REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

الجمهورية اللبنانية
وزارة الصحة العامة

Guidelines for the Quality Module3: Part P Finished Product

February 2022

Quality Module for Drug Registration
Evaluation Report

Of the part P of module 3

Drug Name dosage form & Strength

Manufacturer:

Applicant:

ICH: Quality Guidelines:

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

Analytical Validation : Q2(R1)

Impurities: Q3A (R2)-Q3B(R2)-Q3C(R4)-Q3D(R1)

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

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M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

WHO Technical Report series (TRS):

Number 902 Annex 9 Guidelines on packaging for pharmaceutical products

Number 953 Annex 2 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

Number 970 Annex 4 Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Program: Quality part

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, which should include the physical description, available strengths, release mechanism, as well of any other distinguishable characteristics. • Composition i.e., list of all components of the dosage form,	**ICH Q6A** **ICH Q6B**	The composition (e.g., components of the capsule shell, coloring blends, 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. **This mean that we must have a module 3-part P for the solvent** The use of an over-fill should be indicated.	

		and their amount on a per-unit basis (including overdosages, if any) • Function of the components, and a reference to their quality standards (e.g., compendia monographs or manufacturer's specifications) • Type of container and closure used for the dosage form **and accompanying reconstitution diluent, if applicable.**			
3.2. P.2	**Pharmaceutical development**	**The 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 distinguished from routine control tests conducted according to specifications.	**Q6A and Q6B And Q8(R2) WHO TRS Number 970 Annex 4**		

		Additionally, 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. **The pharmaceutical development section can include elements defining the Quality Target Product Profile (QTPP) of the drug product as it relates to quality, safety and efficacy. Critical Quality attributes (CQAs) of the drug product should be identified.**			

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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, 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. Specific attributes (CQAs) of the drug substance that can impart manufacturability should be identified (e.g., particle size distribution). Additionally, specific attributes (CQAs) of the drug substance that can be affected by manufacturing conditions and consequently have an impact on the drug product CQAs		Solubility/quantitative aqueous pH solubility profile should be provided, when applicable (e.g., for solid orals).	

		should be identified (e.g., assay and impurities CQAs due to sensitivity of the drug substance to light, heat, moisture or environment)			
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. The use of antioxidant(s) and / or preservative(s), and their concentration(s) should be explained, fully justified and submitted, if applicable.			A compatibility studies must be performed.
3.2. P.2.2	Drug Product				
3.2. P.2.2.1	Formulation Development.	A summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The formulation development should use a systematic, science and risk-based approach, as described in ICH Q8. The rationale should be linked to QTPP. All CQAs and the critical process	**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 preformulation to formulation to pilot to production. **Trials of preformulation to optimize the formula must be provided.**	**Some slides from Dr. Sawaya to illustrate:**

		parameters (CPPs) should be identified, and a Control Strategy should be proposed to ensure the batches meet the predetermined specification. 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, physicochemical properties) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.		**If it is a generic product: a comparison with the innovator product must be provided.** **For solid dosage forms as tablets and capsules:** 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 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 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	**Dissolution** afssaps Drug → Solubility Formulation → Immediate release dosage form; Delayed release dosage form; Extended release dosage form Apparatus → Basket method; Paddle method; Other methods Dissolution Medium → Aqueous Medium, pH; Type and amount of surfactant; Agitation. Dissolution Sampling times → One time, two times, or Multiple times with profile. **Comparative dissolution testing** **Dissolution conditions (study design)** afssaps Apparatus (choice): . Paddle, 50 (75) rpm or . Basket, 100 rpm Dissolution media (All three media for Full comparison): 1. Buffer pH 6.8 or simulated intestinal fluid without enzymes; 2. Buffer pH 4.5; 3. 0.1 M HCl or buffer pH 1.2 or simulated gastric fluid without enzymes Volume of media: 900 ml or less Temperature: 37°C ± 0,5°C. **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).**

