Guide for the Quality Module 3 - Part P

Finished Product

Prepared by the Technical Subcommittee's experts under the supervision of Dr. Rita Karam, Head of Quality Assurance of Pharmaceutical Products

Drug Name dosage form & Strength

Manufacturer:

Applicant:

ICH: Quality Guidelines:

Stability Q1A(R2)-Q1B-Q1C-Q1D-Q1E

AnalyticalValidation : Q2(R1)

Impurities: Q3A(R2)-Q3B(R2)-Q3C(R4)

Pharmacopoeias: Q4B with annexes 1 to 12.

Quality of Biotechnological products Q5A(R1)-Q5B –Q5C-Q5D-Q5E

Specifications : Q6A-Q6B

Good Manufacturing Practice : Q7

Pharmaceutical Development : Q8(R2)

Quality Risk Management : Q9

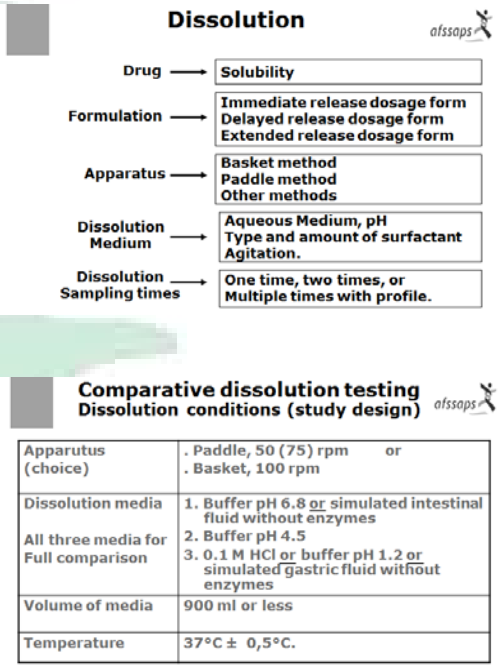
Pharmaceutical Quality System : Q10

Development and manufacture of drug substances Q11

Lifecycle management Q12

Section	***Module 3 Quality***	**MAQ_R1** **Guide for quality submission**	***ICH***	**Product evaluation**	**Comments**
3.2.P	**Drug Product:**				
3.2.P.1	**Description and Composition of the Drug Product.**	A description of the drug product and its composition should be provided. The information provided should include: • Description of the dosage form; • Composition, • Function of the components, and a reference to their quality standards • Type of container and closure used for the dosage form	**ICH Q6A** **ICH Q6B**	The composition (e.g., components of the capsule shell, components of ink ***used on the drug product***) should also be included. If the diluent is co-packaged with the drug product, the information on the diluent should be placed in a separate Drug Product section. The use of an over-fill should be indicated.	
3.2.P.2	**Pharmaceutical development**	**T**he Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application**.** The studies described here are	**Q6A and Q6B And Q8(R2)**		

		distinguished from routine control tests conducted according to specifications. In addition , this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility , product performance and drug product quality . Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.			
3.2.P.2.1	Components of the Drug Product				
3.2.P.2.1.1	Drug Substance.	The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, and particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.			

		For combination products, the compatibility of drug substances with each other should be discussed.			
3.2.P.2.1.2	Excipients	The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.			A compatibility studies must be performed.
3.2.P.2.2	Drug Product				
3.2.P.2.2.1	Formulation Development.	A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.	**Q8(R2)**	This section describes how the final formulation was arrived at. It should give a brief history of the development including the failures along the way. We must try to establish that there is a logical and scientific basis for choosing the proposed formulation from pre formulation to formulation to pilot to production. Comparative dissolution test between test product and reference product(on 3 pHs) Comparative dissolution test among strengths (on 3 pHs). • At least 12 units should be used for each profile determination. • The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both the profiles should be the same (e.g., for IR products 15, 30, 45, 60 minutes; for ER products 1,2,3,5,and 8 hours). • For products which are rapidly dissolving, i.e., more than 85% in 15 minutes or less, a profile comparison is not necessary. **Difference Factor f1** is a measure of relative error between the two	**Some slides from DrSawaya to illustrate:** 

