National Pharmaceutical Control Bureau
MINISTRY OF HEALTH MALAYSIA

Process Validation (PV)

World Health Organization
WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

PIC/S
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

QUALITY SYSTEM
SIRIM
Certified to ISO 9001:2000
Cert. No: AR 2293

STANDARDS MALAYSIA
ACCREDITED LABORATORY
MS ISO/IEC 17025:2005
NO: SAMM 450

Overview on ASEAN Guideline on PV Requirements

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National Pharmaceutical Control Bureau
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Overview on ASEAN Guideline on PV Requirements

Topics of the Session

1. **Process Validation Definition by ASEAN PV Guide**
2. **PV Data Submission Requirement**
3. **Content of Development Report**
4. **Content of Validation Scheme**
5. **Content of Validation Report**
6. **Process Validation type/ approach**
7. **Notes on Retrospective Validation & Concurrent Validation**
8. **Change control**

Overview on ASEAN Guideline on PV Requirements

1. Process Validation Definition by ASEAN PV Guide

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

1. Process Validation Definition by ASEAN PV Guide

Process Validation is a means of ensuring that manufacturing processes are capable of consistently producing a finished product of the required quality. It involves providing documentary evidence that key steps in the manufacturing process are consistent and reproducible. A validated manufacturing process is one that has been proven to do what it purports or is presented to do.

The term 'validation' is intended to apply to final verification at the production scale.

Typically a minimum of three consecutive production batches should be successfully validated prior to the marketing of the product.

2. PV Data Submission Requirement

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

2. PV Data Submission Requirement

Option 1:

The submission should include a validation report on three consecutive successfully validated production batches.

Option 2:

In circumstances where submission of data on 3 consecutive production batches is not feasible at the time of application, the following can be submitted to DRA to obtain marketing approval.

Document required:

a) Development pharmaceutics report; and

b) Validation data on 1 pilot batch with validation scheme on production scale batches.

2. PV Data Submission Requirement

In addition, the applicant is required to fulfill the following standard commitments:

- To undertake that 3 consecutive full production batches are successfully validated before the product is marketed, subjected to concurrence by the DRA
- To submit the report to the Drug Regulatory Authority (DRA) within a specified time frame, or to make the information from these studies available for verification post authorization by DRA according to national procedure.

Note for option 2:

Option 2 is not recommended for biological/biotechnological product, product manufactured using non standard method of manufacture, such as non-standard methods of sterilization and aseptic processing, and other specialized products such as modified release dosage form.

2. PV Data Submission Requirement

Updates for option 2:

a) Development pharmaceutics report; and

b) Validation data on 1 pilot batch OR validation scheme on production scale batches.

(Version 2.0: Draft version for 18th ACCSQ-PPWG meeting (Jun 2011))

CHANGE TO:

a) Development pharmaceutics report; and

b) Validation data on 1 pilot batch WITH validation scheme on production scale batches.

(Version 3.0: Version adopted in 19th ACCSQ-PPWG meeting (Jul 2012))

2. PV Data Submission Requirement

Why is validation data on 1 pilot scale batch needed for Option2?

1. The role of pilot scale batches is to provide data **predictive** of the production scale product. It provides the link between process development and industrial production of the product.

If pilot batch data not predictive of production scale (non-standard method), option2 is not applicable

2. PV Data Submission Requirement

ABC Manufacturing Sdn Bhd
8, Jalan Telawi,
Kawasan Perindusrian Bangi,
Selangor

30 Julai 2014

National Pharmaceutical control Bureau,
Ministry of Health,
Jalan University,
Petaling Jaya,
Selangor
Dear Sir/Madam

LETTER OF COMMITMENT
RE : Process Validation for New Product Registration
Product : ABC Amlodipine 5 mg Tablets

We wish to inform you that we will undertake that 3 consecutive productions batches are successfully validated before the product is marketed.

Your consideration and cooperation is much appreciated.
Thank you.

Your Sincerely,
ABC Manufacturing Sdn Bhd

Ms Khoo Sze Ni
Manager,
Regulatory Affair

Example of commitment letter

2. PV Data Submission Requirement

Option 3:

- For products that have been approved by a reference agency; the applicant is required to provide a declaration statement to the effect that the same pre-approval dossier pertaining to process validation that have been submitted to the reference regulatory agency are submitted to DRA for evaluation.
- Under certain circumstances where validation documents may not form part of the pre-approval dossier, the DRA may request for Validation Report or Validation Scheme.
- In addition the applicant is required to undertake that 3 consecutive full production batches are successfully validated before the product is marketed and to submit the report to DRA upon request.