				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.	
3.2. P.2.2.2	Overages.	Any overages in the formulation(s) described in 3.2.P.1 should be justified. Overage for the sole purpose of extending the shelf life of the drug product is not acceptable. However, if the overage is required to make up for a validated loss during the manufacturing process (e.g., loss		Only in two cases: -To compensate losses -For vitamin preparations.	

		during vacuum transfer) or to fill void space (e.g., excess coating solution to fill the tubing) it should be presented along with justification and supporting data for the necessity and quantity of the overage.			
3.2. P.2.2.3	Physiochemical & biological properties.	Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, particle size of the 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. Scored tablets: if the proposed dosage form is a scored tablet, additional information should be provided with respect to its design such as geometry of the tablet and break-line, choice of manufacturing process (e.g., hardness that would be conductive to splitting the tablet).		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.	

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3.2. P.2.3	Manufacturing process development.	**The selection and optimization of the manufacturing process described in 3.2.P.3.3, 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.	**Q8, Q9 and Q10**	The progress from peformulation 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			Connections with stability 3.2. P.8

		construction with the dosage form (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). The information that should be included for the qualification of the container closure system includes packaging materials that: a) come in direct contact with the dosage form (container, closure, liner, desiccant). b) are used as a protective barrier to help ensure stability or sterility. c) are used for drug delivery. d) are necessary to ensure drug product quality during transportation.			
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	**Q4B ANNEX 4A(R1) Q4B ANNEX 4B(R1)**		Connections with stability 3.2. P.8

		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 4C(R1) Q6A Q1A**		
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. For sterile drug products, results of studies should be provided demonstrating compatibility (e.g., hold time studies, extractables and leachable data, ICH Q3D compliance) with manufacturing equipment (e.g., coated vessels, sterilization filters, transfer tubing).	**Q3D**	There should be a separate Drug Product (Diluent) section for co-packaged diluents. Choice and development of co-packaged diluents should be included. **For parenteral product in powder (lyophilized, for example), the stability data, after dilution or reconstitution, must be provided at room temperature and in the fridge.**	
3.2. P.3	**Manufacture**				

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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. This includes the facilities involved in the manufacture (fabrication), packaging and release and stability testing of the drug product (quality control).			
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)**	**The production batch size must be provided.** **For multiple batch sizes, the batch formula for each batch size is to be provided.**	
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**	**Q6B** **Q8(R2)**		

		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 homogenizer) and working capacity, where relevant. Steps in the process should have the 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). For sterile drug products, details of validated sterilization parameters (e.g. load size, autoclave program, gamma radiation dose, processing aids) and equipment (e.g. compounding vessels, sterilizing filters, filling syringes) should be listed for the drug product and all relevant stages of the manufacturing process (e.g. for the washing, sterilization and dehydrogenation of packaging components). Also, each container of an injectable drug product should be filled with a volume that slightly exceeds the content indicated in the product labeling. These excess volumes (i.e., also known as overfills, which are not to be confused with overages) are intended to ensure the minimum			

		required extractable volumes to allow for correct dosage delivery. 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 (e.g., co-precipitates, API micronized by the drug product manufacturer, bulk tablets and solutions). In-process tests are performed during manufacturing for the purpose of adjusting process parameters within an operating range to ensure the entire batch meets the expected quality attributes.	**Q2A** **Q2B** **Q6A** **Q6B**		

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3.2. P.3.5	Process validation **and/or evaluation**	Description, documentation, and results of the validation and/or evaluation studies should be provided 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. Traditional process validation is generally performed prospectively, using three consecutive commercial size batches. Continuous Process Verification (CPV) is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated and could be applied to drug products developed with Quality by Design (QbD) principles (ICH Q8)	**Q6B** **Q8**	**Content of process validation protocol**: - Short description of the process with a summary of the critical processing steps. - Drug product specifications (at release). - 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 **We must have the process validation protocol and the process validation report with results.** **The sterilization method for parenteral products must be validated.** **For sterile products validation of the sterilization process (es) should be completed prior to submission and a summary of these process validation studies should also be provided. The**	