				curves of dissolution **Similarity Factor f2** Using an average difference of 10% between two dissolution profiles at all sampling time points: f2 is about 50 A test batch dissolution is therefore considered similar to that of the reference batch if the f2 value of the two true profiles is not less than 50. • Ideally for curves to be similar: – f1 should be close to 0, and – f2 should be close to 100 • Practical considerations: – f1 between 0 to 15 and – f2 between 50 to 100 **Or** **A summary** of dissolution development can be included in 3.2.P.2.2.3, with cross-reference to studies in Module 5, as considered appropriate.	**Comparative dissolution testing** **Profile similarity determination** afssaps • **If both products show 85 % dissolution in 15 minutes : profiles are similar.** • **If not : Calculate the f2 value (similarity factor).**
3.2.P.2.2.2	Overages.	Any overages in the formulation(s) described in 3.2.P.1 should be justified		Only in two cases : -To compensate losses -For vitamin preparations.	
3.2.P.2.2.3	Physiochemical & biological properties.	Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, re dispersion, reconstitution, particle size distribution, particle size of the		A summary of dissolution development should be included in 3.2.P.2.2.3, with cross-reference to studies in Module 5, as considered appropriate.	

		lend/granules flow , properties which might affect capsule filling or tableting , aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed			
3.2.P.2.3	Manufacturing process development.	The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Identify critical steps. Identify key validation parameters in term of mixing times , drying times and temperature Where relevant, the method of sterilization should be explained and justified. Differences between the manufacturing process (es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.		The progress from pre formulation to formulation to pilot to production scale batches should be shown to be logical, reasoned and continuous.	
3.2.P.2.4	Container closure system.	The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form			Connections with stability 3.2.P.8

		(including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).			
3.2.P.2.5	Microbiological attributes.	Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.	**Q4B ANNEX 4A(R1) Q4B ANNEX 4B(R1) Q4B ANNEX 4C(R1)**		Connections with stability 3.2.P.8
3.2.P.2.6	Compatibility.	The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.		There should be a separate Drug Product (diluent) section for co-packaged diluents. Choice and development of co-packaged diluents should be included.	
3.2.P.3	**Manufacture**				
3.2.P.3.1	Manufacturer(s) .	The name, address, and responsibility of each manufacturer, including contractors, and each proposed			

		production site or facility involved in manufacturing and testing should be provided.			
3.2.P.3.2	Batch Formula.	A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.	**Q8(R2)**		
3.2.P.3.3	Description of Manufacturing Process and Process Controls	A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified. A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant. Steps in the process should have the	**Q6B** **Q8(R2)**		

		appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated. Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3). Additionally for Biotech see 3.2.A.1 for facilities , if appropriate .			
3.2.P.3.4	Control of Critical steps& intermediates.	Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled. Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.	**Q2A** **Q2B** **Q6A** **Q6B**		
3.2.P.3.5	Process validation	Description, documentation, and results of the validation and/or evaluation studies should be provided	**Q6B**	**Content of process validation protocol**: -Short description of the process with a summary of the critical processing steps. -Drug product specifications (at release).	

		for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.		-Details of the analytical methods. -Acceptance criteria -sampling plan (where, when and how samples are taken). -details of the methods of recording and evaluation results. -proposed time frame. -batch analytical data. -certificate of analysis. -batch production record -report on unusual findings , modifications or changes found necessary with appropriate rational -conclusion	
3.2.P.4	**Control of Excipients**				
3.2.P.4.1	Specifications.	The specifications for excipients should be provided.	**Q6A and Q6B**		Certificates of analysis(COA)s from quality control lab(applicant) and from suppliers(vendors) must be provided.
3.2.P.4.2	Analytical Procedures.	The analytical procedures used for testing the excipients should be provided, where appropriate.	**Q2A and Q6B**		
3.2.P.4.3	Validation of Analytical Procedures	Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.	**Q2A, Q2B, and Q6B**		
3.2.P.4.4	Justification of specifications.	Justification for the proposed excipient specifications should be provided, where appropriate.	**Q3C and Q6B**		
3.2.P.4.5	Excipients of Human or	For excipients of human or animal origin, information should be provided	**Q5A, Q5D,**		Certificate of TSE/BSE, presence or absence should be provided from suppliers.