2. PV Data Submission Requirement

Annex D Glossary

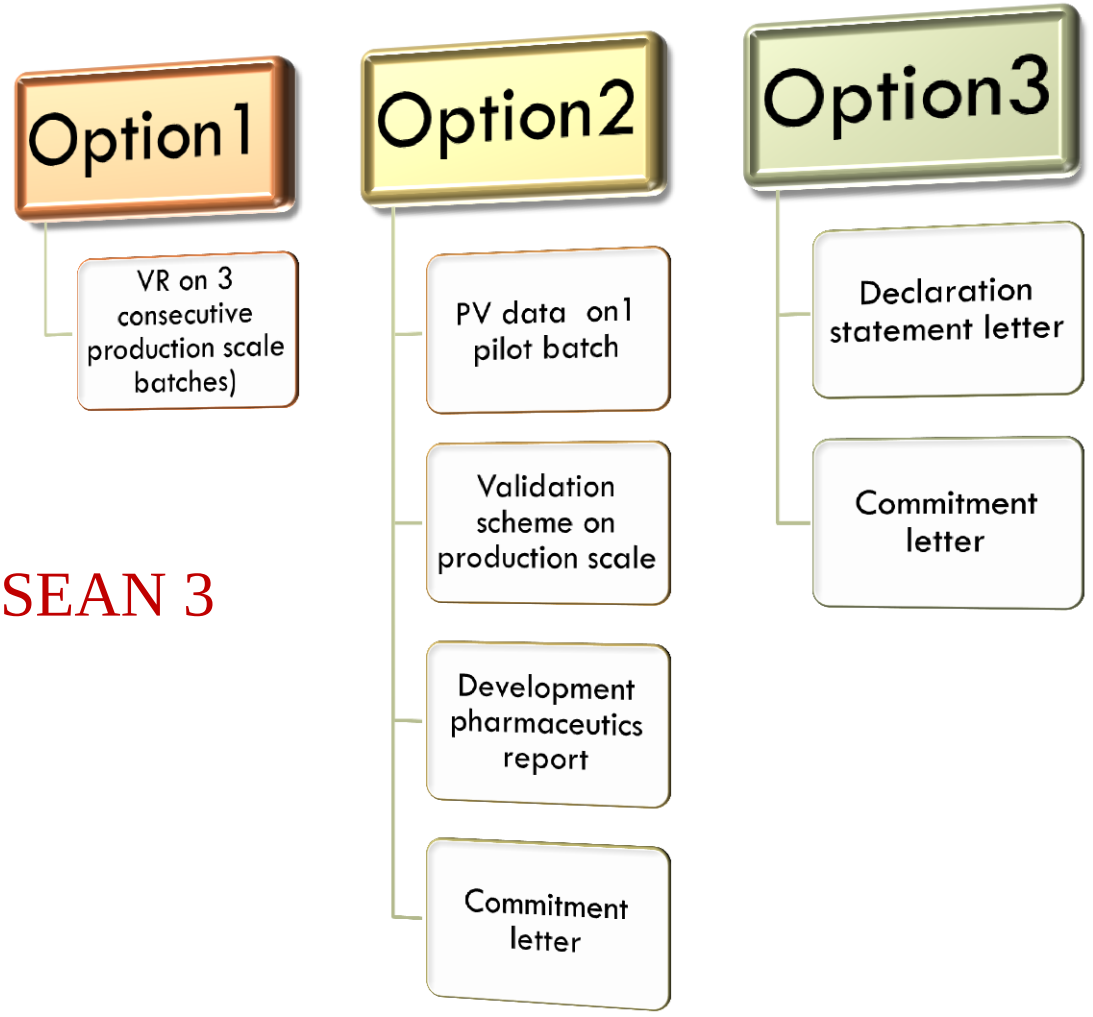
Production Batch

A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Pilot batch

These may be used in the development or optimization stage. Pilot batch size should correspond to at least 10% of the future industrial-scale batch. (For oral solid dosage form: 10% or 100,000 units whichever is the greater otherwise justified)

2. PV Data Submission Requirement



Summary of ASEAN 3 approach

2. PV Data Submission Requirement

Types of document required during data submission:

- Pharmaceutical Development Report
- Process Validation Scheme
- Validation Report

3. Content of the Development Report

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

3. Content of the Development Report

The report on pharmaceutical development or development pharmaceuticals should address the following:

a) Rationale for selecting the dosage form

b) Choice of product components (active substance and excipient)
   - Compatibility consideration
   - Physico-chemical characteristic

c) Formulation of product
   - Use of overages
   - Effect of pH and other parameters
   - Effect of antioxidants, solvents, chelating agents, type/concentration of antimicrobial agents, etc
   - Stability, homogeneity and batch reproducibility considerations

3. Content of the Development Report

d) Choice of manufacturing process, including sterilization procedures

e) Choice of containers and packaging materials

- Container-closure integrity
- Sorption and leaching issues

f) Microbial attributes of dosage form

g) Compatibility of drug product with diluents or dosage device (e.g precipitation of drug substance in solution, sorption on injection vessels etc) throughout shelf life of drug product

4. Content of Validation Scheme

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

4. Content of Validation Scheme

Process Validation Scheme outlines the formal process validation studies to be conducted on the production scale batches. It should contain, but not limited to, the following:

a) A description of the manufacturing process with a schematic drawing or flow chart
b) A summary of the critical processes, control variables and justification for their selection
c) Finished product specification (release)
d) Details of analytical methods (reference to the dossier)

4. Content of Validation Scheme

e) In process controls proposed with acceptance criteria
f) Additional testing intended to be carried out (e.g. With proposed acceptance criteria and analytical validation appropriate)
g) Sampling plan – where, when and how samples are taken
h) Details of methods for recording and evaluation of results
i) Proposed time frames for carrying out the studies
j) Critical equipment/facilities to be used (for example, measuring/recording equipment together with its qualification and calibration status) (updates: Version 3.0: Version adopted in 19th ACCSQ-PPWG meeting (JUL 2012)

5. Content of Validation Report

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

5. Content of Validation Report

The content of report should include, but not limited to the following:

a) Summary

b) Introduction

c) Batches (for example, date of manufacture, batch size(used for validation

d) Manufacturing equipment

e) Critical process steps and parameters

f) Acceptance criteria

g) Sampling plan

5. Content of Validation Report

h) Tabulation of the test result

i) Batch analysis

j) Evaluation of data, including statistical process control analysis

k) Evaluation of data, including comparison against acceptance criteria

l) Discussion on deviations and out of specification result

m) Conclusion and recommendation

**Where appropriate a description of the manufacturing process with a schematic drawing or flow chart may be required by the DRA

5. Content of Validation Report

a)b) Summary and Introduction

Overall Summary

The manufacturing process for Amlodipine 5 mg Film Coated Tablets uses a standard high shear wet granulation approach. Granules are dried, blended, compressed using rotary compression machine and the coated to produce Amlodipine 5 mg Film Coated Tablets.