				following data should be included in validation reports: **a) Process parameters of the sterilization cycle.** **b) Washing, treatment, sterilizing, and dehydrogenation of containers, closures, and equipment.** **c) Filtration of solutions.** **d) The lyophilization cycle.** **e) The integrity test of filled and sealed container closures.** **f) Final inspection of the product.** **For sterile products which undergo aseptic processing, the aseptic manufacturing process should also be validated.**	
3.2. P.4	**Control of Excipients**				
3.2. P.4.1	Specifications.	The specifications for excipients should be provided. This would include the specifications for all excipients, including processing aids that do not appear in the final drug product (e.g., solvents, nitrogen, silicone for stoppers).	**Q6A and Q6B**		Certificates of analysis (COA)s from quality control lab(applicant) and from suppliers(vendors) must be provided.

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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 Animal Origin.	For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in 3.2.A.2).	**Q5A, Q5D, and Q6B**		**Certificate of TSE/BSE, presence or absence should be provided from suppliers.** **A current certificate of suitability provided by EDQM may be used as an attestation.**
3.2. P.4.6	Novel Excipients.	For excipient(s) used for the first time in a drug product, at a greater daily exposure than normally administered 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. A list of general characteristics, specific standards, tests and limits for results for the drug product must 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 (compendial and house methods).	**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. It is generally expected that a minimum of three batches of each strength should be manufactured at a minimum of pilot scale from each proposed commercial manufacturing site, and that complete analytical results should be provided for those batches.	**Q3B, Q3C, Q6A, and Q6B Q2 and Q3D**	Signed COAs for the submission batches should be provided. Typical spectrums (IR/UV) and chromatograms for the relevant tests (HPLC) are required. **Quality control manager and quality assurance manager must sign the COA's.**	

		A pilot scale batch of a drug product is a batch manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. In addition, • For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger. • For liquid dosage forms (including lyophilized powders for reconstitution into a solution), a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 20 liters, whichever is the larger. If the maximum proposed commercial batch size is less than 20 liters, the executed batches included in the drug submission should be manufactured at the maximum proposed commercial batch size.			

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". This information would include degradation products (e.g., from interaction of the drug substance with excipients or the container closure system), solvents in the manufacturing process for the drug product, etc.	**Q3B, Q5C, Q6A, and Q6B Q3D M7**		
3.2. P.5.6	Justification of Specification.	Justification for the proposed drug product specification(s) should be provided. The recommended placement for the overall control strategy is here, preferably in tabular format, and should identify the critical quality attributes (CQAs)of the drug product and indicate the various control points in the manufacturing process (e.g., material attributes and/or process parameters) which contribute to the effective control of each CQA, including whether it is tested in the finish product specification. Justification for tests not considered	**Q3B, Q6A, and Q6B Q3D**		

		necessary to include in the specification should be provided (e.g., tests conducted during development or CQAs whose control is assured by a manufacturing process design space). The overall elemental impurity control strategy should be justified based on Q3D.			
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**	**COA's from suppliers of the reference standards or materials must be provided.**	
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-compendial methods (with validation) should be included where appropriate.	**TRS Number 902- annex 9**		**Certificates of analysis (COA's) from quality control lab(in-house) and from suppliers(vendors) must be provided and signed.**

		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 in 3.2.P.2. **Provide a description and specifications for the packaging components that:** a) come in direct contact with the dosage form (container, closure (e.g., rubber stoppers), liner, desiccant). b) are used as a protective barrier to help ensure stability or sterility (e.g., nitrogen headspace). c) are used for drug delivery (e.g., syringe, dropper, measuring cup). d) are necessary to ensure drug product quality during transportation.			
3.2. P.8	**Stability:**		**Q1A , Q1B , Q1C ,**	**Some slides from Dr Sawaya to illustrate:**	

			Q1D , Q1E	• **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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Overall stability program (details)

	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	

Testing parameters

Specific testing parameters depending on the dosage form:

Examples :

- **Tablets : dissolution (or disintegration if justified), water content, hardness, friability...**
- **Oral solutions and suspensions : formation of precipitate, pH, viscosity, extractables, polymorphic conversion...**
- **Powders for injection solution : color, reconstitution time, water content. When reconstituted, clarity, color, pH, particulate matter, sterility and endotoxins....**

