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ASEAN – QUALITY REQUIREMENTS FOR GENERIC FILLING

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ASEAN – 'QUALITY' REQUIREMENTS FOR GENERIC FILLING

Process Validation Requirements for ASEAN Countries

ASEANrequires Process Validation report on three consecutive production batches which should include:

- Summary
- Introduction Batches used for validation
- Manufacturing equipment
- Critical process steps and parameters Acceptance criteria
- Sampling plan
- Tabulation of the test results
- Batch Analysis
- Evaluation of data
- Statistical process control analysis
- Evaluation of data including comparison against Acceptance criteria
- Discussion on deviations and out of specification results
- Conclusion and recommendations

If Validation report for three consecutive batches is not available then the below said can be submitted:

A. Development pharmaceutics report, which should cover

a) Rationale for selecting the dosage form

b) Choice of product components which should include Active substance and Excipients

- Compatibility considerations
- Physico -chemical characteristics

c) Formulation of product

- Use of overages
- Effect of pH and other parameters
- Effect of antioxidants, solvents, chelating agents,
- Type/concentration of anti-microbial agentsetc
- Stability, homogeneity and batch reproducibility considerations

d) Choice of manufacturing processes, including sterilization procedures

e) Choice of containers and packaging materials which includes

- Container-closure integrity

Sorption and leaching issues

B. Validation report on 1 pilot batch or validation scheme with a commitment by theapplicant that the Process validation will be done on three consecutive production batches before the drug is marketed.

Bioequivalence Requirements for ASEAN

1. Demographic Requirement

AGE	BMI	SEX
18-55	18 and 25 kg/m^2	Both

2. Diet and Fluid Requirement

Diet	Fluid Intake
No food is allowed for at least 4 hours post dose. Meals taken after dosing should be Standardized in regard to composition and Time of administration during an adequate period of time	Test and reference products should be administered with a standardized Volume of fluid.
In Fed Conditions	
In fed conditions, the timing of administration of the	Water is allowed as desired except for one hour before

drug product in relation to food intake is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, it is Recommended that subjects should start the Meal 30 minutes prior to administration of the drug product and eat this meal Within 30 minutes.	and one hour after drug administration. Hot drink or juice may be provided after 3 hours of drug administration.

- Standard meals for each study Periods can be provided no less than 4 hours after drug administration

Requirements for Fasting Conditions
At least 8 hours prior to administration of the products. If the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food intake related to food interaction effects the study should be designed accordingly.

Fed Study Requirements
Not Required.

Stability Studies Requirements
The stability studies to be conducted on drug substances or drug product depends on the climatic zones in which that region comes:

Climatic Zones
Zone I: Temperate zone
Zone II: Mediterranean/subtropical zone
Zone III: Hot dry zone
Zone IV:
a) Hot humid/tropical zone
b) ASEAN testing conditions hot/higher humidity

Stress Testing Requirements
Drug Substances
Majorly focus on the stability testing requirements for drug products.

Drug Product
Stress testing conditions is 40°C ± 2°C/75% RH ± 5% RH which is same as accelerated storage conditions.

Photo-Stability Testing Requirements
For Drug Substances
ASEAN guidelines majorly focus on the stability testing requirements for drug products. The drug products covered in this guideline include Generics and Variations along with NCEs. But if in the case (Photosensitive Drug substances) if there is a need of testing then appropriate, can be followed according to the ICH guidelines.

For Drug Products
Photo stability testing should be conducted on at least one primary batch of the drug product if appropriate.

Long-Term Stability Testing Requirements
For Drug products
Since ASEAN is placed under group IV-B of ICH climatic Zones, it requires the submission of long term stability data at 30°C ± 2°C/75% RH ± 5% RH and should cover minimum 12 months duration on at least two primary batches for conventional dosage form and stable drug substances and minimum 3 batches for critical dosage form or unstable drug substances.

Testing Frequency
Testing frequency for the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through them proposed shelf life.

Batch Selection
At the time of submission, stability data should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing and where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

There are two conditions in ASEAN guideline for selection of Batches
I. For conventional dosage forms (e.g., immediate release solid dosage forms, solutions) and when the drug substances are known to be stable, stability data on at least two pilot scale batches are acceptable.
II. For critical dosage forms (e.g., prolonged release forms) or when the drug substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should beat least of a pilot scale; the third batch may be smaller.