	Animal Origin.	regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in 3.2.A.2).	**and Q6B**		
3.2.P.4.6	Novel Excipients.	For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3).		.	
3.2.P.5	**Control of Drug Product**				
3.2.P.5.1	Specification(s)	The specification(s) for the drug product should be provided.	**Q3B, Q6A and Q6B**	Are the specifications coherent with the dosage form proposed? Is there any differentiation between release specifications and shelf-life ones , specially related to "assay" and related substances content" parameters?	
3.2.P.5.2	Analytical Procedures.	The analytical procedures used for testing the drug product should be provided.	**Q2A and Q6B**		
3.2.P.5.3	Validation of Analytical Procedures.	Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.	**Q2A, Q2B and Q6B**	Validation protocols and reports, with acceptance and rejection criteria and specifications and experimental data, for all analytical chemistry methods developed and used for the characterization of a drug substance and proposed drug product are to be	

				included within the designated sections. These methods may include, but are not limited to (*i*) identity assays for a drug substance, intermediates, and excipients; (*ii*) content assays for a drug substance, intermediates, and excipients; (*iii*) impurity profiling and quantification assays for a drug substance and proposed drug product; (*iv*) dissolution assays for a proposed drug product or drug products if more than one is included in the marketing application; and (*v*) stability-indicating assays for a drug substance and proposed drug product **The report, data sheets and typical chromatograms should be provided.**	
3.2.P.5.4	Batch Analyses	A description of batches and results of batch analyses should be provided.	**Q3B, Q3C, Q6A, and Q6B**	Signed COAs for the submission batches should be provided. Typical spectrums (IR/UV) and chromatograms for the relevant tests (HPLC) are required.	
3.2.P.5.5	Characterization of Impurities.	Information on the characterization of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".	**Q3B, Q5C, Q6A, and Q6B**		
3.2.P.5.6	Justification of	Justification for the proposed drug product specification(s) should be	**Q3B, Q6A,**		

	Specification.	provided.	**and Q6B**		
3.2.P.6	Reference standards or materials.	Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".	**Q6A and Q6B**		
3.2.P.7	Container Closure System.	A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendia methods (with validation) should be included where appropriate. For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. Suitability information should be located in 3.2.P.2.			Certificates of analysis from quality control lab (in-house) and from suppliers(vendors) must be provided.
3.2.P.8	**Stability :**			**Some slides from Dr. Sawaya to illustrate:**	

				• **The purpose of stability testing is to provide <u>evidence</u> on how the quality of a drug substance or drug product <u>varies with time</u> under the influence of a variety of environmental factors such as <u>temperature, humidity and light</u>.** • **Stability testing permits the establishment of recommended storage conditions, retest periods, and shelf-lives**. • **Stress testing – forced degradation (Drug product)** Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products. • **Formal stability studies** Long term, intermediate and accelerated studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.	

				Stress Testing of the Drug Product afssaps **Study depends on the type of drug product (pharmaceutical form, properties)** • **Photostability** • **Heat : 60 °C for up to 1 month** • **Cycling conditions (emulsions, solutions for injection)** **Photostability testing (Q1B)** afssaps **Two types of studies :** • **Forced degradation study to generate potential degradation products** • **Confirmatory study to confirm product and package performance :** **Overall illumination NLT 1.2 million lux hours + near UV energy NLT 200 watt hrs per sq. meter**	