The formulation used for three process validation batches (M10001, M10002. M10003) manufactured using MPM Dales API at ABC Manufacturing Sdn Bhd is qualitatively and quantitatively identical to the proposed commercial formulation presented in the Module 3.2.P.6 of the registration dossier and the manufacturing process is representative of hat proposed for commercial production.

The process validation carried out demonstrates that the manufacturing process for Amlodipine 5 mg Film Coated Tablets will consistently yield a product which meets the specifications.

Objective

The objective of this validation programme wad to validate the manufacturing process used in the manufacture of Amlodipine 5 mg Film Coated Tablets at batch size 300000 tablets

5. Content of Validation Report

c) Batches (date of manufacture, batch size) used for validation

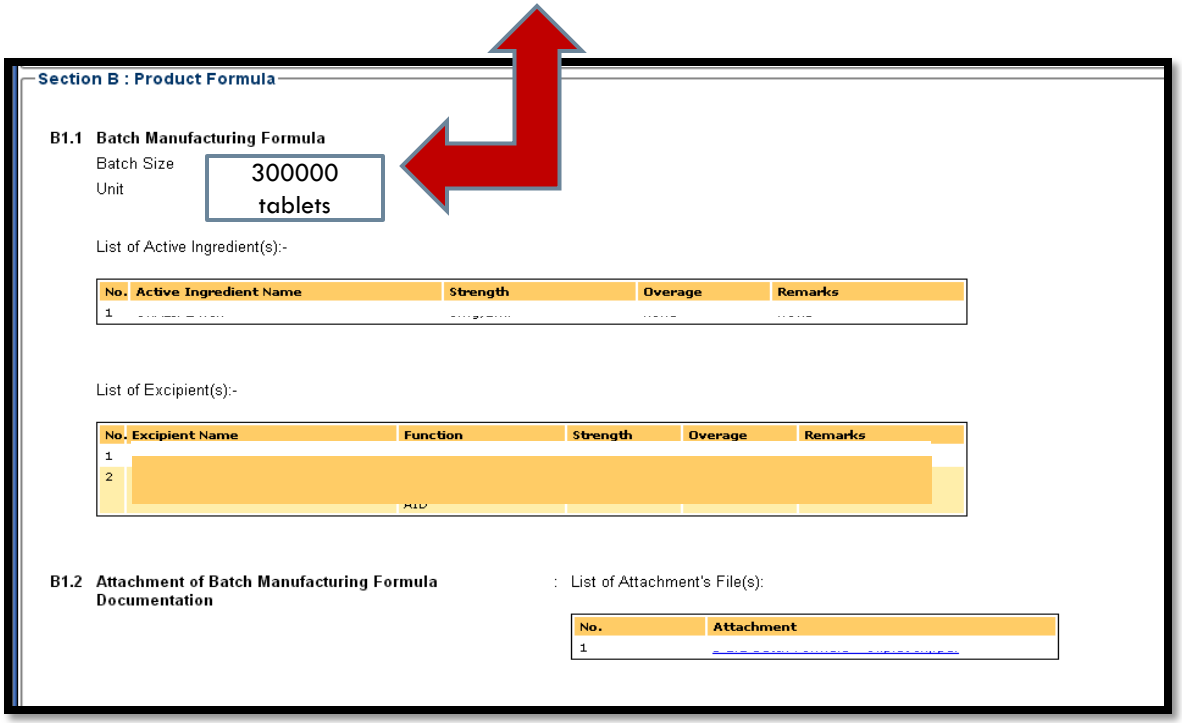
Batch details:

Batch number	Strength	Manufacturing date	Batch size
M10001	300 mg	6 January 2011	300000 tablets
M10002	300 mg	7 January 2011	300000 tablets
M10003	300 mg	8 January 2011	300000 tablets

Please ensure that the proposed batch size in B1.2 is tally with validated batch size!!

5. Content of Validation Report

The validated batch size should be the same as the commercial production batch size proposed in B1.1 & B1.2



What is an acceptable validation lot size?

The validation lot size should be the same size as an intended standard commercial scale lot. If a range in lot size is proposed for commercial process, the variation in lot size should be demonstrated not to adversely impact the quality characteristics of the finished product.

5. Content of Validation Report

d) Manufacturing equipment

Equipment List

Equipment type	Id number	Manufacturer	Capacity	Model no.	Class
Granulator	PMG-06	PMS Thailand	300kg	MG 300	?
Fluid Bed Drier	FBD-06	Narong Thailand	300 kg	Narong FBD	?
Blender	PBL-06	Sen Jin	100-200L	V-Blender 200	?
Tablet press	PTP-06	Manesty	N/A	PT 300	?
Thai coater-49’	PTC-06	PMS Thailand	N/A	150	?
Blister machine	BLM-06	Medisel (Germany)	N/A	CP 400	?

Please ensure that the class (operating principle) of each major equipment is indicated!!

Refer Annex A1: Guidance on Process Validation Scheme For Solid Oral Dosage products

5. Content of Validation Report

e) Critical process steps and parameters

Critical Process step and parameter

Process	Equipment	Process parameter	
Granulation	Granulator	Time setting	20minutes±3minutes
		Impeller & chopper	On/ off
Drying	Fluid Bed Dried	Drying temp	45°C±5°C
		Drying time	10 minutes
Blending	Blender	Blending speed	15 rpm
		Blending time	5 minutes
Lubrication	Blender	Blending time	3 minutes
Tablet compression	Tablet press	Individual weight	150 mg ± 7.5%
		Thickness	4.00mm0.04mm
		Friability	NMT 1.o%
		Hardness	4kP -20kP
		Tabletting speed	Minimum: 15 rpm Optimum: 20 rpm Maximum: 25 rpm
Coating	Thai coater-49’	Inlet temperature	85°C-95°C
		Outlet temperature	55°C-65°C
		Spray rate	0.5-4 rpm
		Air flow rate	40-100g/min

