ASEAN GUIDELINE ON SUBMISSION OF MANUFACTURING PROCESS VALIDATION DATA FOR DRUG REGISTRATION

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1. INTRODUCTION

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. SCOPE

This guideline is intended to outline the regulatory requirements with respect to the manufacturing process validation studies which falls under the remit of drug registration and to guide the applicant in preparing the dossiers for the product licence application. These requirements are not intended for regulating the manufacture of active substance and other starting materials, but intended to apply to data generated to evaluate or validate the manufacturing process of the finished product. For biotechnological and biological products, more extensive data may be required.

3. DATA SUBMISSION REQUIREMENTS

Option 1 - The data submission should include a validation report (see Content of 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 :

Documents required:
a) Development pharmaceutics report; and
b) Validation report on 1 pilot batch or validation scheme

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;
- 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 authorisation by DRA according to national procedure.

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 dossiers

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 dossiers, 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.

4. CONTENT OF DEVELOPMENT PHARMACEUTICS

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

a) Rationale for selecting the dosage form

b) Choice of product components (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 agents, etc
- Stability, homogeneity and batch reproducibility considerations

d) Choice of manufacturing processes, including sterilization procedures

e) Choice of containers and packaging materials
- Container-closure integrity
- Sorption and leaching issues

The development pharmaceutics report should establish that the type of dosage form selected and the formulation proposed are appropriate for the intended (medicinal) purpose specified in the application for drug registration. It should also identify the formulation and processing aspects that are critical for batch homogeneity and reproducibility, and that hence have to be monitored routinely. The development pharmaceutics report (and the pilot batch report, where applicable) should provide a link to the validation scheme proposed for the manufacture of production scale batches.

5. CONTENT OF VALIDATION SCHEME

Process validation scheme outlines the formal process validation studies to be conducted on the production scale batches. It should contain the following information:

a) A short description of the manufacturing process in 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)
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

6. CONTENT OF VALIDATION REPORT

The following information should be provided in the report:

a) Summary
b) Introduction
c) Batches used for validation
d) Manufacturing equipment
e) Critical process steps and parameters
f) Acceptance criteria
g) Sampling plan
h) Tabulation of the test results
i) Batch Analysis
j) Evaluation of data, and where applicable, including statistical process control analysis
k) Evaluation of data including comparison against acceptance criteria
l) Discussion on deviations and out of specification results
m) Conclusion and recommendations

Where appropriate a short description of the manufacturing process in a schematic drawing or flow chart may be required by the DRA.

7. NOTES ON RETROSPECTIVE VALIDATION & CONCURRENT VALIDATION

7.1 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 analysed, to demonstrate that the manufacturing process is under control and `capable'. A Cpk (Process Capability) of 1.0, 1.33 and 2.0 represents a 3, 4, 6 sigma respectively. The measurement of Cp or Cpk will be accepted as one of the statistical methods for analysing the process control.

7.2 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. The applicant should seek prior consent from DRA before submitting the application to register any drug product that uses concurrent validation approach.

8. CHANGE CONTROL

Procedures are required to manage, plan and document the changes proposed in the manufacturing processes. Adequate supporting data should be generated to show evidence that the revised process would still ensure that the product meets the desired quality and approved specification.

Minor changes in SOP's, environment, equipment etc are unlikely to require regulatory approval if they can be shown not to affect the quality of the finished product.

Other types of changes that would have significant impact on the quality of the finished product would require prior regulatory approval. Such significant changes include changes to process (e.g. mixing times, drying temperatures, sterilization process), change of equipment that involves different design and operating parameters. The applicant should submit appropriate supporting data for these changes.

9. EXAMPLES OF CONTROL VARIABLES AND TEST ATTRIBUTES IN THE MANUFACTURE OF COMMONLY AVAILABLE PHARMACEUTICAL DOSAGE FORMS

The ASEAN GMP Operating Manual should be referred to for examples of control variables and test attributes that are applicable to the manufacture of commonly available pharmaceutical dosage forms.

10. TABLE OF CONTENTS OF PROCESS VALIDATION DOCUMENTATION

Annex 1 is a form that needs to be completed by the applicant for checking purpose.

11. GLOSSARY

Annex 2 gives definitions of the terms used in the guideline.

ANNEX 1 *TABLE OF CONTENT OF PROCESS VALIDATION DOCUMENTATION*

I. Document Submission (tick if submitted)**:**

	Document	Check Box	**Enclosure**	**Page**
a)	Development Pharmaceutics Report	☐	_____	_____
b)	Validation Scheme	☐	_____	_____
c)	Validation Report			
	○ Pilot batch	☐	_____	_____
	○ 3 full production batches	☐	_____	_____

II. Details of Validation:

a) Manufacturing site at which the validation is carried out:

No.	Name of manufacturer	Country

b) Type of Validation:

- ☐ Retrospective
- ☐ Prospective
- ☐ Concurrent
- ☐ Others; please specify: _____

c) Number of batches validated: _____

d) Details of batches:

Batch Number	Batch Size	Batch Type (production/pilot/experimental)

ANNEX 2 GLOSSARY

Concurrent Validation

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

Finished Product

A product that has undergone all stages of production and quality control, including packaging in its final container and labelling.

Production Scale Batches

These batches are of the size, which will be produced during routine marketing of the product.

Pilot Batches

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 forms this size should be at least 10% or 100,000 units whichever is greater unless otherwise justified.

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.

Prospective Validation

Establishing 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.