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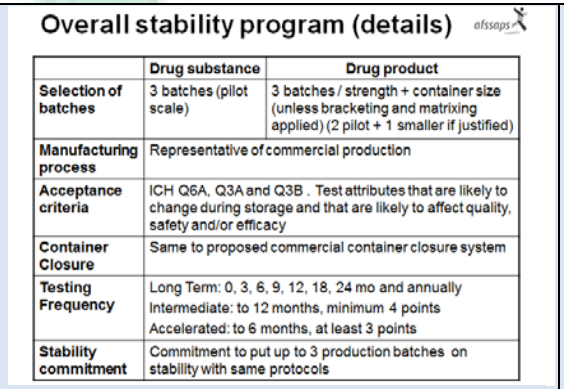
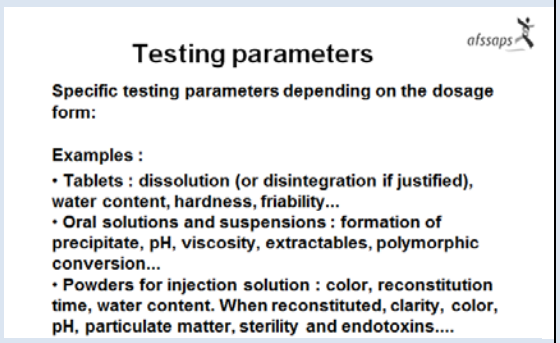


	Drug substance	Drug product
Selection of batches	3 batches (pilot scale)	3 batches / strength + container size (unless bracketing and matrixing applied) (2 pilot + 1 smaller if justified)
Manufacturing process	Representative of commercial production	
Acceptance criteria	ICH Q6A, Q3A and Q3B . Test attributes that are likely to change during storage and that are likely to affect quality, safety and/or efficacy	
Container Closure	Same to proposed commercial container closure system	
Testing Frequency	Long Term: 0, 3, 6, 9, 12, 18, 24 mo and annually Intermediate: to 12 months, minimum 4 points Accelerated: to 6 months, at least 3 points	
Stability commitment	Commitment to put up to 3 production batches on stability with same protocols	



Look for more details in 3.2.P.8.3

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Storage conditions

afssaps

- **Based on analysis of effects of climatic conditions in the 3 regions (EC, Japan USA)**
- **Mean kinetic temperature derived from climatic data**
- **4 climatic zones defined according to W. Grimm ***

Climatic zone	Definition
I	Temperate climate
II	Mediterranean and subtropical climate
III	Hot and dry climate
IV	Hot and humid climate

The ICH Q1A (R2) guideline adresses climatic zones I and II

Storage conditions

Intended Storage Conditions	Stability studies	Study conditions	Submission requirement
General case	Long term*	25°C±2°C / 60% ± 5% RH or 30°C±2°C / 65% ± 5% RH	12 months
	Intermediate**	30°C ±2°C / 65% ± 5% RH	6 months
	Accelerated	40°C ±2°C / 75% ± 5% RH	6 months
Refrigerated	Long term	5°C ±3°C	12 months
	Accelerated	25°C ±2°C / 60% ± 5% RH	6 months
Freezer	Long term	-20°C ±5°C	12 months

*It is up to the applicant, to decide whether long term stability is performed at 25°C ±2°C/60% ± 5%RH or 30°C ± 2°C/65% ± 5%RH.
** If 30°C ± 2°C/65% ± 5%RH is the long-term condition, there is no intermediate condition

Evaluation of stability data (Q1E)

afssaps

Extrapolation /best case

- **No significant change at accelerated conditions within 6 months**
- **Long term data show little or no change over time and little or no variability**
- **Accelerated data show little or no change over time and little or no variability**
- **Statistical analysis is normally unnecessary**
- **An extrapolation can be accorded up to twice the real time stability data (X) however limited to length of real time stability + 12 months (NMT X + 12 months)**

				Labelling statements afssaps **Testing condition where stability has been shown** / **Required labelling statement** / **Additional labelling statement, where relevant** 25°C/60%HR (long term) 40°C/75%HR (accelerated) Or 30°C/65%HR (long term) 40°C/75%HR (accelerated) — None — Do not refrigerate or freeze 25°C/60%HR (long term) 30°C/60 or 65%HR (intermediate) or 30°C/65%HR (long term) — Do not store above 30°C Or store below 30°C — Do not refrigerate or freeze 25°C/60%HR (long term) — Do not store above 25°C Or store below 25°C — Do not refrigerate or freeze 5°C ± 3°C (long term) — Store in a refrigerator Or store and transport refrigerated — Do not freeze Below zero — Store in a freezer or store and transport frozen	
3.2.P.8.1	Stability Summary and Conclusion	The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.	**Q1A, Q1D, Q1B, Q3B, and Q5C, Q6A**	**IF** • Long-term and accelerated data showing little or no change over time and little or no variability **Than** • Extrapolation of re-test period or shelf life beyond the period covered by long-term data can be proposed. • The proposed re- test period or shelf life can be UP to TWICE, but should not be more than 12 months beyond the period covered by long-term data (X). **(Max: X + 12 months).**	
3.2.P.8.2	Post-approval Stability	The post-approval stability protocol and stability commitment should be	**Q1A and**	**IF** • At the time of submission:	