Please ensure that the propose critical process parameter in P3.2 is tally with the validated critical process parameter during PV study

5. Content of Validation Report

P3.2 Manufacturing Process and Process Control

GRANULATION
Add the Amlodipine and the binder solution in the granulator. Set the time for granulation 20 minutes with chopper off and impeller on.
DRYING
After granulation, dry the granules in FBD for 10 minutes with drying temperature 45±5°C until reach LOD 2.00-5.00%w/w
BLENDING
Blend the granules in the V-blender for 5 minutes and add Magnesium Stearate for lubrication and blend for 3 minutes.
TABLET COMPRESSION
Compress the bulk blend using tablet press machine at speed 15-25 rpm.
FILM COATING
Prepare the coating solution and set the coating pan with inlet temp. 85-95°C and spray rate 0.5-4.0 rpm.
PACKING
Pack the film coated tablet into the blister pack.

Example of description of manufacturing process in quest system

5. Content of Validation Report

P3.2 Manufacturing Process and Process Control

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical step and points at which process controls, intermediate tests or final product controls are conducted should be identified.

- The full description of manufacturing process must sufficient details to cover the essential point of each stage of manufacture
- For sterile product the description includes preparation and sterilization of components (ie, container, closures, etc)

(THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE PART II: QUALITY)

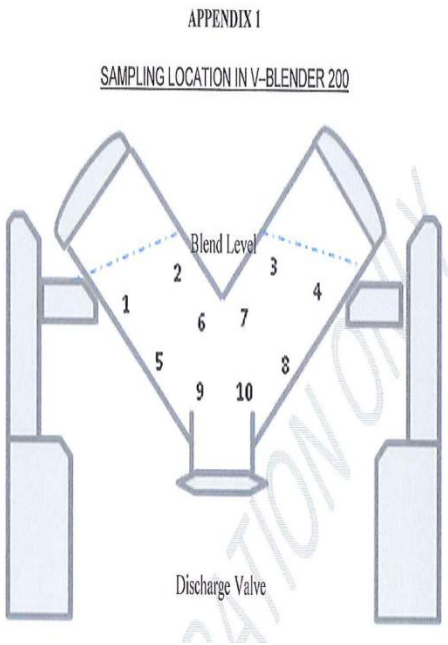
5. Content of Validation Report

f) Acceptance criteria

Process	Test	Acceptance criteria
After Drying	Moisture content	2.00-5.00%w/w
After Blending	Blending uniformity	85-115%, RSD ≤6.0%
	Bulk blend	Info only
	Particle size	Info only
	Moisture content	2.00-5.00% w/w
Tablet compression	Appearance	White round shape tablet
	Tablet thickness	4.00mm±0.40mm
	Individual weight	150 mg±7.5%
	Hardness	4-20 kp
	Friability	NMT 1.0%
	Disintegration test	NMT 15 minutes
	Assay	95-105% of labelled amount
	Uniformity of content	The acceptance value of the first 10 dosage unit is ≤15%
Coating	Appearance	Pink film coated round shape tablet
	Assay	95-105% of labelled amount
	Dissolution	NLT 80% in 30 minutes
	Related substance	Impurity D –NMT 0.1% Total Impurity –NMT 1.0%

5. Content of Validation Report

g) Sampling plan



Process	Test	Equipment /location	Sampling point	Sample size
After Drying	Moisture content	FBD bowl	Composite of top, middle, bottom	10 g
After Blending	Blending uniformity	V-Blender 200	10 points	5g
	Bulk blend		Composite of top, middle and bottom	80g
	Particle size			
	Moisture content			
Tablet compression	Appearance	Tablet Press Manesty	Beginning, middle, end; Composite sample	150 tablets
	Tablet thickness			
	Individual weight			
	Hardness			
	Friability			
	Disintegration test			
	Assay			
	Uniformity of content			
Coating	Appearance	Coating pan	After coating	150 tablets
	Assay			
	Dissolution			
	Related substance			

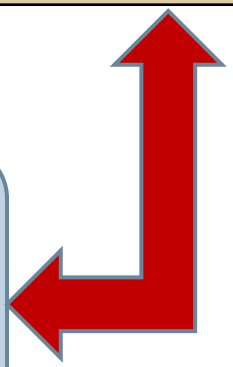
Please ensure that the sampling plan and acceptance criteria defined are adequate to ascertain that the manufacturing process is well controlled and robust

5. Content of Validation Report

h) Tabulation of the test results

Drying process

Moisture content (2.00-5.00% w/w)			
	M10001	M10002	M10003
Top	2.70	2.70	2.30
Middle	2.50	3.10	2.90
Bottom	3.00	2.40	6.00



Justification is needed for not meeting the acceptance criteria of the process validation and may need to re-validate the process before releasing the said product batches

5. Content of Validation Report

Blending process

Blend uniformity (85-115%, RSD≤6%)			
	M10001	M10002	M10003
L1	86	89	90
L2	93	92	93
L3	87	86	95
L4	89	94	91
L5	92	90	86
L6	96	95	96
L7	90	88	87
L8	91	89	90
L9	86	92	88
L10	93	94	89
Min	87	86	88
Max	93	95	96
RSD	3%	1.8%	3%

Please ensure that the result provided is according to the sampling plan!