In ASEAN countries storage condition is also provided for the study, based on the type of container, which is as follows:

- Products in primary containers permeable to water vapour - 30°C ± 2°C/75% RH ± 5% RH
- Products in primary containers impermeable to water vapour - 30°C ± 2°C/RH not specified

Accelerated Testing Requirement
In accelerated stability tests, a product is stored at exaggerated storage conditions (such as temperature, humidity, p^H). Temperature is the most common acceleration factor used for pharmaceuticals because its relationship with the degradation rate is well known. Humidity and pH also have acceleration effects. Accelerated testing is designed to increase the rate of

chemical degradation or physical change of a drug product by using these studies can be used to support the long-term stability studies.

For Drug products: The Accelerated Testing should cover a minimum of 6 months duration. For the Accelerated testing the storage conditions are given as 40°C ± 2°C/75% RH ± 5% RH.

Testing Frequency

At the accelerated storage condition, a minimum of three time points, including the initial and final time points.

COPARISION OF QUALITY REQUIREMENTS

PART-II	QUALITY			Philippines	Myanmar	Cambodia	Malaysia	Indonesia
Section A:	**Table of Contents**			Yes	Yes	Yes	Yes	Yes
Section B:	**Quality overall Summary**							
	S	**DRUG SUBSTANCE**						
	S1	**General Information**						
		1.1	Nomenclature	Yes	Yes	Yes	Yes	Yes
		1.2	Structural Formula	Yes	**Absolute stereochemistry**	Yes	Yes	Yes
		1.3	General Properties	Yes	Yes	Yes	Yes	Yes
	S2	**Manufacturer**						
		2.1	Manufacturer (s)	Yes	Yes	Yes	Yes	Yes
		2.2	Description of Manufacturing Process and Process Controls	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		2.3	Control of Materials	Yes	Yes	Yes	Yes	Yes
		2.4	Control of Critical steps and Intermediates	Yes	Test and acceptance criteria with Justification including experimental data	Not required for generic products	Yes	Yes
		2.5	Process validation and/or Evaluation	Yes	Yes	Yes	Yes	Yes
		2.6	Manufacturing Process Development	Yes	Yes	Yes	Yes	Yes
	S3	**Characterization**						
		3.1	Elucidation of structure and other characteristics	Yes	Yes	Yes	Yes	Yes
		3.2	Impurities	Yes	Yes	Yes	Yes	Yes
	S4	**Control of Drug Substance**						
		4.1	Specification	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		4.2	Analytical procedures	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		4.3	Validation of analytical procedures	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		4.4	Batch analysis	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		4.5	Justification of specification		For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
	S5	**Reference standards or Materials**		Yes	Yes	Yes	Yes	Yes
	S6	**Container Closure System**		Yes	Yes	Yes	Yes	Yes
	S7	**Stability**		Yes	Yes	Yes	Yes	Yes
	P	**DRUG PRODUCT**						

	P1	**Description and composition**		Yes	Yes	Yes	If colorants are there we need to give composition.	If colorants are there we need to give composition.
	P2	**Pharmaceutical development**						
		2.1	Information on Development studies	Yes	Yes	Yes	Yes	Yes
		2.2	Components of the drug development Studies		Yes	Yes	Yes	Yes
		2.3	Finished product		Yes	Yes	Yes	Yes
		2.4	Manufacturing Process Development		Yes	Yes	Yes	Yes
		2.5	Container Closure System		Yes	Yes	Yes	Yes
		2.6	Microbiological Attributes	We have to provide physical and chemical properties from PDR.	Yes	Yes	Yes	Yes
		2.7	Compatibility	We have to provide comparative dissolution data for pilot batch	Yes	Yes	Yes	Yes
	P3	**Manufacturer**						
		3.1	Batch Formula	Yes	Yes	Yes	Yes	Yes
		3.2	Manufacturing process and process control	In addition we have to provide equipment details and quantity of excipients and API in Manufacturing process.	Yes	Yes	Complete manufacturing process in detail for each and every step with quantities of each material along with equipment's used.	Yes
		3.3	Control of Critical steps and intermediates	Have to provide in process checks as per process validations, BMRs,	Yes		IPQC parameters with frequency of testing and quantity of sample taken for analysis.	Yes
		3.4	Process validation and/or evaluation	Have to provide brief details	Yes	Yes	3 batches data of PVP & PVR	3 batches data of PVP & PVR
	P4	**Control of excipients**						
		4.1	Specifications	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	COA of excipients should enclose.
		4.2	Analytical procedures	Yes	Yes	Yes	Yes	Yes