	Protocol and Stability Commitments.	provided.	**Q5C**	At least 2 pilot scale batches + 1 "lab scale" □ Accelerated studies up to 6 months □ Long term up to 12 months **Than** Stability Commitment: . to continue the stability studies post approval □ to place the first 3 production batches on stability studies. • After a new product is approved: □ First 3 production batches: 1. Accelerated studies 2. Long term studies through the proposed shelf life. Thereafter, one batch per year. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program.	
3.2.P.8.3	Stability Data	Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, and narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.	**Q1A, Q1B, Q1C, Q1D, Q2A, Q2B Q3B and Q5C**	**Stability testing of FP may involve monitoring:** • appearance • loss of API • formation of degradation products (ICH Q3B), • changes in drug disintegration and dissolution, • loss of package integrity, • Microbial contamination. • **Some specifications parameters depend on pharmaceutical form** – Tablets: dissolution (or disintegration if justified), water content, hardness, friability…	Example of stability data sheet:

				-Hard gelatin capsules: brittleness, dissolution (or disintegration if justified), water content and microbial bio burden. -softgelatin capsules: dissolution(or disintegration if justified), microbial bioburden, pH , leakage , and pellicle formation. -Emulsions:phase separation , pH , viscosity , microbial bioburden, mean size and distribution of dispersed globules. – Oral solutions and suspensions: formation of a precipitate, clarity for solutions, pH, viscosity, microbial bio burden, extractable , leachable, polymorphic conversion when applicable. Additional tests for suspensions include redispersability, rheological properties , mean size , and distribution of particles. – Small-Volume Parenterals: Color , Clarity of solutions, particulate matter , pH, sterility , endotoxins . Powder for injectable solution: color, reconstitution time, water content. After reconstitution: clarity, color, pH, particles, sterility, endotoxins/pyrogens, and particulate matter. Suspensions for injection should include additional particle size distribution, re dispersability , and rheological properties. Emulsions for injection should include phase separation, viscosity , mean size , and distribution of dispersed globules. -Large-Volume Parenterals: Color , Clarity of solutions, particulate matter , pH, sterility , endotoxins/pyrogens , and volume. -Suppositories: softening range , dissolution at 37degreesC.	

-Topical ,ophthalmic, and otic preparations:
Clarity, homogeneity, pH , resuspendability (for lotions), consistency , viscosity, microbial bio burden , and water loss should be tested. For ophthalmic and otic products additional attributes should include sterility, particulate matter and extractable.
-Metered-Dose inhalers and Nasal Aerosols: content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate , microbial bio burden, valve delivery , extractable , leachable from plastic and elastomeric components.

The batches must have same:
1. Formula
2. Packaging
3. Raw material source
4. Manufacturing process

If one of these parameters change : other stability studies are required.

In some cases , we can use :

• Bracketing :
– bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors
(e.g., strength, container size and/or fill) 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.

Bracketing

Applicable	• Same Pharmaceutical form for all strength • Same packaging
Applicable with justification (based on supporting data)	Change in DS and excipients concentration
Non applicable	Different excipients used