5. Content of Validation Report

Tablet compression

Individual tablet weight (150mg±7.5%)			
	M10001	M10002	M10003
Beginning	Min: 149 Max: 154	Min: 148 Max: 152	Min: 147 Max: 152
Middle	Min: 148 Max: 153	Min: 149 Max: 151	Min: 150 Max: 154
End	Min: 150 Max: 155	Min: 147 Max: 154	Min: 149 Max: 153

5. Content of Validation Report

Tablet compression

Test	Acceptance criteria	Batch number		
		M10001	M10002	M10003
Appearance	White round shape tablet	White round shape tablet	White round shape tablet	White round shape tablet
Tablet thickness	4.00mm±0.40mm	Min:4.2mm Max:4.4mm	Min: 3.8mm Max:4.2mm	Min: 3.9mm Max:4.4mm
Hardness	4-20 kp	11 -18kp	8-12kp	9-13kp
Friability	NMT 1.0%	0.5%	0.5%	0.6%
Disintegration test	NMT 15 minutes	7 minutes	6 minutes	7 minutes
Assay	95-105% of labelled amount	99%	99%	101%

5. Content of Validation Report

Coating process

Dissolution (NLT 80% in 30 minutes)																		
	M10001						M10002						M10003					
	10 min	15 min	20 min	30 min	45 min	60 min	10 min	15 min	20 min	30 min	45 min	60 miN	10 min	15 min	20 min	30 min	45 min	60 min
1	60%	70%	75%	80%	80%	85%	60%	70%	75%	80%	80%	85%	60%	70%	75%	80%	80%	85%
2	60%	65%	80%	90%	90	90%	60%	65%	80%	90%	90	95%	60%	65%	80%	90%	90	95%
3	55%	60%	70%	80%	80%	85%	55%	60%	70%	80%	80%	85%	60%	60%	75%	80%	80%	80%
4	60%	60%	80%	90%	90%	95%	60%	60%	75%	80%	90%	90%	60%	60%	80%	90%	90%	95%
5	55%	65%	70%	80%	85%	85%	55%	65%	70%	80%	85%	85%	55%	65%	70%	80%	85%	85%
6	60%	65%	70%	80%	90%	90%	60%	65%	70%	80%	90%	90%	60%	65%	70%	80%	80%	90%
Mean	60%	65%	70%	80%	85%	90%	60%	65%	75%	80%	85%	90%	60%	65%	75%	80%	90%	90%

5. Content of Validation Report

Coating process

Test	Acceptance criteria	Batch number		
		M10001	M10002	M10003
Appearance	Pink film coated round shape tablet	Pink film coated round shape tablet	Pink film coated round shape tablet	Pink film coated round shape tablet
Assay	95-105% of labelled amount	97%	99%	101%

Result for related substance??

Please ensure that all test result is provided according to the sampling plan!!

5. Content of Validation Report

i) Batch analysis

Test	Specification	Result		
		M10001	M10002	M10003
Description	Pink film coated round tablet	Pink film coated round tablet	Pink film coated round tablet	Pink film coated round tablet
Identification by HPLC	The retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the Assay.	The retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the Assay.		
	The ultraviolet absorption spectrum of the standard and sample solutions exhibit maxima at the same wavelength	The ultraviolet absorption spectrum of the standard and sample solutions exhibit maxima at the same wavelength		
Ave wt.	155.25mg±7.5%	157mg	158 mg	155 mg
Uniformity of Dosage	Not more than 15	8.4	8.0	9.2
Hardness	4-20 kp	11kp	12kp	8kp
Friability	NMT 1.0%	0.5%	0.5%	0.6%

5. Content of Validation Report

Test	Specification	Result		
		M10001	M10002	M10003
Dissolution	NLT 80% in 30 minutes	90%,94%,95%,96%, 98%, 100%	90%,95%,97%,98%, 99%, 100%	90%,94%,95%,96%, 99%, 100%
Related substance Impurity D Total impurities	 Nmt 0.1% Nmt 1.0%	 0.01% 0.05%	 0.01% 0.05%	 0.01% 0.05%
Assay	95-105% of labelled amount	99%	99%	101%
a) Microbial enumeration test Total aerobic microbial count Total combined yeast and mold count	 NMT 1000 CFU per g NMT 100 CFU per g	 60 CFU per g ≤10 CFU per g	 50 CFU per g ≤ 10 CFU per g	 40 CFU per g ≤ 10 CFU per g
b) Test for specified microorganism *E. coli* *Salmonella* *Staph. Aeureus* *Pseudomonas aeruginosa*	 Should be absent Should be absent Should be absent Should be absent	 Absent Absent Absent Absent	 Absent Absent Absent Absent	 Absent Absent Absent Absent

5. Content of Validation Report

j) Evaluation of data including statistical process control analysis

Individual tablet weight (150mg±7.5%)			
	M10001	M10002	M10003
Beginning	Min: 149 Max: 154	Min: 148 Max: 152	Min: 147 Max: 152
Middle	Min: 148 Max: 153	Min: 149 Max: 151	Min: 150 Max: 154
End	Min: 150 Max: 155	Min: 147 Max: 154	Min: 149 Max: 153

Blend uniformity (85-115%, RSD≤6%)			
	M10001	M10002	M10003
L1	86	89	90
L2	93	92	93
L3	87	86	95
L4	89	94	91
L5	92	90	86
L6	96	95	96
L7	90	88	87
L8	91	89	90
L9	86	92	88
L10	93	94	89
Min	87	86	88
Max	93	95	96
RSD	3%	1.8%	3%

** Statistical analysis (Min, Mean, Max, RSD, etc) whenever appropriate and feasible

5. Content of Validation Report

k) Evaluation of data including comparison against acceptance criteria

Individual tablet weight (150mg±7.5%)			
	M10001	M10002	M10003
Beginning	Min: 149 Max: 154	Min: 148 Max: 152	Min: 147 Max: 152
Middle	Min: 148 Max: 153	Min: 149 Max: 151	Min: 150 Max: 154
End	Min: 150 Max: 155	Min: 147 Max: 154	Min: 149 Max: 153

Remark: The results obtained for individual weight meet the acceptance criteria of 150 mg± 7.5%

5. Content of Validation Report

l) Discussion on deviations and out of specification results

Deviations (if any)

No deviations were observed during the process.