		4.3	Excipients of Human and Animal Origin	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		4.4	Novel Excipients	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		Control of finished product		Yes	Yes	Yes	Specification should be typed along with pharmacopoeia reference of each test.	Yes
		5.1	Specifications	Yes	Yes	Yes	Yes	Yes
		5.2	Analytical procedures	Yes	Yes	Yes	FP chromatograms as required	Yes
	P5	5.3	Validations of analytical procedures	Yes	For NCE/Biotech/New for Myanmar- experimental data	Yes	Complete AMV raw data is mandatory	Complete AMV raw data is mandatory
		5.4	Batch analysis	Have to provide raw data for samples COA and API COA with raw data	Yes	Yes	Yes	Yes
		5.5	Characterization of impurities	Yes	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes
		5.6	Justification of specification(s)	Yes	Yes	Yes	Yes	Yes
	P6	**Reference standard or materials**		Yes	Yes	Yes	Yes	Along with working standard we need to provide Reference standard COA.
	P7	**Container closer system**		Yes	Yes	Yes	Photo of the product (complete Blister + carton)	Should enclose Specification, STP & COA for primary, secondary & tertiary packing materials.
	P8	**Stability**		Yes	Yes	Yes	3 batches with Accelerated at 40/75 and long term at 30/75 condition. If we don't have shelf life stability we need to provide Stability commitment letter for 24 months data.	3 batches with Accelerated at 40/75 and long term at 30/75 condition.
	P9	**Product interchangeability Equivalence evidence**		Yes	Invitro- Comparative dissolution In Vivo- Bioequvalence study	Yes	Complete BE study report along with CDP in three way	Complete BE study report. We have to conduct CDP if the

						(test Vs our innovator and our innovator Vs Malaysia innovator)	Indonesia originator manufacturing site is different with our BE innovator manufacturing site.
Section	**Section C**						
S	**DRUG SUBSTANCE**						
S1	**General Information**						
	S1.1	Nomenclature	Yes	Yes	Yes	Yes	Yes
	S1.2	Structural Formula	Yes	Yes	Yes	Yes	Yes
	S1.3	General Properties	Yes	Yes	Yes	Yes	Yes
S2	**Manufacturer**						Yes
	S2.1	Manufacturer (s)	Yes	Yes	Yes	Yes	Yes
	S2.2	Description of Manufacturing Process and Process Controls	Yes	Yes	Yes	Yes	Yes
	S2.3	Control of Materials	Yes	Yes	Yes	Yes	Yes
	S2.4	Controls of critical steps on intermediates	Yes	Yes	Yes	Yes	Yes
	S2.5	Process validation and/or evaluation	Yes	Yes	Yes	Yes	Yes
	S2.6	Manufacturing process development	Yes	Yes	Yes		Yes
S3	**Characterization**						
	S3.1	Elucidation of structure and other characteristics	Yes	Yes	Yes	Yes	
	S3.2	Impurities	Yes	Yes	Yes	Yes	
S4	**Control of Drug Substance**						
	S4.1	Specification	Yes	Yes	API spec should be typed along with pharmacopieal reference.	Yes	
	S4.2	Analytical procedures	Yes	Yes	Yes	Yes	
	S4.3	Validation of analytical procedures	Yes	Yes	Yes	Yes	
	S4.4	Batch analysis	Yes	Yes	Yes	Yes	
	S4.5	Justification of specification	Yes	Yes	Yes	Yes	
S5	**Reference standards or Materials**						
	S6	**Container Closure System**	Yes	Yes	Yes	Yes	
	S7	**Stability**	Yes	Yes	Yes	Yes	
	P. DRUG PRODUCT						
P1	**Description and composition**		Yes	Yes	Yes	Yes	Yes
P2	**Pharmaceutical development**						