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Matrixing
Design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point.
At a subsequent time point, another subset of samples for all factor combinations would be 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.
When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems.
Each storage condition should be treated separately under its own matrixing design.</td>
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<table>
<tr><td colspan="2">Dosage</td><td colspan="3">50 mg</td><td colspan="3">75 mg</td><td colspan="3">100 mg</td></tr>
<tr><td colspan="2">Batch</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td rowspan="3">Container size</td><td>15 ml</td><td>T</td><td>T</td><td>T</td><td></td><td></td><td></td><td>T</td><td>T</td><td>T</td></tr>
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Matrixing
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<tr><td rowspan="6">DOSAGE</td><td rowspan="3">Strength 1</td><td>Batch 1</td><td>T</td><td>T</td><td></td><td>T</td><td>T</td><td></td><td>T</td><td>T</td></tr>
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<tr><td rowspan="3">Strength 2</td><td>Batch 1</td><td>T</td><td></td><td>T</td><td></td><td>T</td><td></td><td>T</td><td>T</td></tr>
<tr><td>Batch 2</td><td>T</td><td>T</td><td></td><td>T</td><td>T</td><td>T</td><td></td><td>T</td></tr>
<tr><td>Batch 3</td><td>T</td><td></td><td>T</td><td></td><td>T</td><td></td><td>T</td><td>T</td></tr>
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<td>NB: If we have real stability data for <u>only two</u></td>
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	Data.				commercial batches and if the active ingredient is stable and if the dosage form is conventional we can accept. NB: For an injectable liquid which is stable at refrigerator storage conditions 5degrees+/-3 degrees for long term, we can accept it , even if it is not conform for accelerated : 25degrees+/- 2degrees .
3.2.P.8.3.2	Accelerated Stability.			Definitions of significant changes of data stored at accelerated conditions **API** Significant change is defined as failure to meet the specification **Drug product** 1. A 5% potency change from the initial assay value; 2. Any specified degrading exceeding its acceptance criteria 3. Failure to meet acceptance criteria for appearance and physical properties (e.g., color, phase separation, resuspendability, delivery per actuation, caking, hardness); and as appropriate to the product type; 4. The pH exceeding its acceptance criteria; and 5. Dissolution exceeding the acceptance criteria for 12 dosage units.	

Critical Remarks:

Some problems found:

-The stability data for long term conditions are provided completely for three batches but one bath has expiration date sixth months later!

- Stability data for three commercial batches are provided for 6 months of accelerated conditions and only for 6 months long term.(not complete)

- The quantity (pilot batch) followed for stability data for each conditions (less than 10% of the commercial or production batch).

-The protocol of stability and annexure are not provided.

- There is no comparison with the innovator drug, that we do not Know it sometimes.

- There is no pharmaceutical or formulation development.

- There is no description of excipients compatibility.

-Parts are not provided: all the 3.2.P.5- Appendix about specifications and analytical methods –the tests procedures and results for packaging materials-

-No dissolution tests studies.

-No certificates of analysis, or not signed.

-No excipient in the formulation but it is mentioned in the leaflet!

-In sterilization, heat penetration studies provided for another product.

-Several tape mistakes: for example: for suppositories, they mention appearance of tablets…

-Data are missing on paper and we must find them on the CD rom or vice versa.

Recommendations:

The part P of module 3will be:

Approve or not or **on "Pending"** for clarifications and more information or details.

ANNEXES

Brief Summary of the ICH Guidelines for testing of Drug Substances and New drug Products :

Table 7.1 Brief Summary of the ICH Guidelines for Testing of Drug Substances and New Drug Products.

Parameter	ICH Stability Testing Requirements	
	Drug Substances[1]	Drug Products[2]
Batch selection:	Data from three primary batches are required	
Container closure system:	The stability studies should be conducted on the drug substance packed in the same container closure system as proposed for storage and distribution	The stability studies should be conducted on the drug product packed in the same container closure system, i.e. both primary and secondary, as proposed for marketing
Specifications:	Combination of physical, chemical, biological and microbiological tests and acceptance criteria that the drug substance/product should meet throughout its shelf-life	
Testing frequency:	Accelerated: 0, 3 and 6 months Intermediate: 0, 6, 9 and 12 months Long term: 0, 3, 6, 9, 12, 18 and 24 months and then every 12 months through the proposed re-testing period	
General storage conditions:	Accelerated: 40 ± 2°C/75 ± 5% RH Intermediate: 30 ± 2°C/65 ± 5% RH Long term: 25 ± 2°C/60 ± 5% RH or 30 ± 2°C/65 ± 5% RH	
Refrigerator storage conditions:	Accelerated: 25 ± 2°C/60 ± 5% RH Long term: 5 ± 3°C	
Freezer storage conditions:	Long term: −20 ± 5°C	
Stability commitment:	If the long term data on does not cover the proposed substance re-test period or product shelf-life granted at the time of approval then a commitment should be made to continue the stability studies to firmly establish the re-test period or shelf-life.	
Evaluation:	Based on the evaluation of the stability data the re-test period of a drug substance or the shelf-life of a drug product should be established.	
Photostability:	For drug substances, photostability testing should consist of two parts: forced degradation testing and confirmatory testing relating to normal handling of the substance.	i) Test on the exposed drug product, then if necessary ii) test on the product in primary package, and then if necessary iii) test on the product in the marketing package.
	The light source can be an artificial daylight fluorescent lamp combining visible and ultraviolet outputs.	