Corrective Action & Prevention Action (CAPA) ???

5. Content of Validation Report

m) Conclusion and recommendation

Recommendations and Conclusion

Recommendations

S. No	Stage	Parameter	Specification	Observation (from 3 batches)	Remarks	Recommendations (if any)
1	compression	Compression speed	N/A	20 RPM	Complies	20 as optimum speed and 15 as slow speed and 25 as high speed

Conclusion

Amlodipine 5 mg Film Coated Tablets manufacturing process was validated in module 3 as per the process validation protocol. The results were reviewed and found meeting the predetermined specifications and quality attribute. Hence, it is concluded that the process has been validated.

6. Process Validation type/ approach

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

6. Process Validation type/ approach

Annex D glossary

Concurrent Validation

Validation carried out during routine production of products intended for sale.

Prospective Validation

Established documented evidence that a process, procedure, system, equipment or mechanism used in manufacture does what it purports to do based on a pre-planned validation protocol.

Retrospective Validation

Validation of a process for a product that has been marketed based upon accumulated manufacturing, testing and control batch data.

7. Notes on Retrospective Validation & Concurrent Validation

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

7. Notes on Retrospective Validation & Concurrent Validation

Retrospective Validation

For existing products already on the market for some time, retrospective validation may be performed. Retrospective validation involves the trend analysis (using control chart, etc) of historical manufacturing and QC data (eg. Results of assays, dissolution test, pH, SG, etc) of the product. Data from 10-20 batches of the product produced using the same stable manufacturing process should be analyzed, to demonstrate that the manufacturing process is under control and `capable'. A Cpk (Process Capability) and/or Ppk (Process Performance) of 1.0, 1.33 and 2.0 represents a 3, 4, 6 sigma respectively. The measurement of Cp, Cpk, Pp or Ppk will be accepted as one of the statistical methods for analyzing the process control.

**Retrospective validation is unacceptable for sterile product.

7. Notes on Retrospective Validation & Concurrent Validation

Concurrent Validation

In the case of orphan drugs, when the number of production batches per year is expected to be low, concurrent validation is acceptable. Other categories of drugs for which have short lives (e.g. radiopharmaceuticals) and that are medically necessary (e.g. drug used to prevent or treat serious or life-threatening disease or medical condition, for which there is no other available source with sufficient supply of that drug or alternative drug available) may be considered on case by case basis. The applicant should seek prior consent from DRA before submitting the application to register any drug product that uses concurrent validation approach.

**Concurrent validation is only allowable for orphan drug with prior approval.

Overview on ASEAN Guideline on PV Requirements

8. Change Control

Nasyrah Amalina Binti Sarginan

Generic Medicine Section,
Product Registration Center

8. Change Control

Changes that require re-validation and prior regulatory approval:

- Changes to process (eg: mixing times, drying temperature, sterilization process)
- Change of equipment that involves different design and operating parameters/principles.

** Applicant should submit appropriate supporting data for these changes

Overview on ASEAN Guideline on PV Requirements

Reference:

- ASEAN Guideline on Submission Of Manufacturing Process Validation Data For Drug Registration
- The ASEAN Common Technical Dossier (ACTD) For The Registration Of Pharmaceuticals For Human Use PART II: QUALITY)
- ANNEX A1: Guidance On Process Validation Scheme For Solid Oral Dosage Products

National Pharmaceutical Control Bureau
MINISTRY OF HEALTH MALAYSIA

Process Validation (PV)

World Health Organization
WHO Collaborating Centre for Regulatory Control of Pharmaceuticals

PIC/S
Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

QUALITY SYSTEM
SIRIM
Certified to ISO 9001:2000
Cert. No: AR 2293

STANDARDS MALAYSIA
ACCREDITED LABORATORY
MS ISO/IEC 17025:2005
No: SAMM 450

Process Validation Scheme For Solid Oral Dosage Products (non-sterile products)

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Process Validation Scheme For Solid Oral Dosage Products

Topics of the Session

1. General information
2. Validation scheme of Solid Oral Dosage Manufacturing process:
    - 2.1 Batch Formula
    - 2.2 Major Equipment and Equipment Class
    - 2.3 Manufacturing Process Description and Process Parameters
    - 2.4 Sampling Plan and Acceptance Criteria
    - 2.5Holding Time for Drug Products

Process Validation Scheme For Solid Oral Dosage Products

1. General information

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1. General information

- The presentation of solid oral dosage formulations are generally capsules, tablets and powder/ granules for solution/ suspension.
- Solid oral dosage could be packaged as unit dosage form such as blisters and sachets or multi units in the form bottles.

1. General information

- Process validation of solid oral dosage form has to be specific to its batch formula and the operating principles of equipment used for its manufacture.
- The process parameter and testing that need to be conducted during process validation are depend on its method of manufacture and its presentation.
- The acceptance criteria should take into consideration the nature of the solid oral dosage, for example drug release characteristics (intermediate release or modified release).

2. Validation scheme of Solid Oral Dosage Manufacturing process:

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2. Validation scheme of Solid Oral Dosage Manufacturing process

2.1 Batch Formula

2.2 Major Equipment

2.3 Manufacturing process Description and Process Parameter

2.4 Sampling plan and acceptance criteria

2.5 Holding time for Drug Product

2.1 Batch Formula

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2.1 Batch Formula

- For execution of the manufacturing process validation, the batch formula of the solid oral dosage has to be well defined.
- All components of the dosage form to be used in the manufacturing process have to be listed, with their amounts on a per batch basis (including overages, if any).