Look for more details in 3.2.P.8.3

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

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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
<table>
<tr><th>Testing condition where stability has been shown</th><th>Required labelling statement</th><th>Additional labelling statement, where relevant</th></tr>
<tr><td>25°C/60%HR (long term)
40°C/75%HR (accelerated)
Or
30°C/65%HR (long term)
40°C/75%HR (accelerated)</td><td>None</td><td>Do not refrigerate or freeze</td></tr>
<tr><td>25°C/60%HR (long term)
30°C/60 or 65%HR (intermediate) or
30°C/65%HR (long term)</td><td>Do not store above 30°C
Or store below 30°C</td><td>Do not refrigerate or freeze</td></tr>
<tr><td>25°C/60%HR (long term)</td><td>Do not store above 25°C
Or store below 25°C</td><td>Do not refrigerate or freeze</td></tr>
<tr><td>5°C ± 3°C (long term)</td><td>Store in a refrigerator
Or store and transport refrigerated</td><td>Do not freeze</td></tr>
<tr><td>Below zero</td><td>Store in a freezer or store and transport frozen</td><td></td></tr>
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<tr>
<td>3.2. P.8.1</td>
<td>Stability Summary and Conclusion</td>
<td>The types of studies conducted, protocols used, and the results of the studies should be summarized. The</td>
<td>Q1A, Q1D, Q1B, Q3B,</td>
<td>IF
• Long-term and accelerated data showing little or no change over time and little or no variability</td>
<td></td>
</tr>
</table>

		summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life. Stability information from accelerated and long-term testing should be provided on at least three primary batches of each strength manufactured and packaged in each type of container closure system proposed for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. For batches that are than pilot scale, the chemistry of degradation and performance indicating tests (e.g., dissolution) should be scale independent. The small-scale batch may be a development batch manufactured in non-GMP research plant, provided it is representative of the impurity profile and functional characteristics of the larger batches.	**and Q5C, Q6A, Q1C, Q1E, TRS Number 953 - Annex2**	**Then** • 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).** **We must have the results of stability table with title or heading the name of the manufacturer or quality lab control and checked by quality control manager and approved by quality assurance manager with signatures and stamps**.	

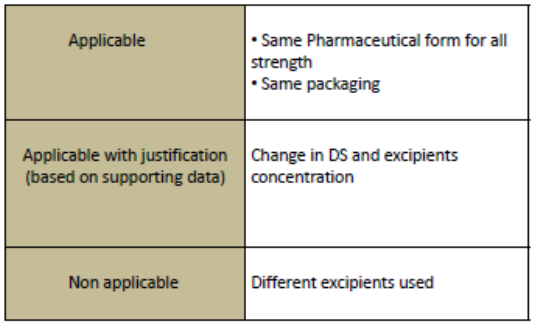
		A transportation study is recommended to support the proposed strategy for shipping and handling the drug product specially when posing a higher risk (e.g., sterile product).			
3.2. P.8.2	Post-approval Stability Protocol and Stability Commitments.	The post-approval stability protocol and stability commitment should be provided.	**Q1A and Q5C**	**IF** • At the time of submission: At least 2 pilot scale batches + 1 "lab scale " □ Accelerated studies up to 6 months □ Long term up to 12 months **Then** 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.**	

Quality Module for Drug Registration Evaluation Report

Of the part P of module 3

3.2. P.8.3	Stability Data	Results of the stability studies should be presented in an appropriate format (e.g., tabular, graphical, 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… -Hard gelatin capsules: brittleness, dissolution (or disintegration if justified), water content and microbial bioburden. -soft gelatin 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,	Example of stability data sheet:

				microbial bioburden, extractables, leachable, polymorphic conversion when applicable. Additional tests for suspension include redispersability, rheological properties, mean size, and distribution of particles. – Small-Volume Parenteral: 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, dispersibility, and rheological properties. Emulsions for injection should include phase separation, viscosity, mean size, and distribution of dispersed globules. - Large-Volume Parenteral: 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 bioburden, and water loss should be tested. For ophthalmic and otic products additional attributes should include sterility, particulate matter and extractables.	