[1]ICH: the unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.
[2]ICH: The dosage form (e.g. tablet, capsule, solution, cream, eye drops) in the final immediate packaging intended for marketing.

Examples of stability data sheet:

STABILITY ANALYTICAL REPORT

Sample Name: Lot#: Study #: Protocol #: Study Start Date: Study Purpose:	Manufacturing Date: Manufacturing Site: Expiration Date: Testing Site: Packaging Site:	Storage condition: Sample Orientation (if applicable): Packaging Information: Packaging Date:

Test Name	Method	Acceptance Criteria	Time Zero Test Date	1 Mo	2 Mo	3 Mo	6 Mo	9 Mo	12 Mo
Pull Date									
Test Date									
LIMS ID									
Appearance									
Assay									
Impurities Individual Total									
Dissolution Average % RSD Range									
Moisture									

Completed By: _____ Date: _____
Reviewed By: _____ Date: _____
Approved By: _____ Date: _____

Stabilité

STABILITÉ
(Tableau à utiliser comme guide seulement)

	COMPRIMÉS	CAPSULES	LIQUIDES ET GELS	ONGUENTS ET CRÈMES	POUDRES	PRÉPARATIONS INJECTABLES	SUPPOSITOIRES	AÉROSOLS
	Soumettre à des essais tous les ingrédients actifs et les autres «éléments» indiqués ci-dessous							
TENEUR			Plus: agents de conservation, anti-oxydants et agents bactériostatiques, si leur efficacité n'a pas été vérifiée dans la section sur la pureté	Plus: agents de conservation, anti-oxydants et agents bactériostatiques, si leur efficacité n'a pas été vérifiée dans la section sur la pureté	Plus: les données complètes des essais sur les formes posologiques reconstituées	Plus: les agents de conservation, les anti-oxydants et les agents bactériostatiques, si leur efficacité n'a pas été vérifiée dans la section sur la pureté		Quantité administrée par pression pour les aérosols-doseurs
	Contenants: (1) apparence des parois internes et couleur de l'intérieur du bouchon (2) intégrité du sceau d'étanchéité (3) apparence et adhérence de l'étiquette							
Caractéristiques physiques	-dissolution -désagrégation -odeur -dureté	-dissolution -désagrégation -condition des capsules (vides)	-odeur -viscosité -densité -pH -limpidité de la solution -précipitation des ingrédients -non-homogénéité des suspensions -homogénéité (gels)	-odeur -texture -pH -homogénéité -précipitation des ingrédients	-odeur -texture -clarté de la solution -homogénéité -pH (après reconstitution) -taille des particules -écoulement (poudres à inhaler)	-clarté -matière particulaires -pH -précipitation des ingrédients -rotation optique -flacons multi-doses : intégrité du produit après son usage initial	-point de fusion -homogénéité	-poids net -poids d'application -pression d'application -pH -efficacité d'application (par exemple, type de vaporisation et taille des gouttelettes) -nombre de doses ou de pressions par emballage
	Contenants: (1) migration de la drogue dans le plastique (2) migration des plastifiants dans la drogue (3) corrosion							
PURETÉ	-humidité	-humidité	-stérilité des produits ophtalmiques -matières particulaires dans les produits ophtalmiques	-stérilité des produits ophtalmiques -matières particulaires dans les produits ophtalmiques	-humidité	-stérilité		
	Essais microbiens							
	Produits de dégradation							