2.1 Batch Formula

Batch formula for Amlodipine Tablet 5 mg for 300000 tablets

Ingredients	Unit composition	Overage	Batch Quantity (300000 tabs)
Core tablets			
Amlodipine	5mg	2%	1.53 kg
Lactose Monohydrate	150 mg	-	45 kg
Maize starch	25 mg	-	7.5 kg
Magnesium Stearate	1.5 mg	-	0.45kg
Total mass of Core Tablet	181.5 mg	-	54.48 kg
Film Coating			
Hydroxy Propyl Methyl Cellulose BP	1.8 mg	10%	0.594kg
Titanium Dioxide BP	0.18 mg	10%	0.059kg
Purified Talc	0.18 mg	10%	0.059kg
Polyethylene Glycol 400BP	0.18 mg	10%	0.059kg
Isopropyl alcohol	q.s	-	7L
	183.84 mg		55.251kg

2.2. Major Equipment and Equipment Class

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2.2 Major Equipment and Equipment Class

- The major equipment, used for the manufacturing process, are to be identified and the class of each equipment be indicated.
- The equipment are broadly categorized by the unit operation (for example, blending and mixing, drying, particles size reduction, granulation, unit dosage, coating, encapsulation, printing, packaging).
- For each operation, the equipment is further categorized by class.

2.2 Major Equipment and Equipment Class

The following lists some examples of equipment class for equipment of each major unit operation, which are non-exhaustive.

Equipment	Equipment Class
Mixing Tank	Convective mixers
Blender	Diffusion blender (Tumble) Convective blender Pneumatic blender
Mill	Fluid energy mill Impact mill Cutting mill Compression mill Screening mill Tumbling mill

** Where information on the equipment class is deemed critical but not made available in the submission, the Drug Regulatory Authority (DRA) reserves the right to request for such information

2.2 Major Equipment and Equipment Class

Equipment	Equipment Class
Granulator	Dry granulator Wet high-shear granulator Wet low-shear granulator Low-shear tumble granulator Extrusion granulator Rotary granulator Fluid bed granulator Spray dry granulator
Dryers	Direct Heating, Static Solids Bed Direct Heating, Moving Solids Bed Direct Heating, Fluidized Solids Bed (Fluid Bed Dyer) Direct Heating, Dilute Solids Bed, Spray Dryer Direct Heating, Dilute Solids Bed, Flash Dryer Indirect Conduction, Moving Solids Bed Indirect Conduction, Static Solids Bed Indirect Conduction, Lyophilization Gas Stripping Indirect Radiant Heating, Moving Solids Bed (Microwave Dryer)
Separators	Vibratory/Shaker Centrifugal
Tablet Press	Gravity Power assisted Rotary (centrifugal) Compression coating
Coating machine	Pan coating Gas suspension Vacuum film coating Dip coating Electrostatic coating
Encapsulator (hard capsule)	Auger Vacuum Vibratory Dosing disk Dosator
Encapsulator (soft capsule)	Positive displacement pump Gravity or force fed Mixers and Mixing Vessels Deaggregators Deaerators Holding Vessels
Powder filler	Vacuum Auger
Blister packaging machine	Plate-type
Bottle packaging machine	None identified

2.3 Manufacturing Process Description and Process Parameters

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2.3 Manufacturing Process Description and Process Parameters

- The manufacturing process may be described or presented in a flow diagram.
- The following process parameters are recommended to be controlled or monitored as part of the process validation and they serve only as examples and may differ depending on the class of equipment used.

2.3 Manufacturing Process Description and Process Parameters

Process Step	Tablet	Capsule	PGS	Process Parameters
Raw Materials Sieving, if required	✓	✓	✓	• Mesh / sieve size
Premix, if required	✓	✓	✓	• Mixing time, speed, load size
Fill liquid mixing, if required	NA	✓	NA	• Mixing time, speed, volume
Dry milling (particle sizing), if applicable	DB	DB	DB	• Screen size • Milling speed • Feed rate
Final Blending	✓	✓	✓	• Blending time, load size, speed • Sieve size, for dry blending, if required
Granulation binder preparation	WG	WG	WG	• Binder amount, concentration • Temperature
Granulation	WG	WG	WG	• Load size • Mixing time, speed • Temperature • Rate of liquid addition • Application spray pattern

2.3 Manufacturing Process Description and Process Parameters

Process Step	Tablet	Capsule	PGS	Process Parameters
Wet milling (if applicable)	WG	WG	WG	• Rounds per minute • Pressure • Temperature
Wet screening (if applicable)	WG	WG	WG	• Mesh / sieve size
Drying	WG	WG	WG	• Drying time • Temperature distribution
Cooling	WG	WG	WG	• Cooling Time • Cooling Set Temperature
Tabletting (including Metal detection and Dedusting)	✓	NA	NA	• Compressing machine settings • Tabletting speed (tbs/hr)
Coating solution / suspension preparation (if required)	✓	✓	NA	• Temperature • Mixing speed / time
Coating (if required)	✓	✓	NA	• Load size • Coating pan settings • Temperature • Spray rate • Rounds per minute • Air flow rate
Printing on product (when required)	✓	✓	NA	• Printing feed rate (units/hr) • Temperature
Capsule filling (including dedusting)	NA	✓	NA	• Capsule machine settings • Machine speed (caps/hr) • Feeding system
Primary packaging	✓	✓	✓	• Machine settings • Machine speed • Feeding speed

2.3 Manufacturing Process Description and Process Parameters

Process Step	Tablet	Capsule	PGS	Process Parameters
Environmental monitoring – throughout manufacturing process (Applicable for heat and / or moisture sensitive products only)	✓	✓	✓	• Temperature • Relative humidity

Where PGS denotes Powder / Granule for Solution / Suspension
DB denotes applicable for Dry Blending only
WG denotes applicable for Wet Granulation only
✓ denotes applicable (if required)
NA denotes Not Applicable

** Where process parameters are deemed critical but not well defined in the submission, the DRA reserves the right to request for such information.