				-Metered-Dose inhalers and Nasal Aerosols: content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, microbial bioburden, valve delivery, extractables, 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 

Quality Module for Drug Registration Evaluation Report

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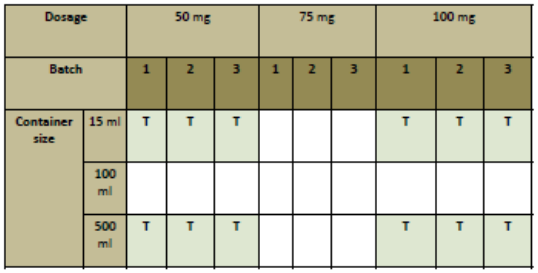
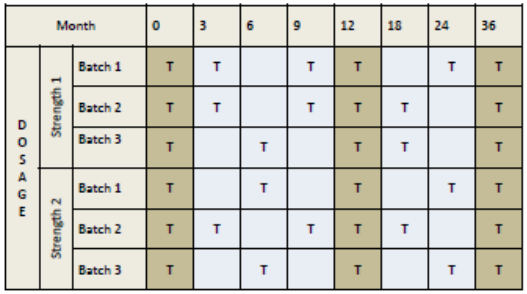
				And: **Matrixing** Design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time, point, another subset of samples for all factor combinations would be tested. The design assumes 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.	 Matrixing 

3.2. P.8.3.1	Real Stability Data.				NB: If we have real stability data for only two 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 degradant 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.	

Quality Module for Drug Registration
Evaluation Report

Of the part P of module 3

Critical Remarks:

Some missing information to provide and clarifications needed in the Module 3-part P:

-There is no formulation development
-We do not know the innovator product and no comparison with it?
-We must have trials to choose the best formula.
-No process manufacturing development.
-In the Process Validation: Why they put: "For Information only"?

-In batch formula: We do not know the batch size?

-For solid dosage forms (tablets and capsules): No dissolution tests in three different pH? (1.2, 4.5 and 6.8 for example)
-Process validation protocol and /or report.
-They say: uncontrolled copy for the results?
They say on the results, the specifications and the procedures are Photocopy for reference only!
-For parenteral products in powder (lyophilized) with solvent, the solvent module 3-part P is missing.
-For compatibility: stability after dilution or reconstitution is missing.
Also, compatibility with solvents as infusions?

-We need COA's for reference standards from suppliers.

- COA's from suppliers of packaging Materials and quality department lab must be provided.
- The post-approval stability protocol and stability commitment are not provided.

Quality Module for Drug Registration
Evaluation Report

Of the part P of module 3

- Stability studies done on three pilot batches less than 10% of industrial batches.

- We have the stability data for two pilot batches only not three.

- The stability data are presented as tables, but they are not signed and no date?
- No title on the stability data of quality control department?
- The stability data are stamped with export stamp; they are not signed by quality control lab.

- We must have the results of stability table with title or heading the name of the manufacturer or quality lab control and checked by quality control manager and approved by quality assurance manager with signatures and stamps. Not only the stamp of export directorate?

- **Several names of the drug product in the dossier which make confusion.**
- **Relation between the manufacturers or production sites is not clear, when there is more than one site.**
- **We have not stability data results for accelerated conditions.**
- **Some subdivisions are empty.**
- **the attachments files are not provided.**

Recommendations:

the part P of module 3 will be:

“Approved” or “Rejected” or **on "Pending"** for clarifications and more information or details.

Quality Module for Drug Registration Evaluation Report

Of the part P of module 3

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 acceptances 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.