P 2.1	Information on development studies			Yes		Yes	Yes	
	P2.2	Components of the Drug Product		Yes		Yes	Yes	
	P. 2.2.1	Active ingredients	Yes	Yes		Yes	Yes	Yes
P.2.2.1	Active ingredients		Yes		Yes	Yes		
P.2.2.2	Excipients			Yes		Yes	Yes	Yes
P2.3	**Finished product**	Yes		Yes		Yes	Yes	Yes
P2.3.1	Formulation Development			Yes		Yes	Yes	Yes
P2.4	Manufacturing process development			Yes		Yes	Yes	Yes
P2.5	Container closer system			Yes		Yes	Yes	
P2.6	Microbiological attributes	We have to provide physical and chemical properties from PDR.		Yes		Yes	Yes	Yes
P2.7	Compatibility	We have to provide comparative dissolution data for pilot batch		Yes		Yes	Yes	Yes

	P3Manufacture		Yes		Yes	Yes	Yes	
	P 3.1	Batch Formula		Yes				
	P 3.2	Manufacturing Process And Process Control	In addition we have to provide equipment details and quantity of excipients and API in Manufacturing process.	Yes	Yes		Yes	Yes
	P 3.3	Control of Critical steps and intermediates	Have to provide in process checks as per process validation, BMRs,	Yes	Yes		Yes	Yes
	P 3.4	Process validation and/or Evaluation	Have to provide brief details	Yes	Yes		Yes	Yes
	P4 Control of excipients							
	P 4.1	Specifications	Yes	Yes	Yes	Yes	Yes	
	P 4.2	Analytical procedures	Yes	Yes	Yes	Yes	Yes	
	P 4.3	Excipients of Human and Animal Origin	Yes	Yes	Yes	Yes	Yes	
	P4.4	Novel Excipients	Yes	Yes	Yes	Yes	Yes	
	P5Control of finished product							
	P 5.1	Specifications	Yes	Yes	Yes	Yes	Yes	
	P 5.2	Analytical procedures	Yes	Yes	Yes	Yes	Yes	
	P 5.3	Validations of analytical procedures	Yes	For NCE/Biotech/New for Myanmar-experimental data	Yes	Yes	Yes	
	P 5.4.	Batch analysis	Yes	Yes	Yes	Yes	Yes	

	P 5.5	Characterization of impurities	For NCE/Biotech/New for Myanmar	Yes	Yes	Yes	Yes
	P 5.6	Justification of specifications	Yes	Yes	Yes	Yes	Yes
	P 6	**Reference standard or material**	Yes	Yes	Yes	Yes	Yes
	P 7	**Container closer system**	Yes	Yes	Yes	Yes	Yes
	P 8	**Stability**	yes	yes	Yes	Yes	Yes
	P 8.1	Stability summary and conclusions	Yes	Yes	yes	Yes	
	P 8.2	Post approval Stability protocol and stability commitment	Yes	Yes	Yes	Yes	Yes
	P8.3	Stability data	Yes	Yes	yes	Yes	Yes
	P 9	**Product interchangeability**	In vitro- Comparatie dissolution In Vivo- Bioequvalence study	Yes	Yes	Yes	Yes

CONCLUSION

ASEAN is a model of a regional integration initiative undergoing dynamic development and changes. It has become one of the most successful regional groupings of developing nations, to promote cooperation, and trade in the face of wider international competition and economic upheavals. Since its inception four decades ago, ASEAN is now at a crucial stage in transforming itself from a regional Association into a dynamic, integrated economic Community.

ASEAN's drug regulatory authorities and industry have worked very close regionally but also increasingly with global organizations to develop a number of harmonized documents. These are the common submission dossier known as the ASEAN Common Technical Dossier and the ASEAN Common Technical Requirements, which are steadily evolving.

Largely they have been realized already, the next step will be to focus on mutual recognition of pharmaceutical registrations and implementing a harmonized placement system. There is still much work to be carried out in the implementation.

The future will show if this can be achieved by the versioned end goal of economic community in 2015. Already now ASEAN can be regarded as an example of having developed a successful pharmaceutical harmonization scheme. ASEAN is increasingly playing a major role in pharmaceutical industry.