2.4 Sampling Plan and Acceptance Criteria

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2.4 Sampling Plan and Acceptance Criteria

- It is the responsibility of the manufacturer to ensure that the sampling plan and acceptance criteria defined are adequate to ascertain that the manufacturing process is well-controlled and robust to produce drug product consistently meeting specifications.
- The following sampling plan and acceptance criteria provide a guide for process validation of a typical solid oral dosage manufacturing process with medium risk indication.

2.4 Sampling Plan and Acceptance Criteria

Stage	Sampling Plan	Test	Acceptance Criteria
Drying, if required	At least 3 samples from at least three different locations or time points throughout the oven chamber or drying process[(1)].	Loss on drying (LOD) – analyze one sample per location	Based on production specification for LOD
Final Blend / Mix	At least 3 samples from at least ten different locations evenly distributed throughout the mixer[(1)] *(Twenty locations for convective blender)*	Blend / Mix uniformity (Assay) – analyze one sample per location	Stage 1 Individual results: Mean ± 10% (absolute) All individual results: RSD ≤ 5.0%
		If required, • Flowability • Density • Appearance	In-house

2.4 Sampling Plan and Acceptance Criteria

Stage	Sampling Plan	Test	Acceptance Criteria
	Composite sample (may be performed as part of release testing)	• *Visual inspection • *Uniformity • *Assay (Potency) • *Impurities • *Microbial contamination • Other internal specifications * May be omitted if next step is tabletting and / or encapsulation.	Uniformity: As per compendia Microbial Limit Test (MLT): As per compendial MLT method Others: Compendia / In-house
Tabletting	Stratified sampling	• Uniformity • Any other internal specifications, if required	Uniformity: As per compendia Others: Compendia / In-house
	Composite sample (may be performed as part of release testing)	• Visual inspection • Uniformity • Assay (Potency) • Friability • **Hardness • **Disintegration • **Dimension • **Dissolution • **Impurities • **Microbial contamination • Other internal specifications ** May be performed after coating and / or encapsulated, if applicable.	Uniformity: As per compendia MLT: As per compendial MLT method Others: Compendia / In-house

2.4 Sampling Plan and Acceptance Criteria

Stage	Sampling Plan	Test	Acceptance Criteria
Capsule filling	Stratified sampling	• Uniformity • Visual inspection • Length of filled capsules	Uniformity: As per compendia Others: Compendia/ In-house
	Composite sample (may be performed as part of release testing)	• Visual inspection • Uniformity • Assay (Potency) • Dimension • Dissolution/ Disintegration • Impurities • Microbial contamination • Other internal specifications	Uniformity: As per compendia MLT: As per compendial MLT method Others: Compendia / In-house
Coating	1 sampling from each coating pan	• Assay (for coating of active only) • Moisture content / residual solvent	Assay: In-house Moisture / solvent: ICH guidelines
	At least ten locations distributed throughout all batch subdivisions[1]	Uniformity	As per compendia

2.4 Sampling Plan and Acceptance Criteria

Stage	Sampling Plan	Test	Acceptance Criteria
	Composite sample (may be performed as part of release testing)	• Visual inspection • Uniformity (for active coating only) • Assay (Potency) • ***Hardness • ***Disintegration • ***Dissolution • ***Impurities • ***Microbial contamination • Other internal specifications *** May be omitted if encapsulated	Uniformity: As per compendia Others: Compendia / In-house
Printing	Stratified sampling	Visual inspection	In-house
Filling of powder / granules into bottles	Stratified sampling	Weight uniformity	Label claim ± 5% (absolute)
Primary packaging (may be performed as part of equipment qualification)	Stratified sampling	• Visual inspection • CCS integrity test, if required	In-house
Environmental Monitoring (Applicable for heat and / or moisture sensitive products only)	Throughout the manufacturing process	• Temperature • Relative humidity	In-house

Where RSD denotes Relative Standard Deviation
ICH denotes International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MLT denotes Microbial Limit Test
CCS denotes Container Closure System

[1]Note: Other sampling plans may be acceptable if they are statistically sound and justified.

**The finished product specifications have to be adequately justified and the analytical methods have to be validated as per ASEAN Guideline for Validation of Analytical Procedures

2.5 Holding time

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2.5 Holding time

- Where holding times are involved as part of the manufacturing process of the bulk drug product (including the premix and intermediate stages), these have to be well justified.
- It is recommended for any holding times to be supported by stability data (degradation studies and/or microbial limit tests).
- Holding times may be performed as part of the main process validation scheme or as a separate exercise.

2.5 Holding time

- Hold time may be established as a deliberate effort in that the samples or batches are withheld for the predetermined holding time before subjecting to analysis.
- Holding tine may also be established as part of the routine manufacturing process, using incurred holding times, which had been supported by data.

**In the case where hold time information is not included in the submission, such information or justification/data to support the omission must be available upon request of the DRA.

2.5 Holding time

6.1 Blend sample:					
Test to be performed	**Acceptance criteria**	**Initial**	**7th Day**	**15th Day**	**21st Day**
Description	White granular powder	*	*	*	*
Content of Amlodipine	(95.0% to 105.0 % of claim.)	*	*	*	*
Microbial Testing Total aerobic microbial count Total yeast and mould count E.coli Salmonella Enterobacteriaceae	Not more than 10^3 cfu/g Not more than 10^2 cfu/g Absent / 1g Not Detected/ 10 g Not more than 10^2 cfu/g	*	*	*	*

Process Validation Scheme For Solid Oral Dosage Products

Reference:

- ANNEX A1: Guidance On Process Validation Scheme For Solid Oral Dosage Products

Process Validation Scheme For Solid Oral Dosage Products

Thank you…