Quality Module for Drug Registration Evaluation Report

Of the part P of module 3

Examples of stability data sheet:

STABILITY ANALYTICAL REPORT

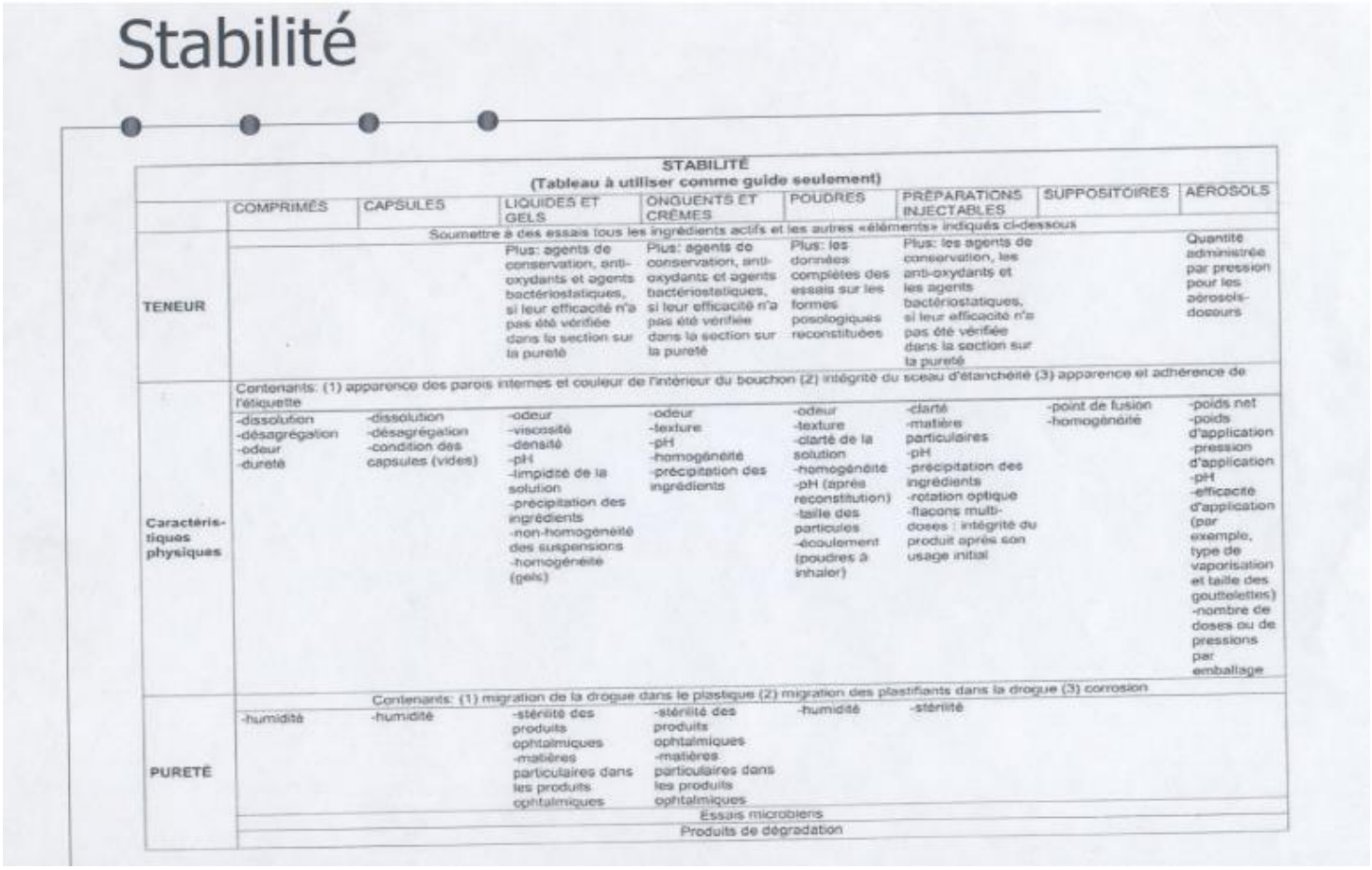
Sample Name: Lot#: Study #: Protocol #: Study Start Date: Study Purpose:	Manufacturing Date: Manufacturing Site: Expiration Date: Testing Site: Packaging Site:	Storage condition: Sample Orientation (if applicable): Packaging Information: Packaging Date:

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: _____

Quality Module for Drug Registration Evaluation Report

Of the part P of module 3



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							