity of pellets / Premix**

Applicant Company:	This section to be filled by the Applicant company
Trade Name:	This section to be filled by the Applicant company
Generic Name(s) + Strength(s):	This section to be filled by the Applicant company
Dosage Form:	This section to be filled by the Applicant company

Detailed Calculations should be provided:

Applicant Company Signature, Date & Stamp:

Annex II

Commitment for storage conditions

تعهد بظروف التخزين المقترحة

بالنسبة للمستحضر التي :

نتعهد نحن شركة /مكتب علمي ..... بتخزين المستحضر عند درجة حرارة لاتزيد عن درجات الحرارة الموجودة في موافقة دراسة الثبات وكذالك الزام جميع الموزعين بذالك في مخازنهم وفي تعاملتهم مع الصيدليات التي تراعي هذه الاشتراطات .

رئيس مجلس ادارة الشركة / مدير المكتب العلمي

Annex III

Commitment for Responsibility "Authenticity of Data Submitted"

يشهد مصنع/مركز ثبات .....بأنه قام بعمل دراسة الثبات الخاصة بمستحضر .....
و مسئول عنها مسئولية كاملة و هذه دراسة مقدمة على

Batch Number	Batch Type	Study Type

التى تمت بمعرفة فريق العمل المكون من :

Performed by (Q.C. Analyst):……
Checked by (Q.C. Head):……..
Authorized by (Q.Assurance Head):……

Stamp : ……

Annex IV

Declaration of API

Product Name, Dosage form, concentration (if applicable)

Batch Type	Batch No.	API	Manufacturer of API	Country of origin

Annex V

Finished Product Specifications:

Product name, Conc. (if applicable) & Dosage form					
Test/	**Method**	**Acceptance criteria**		**Reference**	
		Release specification	**Shelf Specification**	**Analytical procedure**	**Acceptance criteria**
Description					
Identification					
Impurities					
Assay					
etc.					

***in case of difference between release and shelf specification, justification needed.**

Annex VI

Impurities ICH calculations

Maximum daily dose for " API"	**<x mg/day>**		
	Parameter	**ICH threshold or concentration limit**	**Observed results**
Each Degradation product	Reporting Threshold		
	Identification Threshold		
	Qualification Threshold		

Maximum daily dose (i.e. the amount of API administered per day) for the API, corresponding ICH Reporting/Identification/Qualification Thresholds for the degradation products in the FPP

Annex VII

Stress conditions stability study results

Stress Type	Conditions /parameters used	Duration	Degradation %
Acidic			
Alkaline			
Oxidative			
Heating			
Light			
Photostability			
Others(Freeze/Thaw) cycles			

Annex VIII

Stability Summary Table

Test	Acceptance criteria	Results		Significant Change*	Out of Specification (OOS)* Absent/present	Out of Trend (OOT)* Absent/present
		Min	Max			

*If present a scientific justification should be justified

Annex (IX)

Bracketing & Matrixing

Bracketing is defined as the design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all-time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system

Design Example										
Table: Example of a bracketing Design									**Total=27** **Tested=12**	
Strength		**50mg**			**75 mg**			**100 mg**		
Batch		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Container Size	**15ml**	**T**	**T**	**T**				**T**	**T**	**T**
	100 ml									
	500 ml	**T**	**T**	**T**				**T**	**T**	**T**
Key: T=Sample Tested										

Matrixing is defined as the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time, point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems. *In case of bracketing and Matrixing study design and tables should be included.

Design Example

Table: Example of a Matrixing Design "One Third Reduction"									**Total=48 1/3=16 Reduced=10**
Time Point (months)			**0**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Strength	**S1**	**Batch 1**	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
	S2	**Batch 1**	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

Key: T=Sample Tested

Design Example

Table: Example of a Matrixing Design "One Third Reduction"									**Total=48 1/3=16 Reduced=10**
Time Point (months)			**0**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Strength	**S1**	**Batch 1**	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
	S2	**Batch 1**	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

Key: T=Sample Tested

Annex (X)

Stability Commitment

Post-approval Stability Protocol and Stability Commitment

For presentation to concerned authorities of the Arab Republic of Egypt

We **(Applicant)** as Marketing Authorization Holder of **(Product name)**, that is to be registered and marketed in Egypt, confirm the following recommended shelf life, storage conditions and container closure system for this product, based on the present knowledge confirmed by updated long-term stability studies:

Packaging material	Shelf-life	Storage conditions

We commit to ----------

- The application of Stability Studies on Commercial scale Production batches and ongoing Stability studies following the same protocol used in primary batches stability concerning test items, acceptance criteria& frequency of testing**.**
- To complete the ongoing stability study for the product after finishing the long-term stability study of production batches
- To complete shelf study (12 and/ or 24 months) on the submitted pilot batches