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ASEAN Guideline on Process Validation – Questions and Answers

1. Does this guideline also apply to biological/biotechnological products?

This guideline applies to the manufacturing process of the finished product for New Chemical Entities and Generic Drug Applications. The general principles mentioned in the guidelines also apply to biotechnological and biological products. However, more extensive data may be required.

2. For Option 2, should data related to Development Pharmaceutics be also submitted for generic products?

The ASEAN Common Technical Requirement (ACTR) states that Pharmaceutical Development is not required for the Generic Drug Applications. However, if the applicant is not able to submit under option 1 and chooses option 2 under the ASEAN Guideline on Process Validation, the applicant is required to submit the Pharmaceutical Development information as well as validation report on one pilot batch or validation scheme.

3. For option 3, in the absence of pre-approval dossiers pertaining to process validation, would concurrent validation be acceptable?

(Note: ‘pre-approval dossiers’ refer to the set of documents including process validation documents that were used in the submission to a reference country for drug registration application.)

As stipulated in the Guideline, 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. If any approach other than prospective validation is proposed such as concurrent validation, justification should be provided and prior consent from the DRA should be obtained before the submission of the drug registration application.

4. Are orphan drugs subjected to the full registration requirements? Using the concurrent approach, does it mean the product can be released for sale immediately after meeting quality requirements?

Unless otherwise specified by the DRA of the individual Member Countries, orphan drugs are subject to full registration requirements. If the concurrent approach is used, prior consent is required from the DRA.

5. Can Concurrent Validation be used for infrequently manufactured products?

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Concurrent validation can be used for infrequently manufactured products; however the applicant should seek prior consent from the DRA before submitting the application for drug product registration.

- 6. If the validation data submitted for 3 consecutive production batches showed that they fully comply with specifications but do not fulfill the process validation acceptance criteria, would they be approved for marketing?**

The onus is on the manufacturer to ensure that the manufacturing process is well controlled prior to manufacturing the batches for marketing. The manufacturer should provide justification for not meeting the acceptance criteria of process validation and may need to re-validate the process before releasing the said product batches which meet the quality specification for sale.

- 7. What is the acceptable range permitted for critical process parameters?**

A nominal or target value for the critical process parameter with an allowable normal operating range should be defined and justified. There are no fixed formulae for this. The range is established based on scientific data available, process robustness and the expected impact of the critical process parameter on critical quality attributes defined in product specification.

- 8. Can bracketing /matrixing approach be adopted for process validation?**

This approach is not recommended unless it can be justified.

- 9. Should IQ and OQ data be submitted in the process validation study report?**

Installation Qualification IQ, Operational Qualification OQ and Performance Qualification PQ data are not required for submission. However, IQ, OQ and PQ should be performed satisfactorily as a prerequisite to validation studies. Complete data report should be made available for site inspection by relevant regulatory authorities.

- 10. Should homogeneity data be submitted together with the validation report?**

Homogeneity and blend uniformity data must be included in the validation protocol where homogeneity is a critical quality attribute.

- 11. 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.

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12. Should validation batches be placed on stability program?

It is not a requirement but it would be good practice to place at least 1 concurrent validation batch or 3 prospective batches on stability program. This provides efficient use of resources as well as fulfills the commitment to submit stability data on 3 full scale batches.

13. When can we submit the result of 3 consecutive full production batches if the results are not available at the point of application and either option 2 or option 3 is chosen?

If option 2 or option 3 is chosen, process validation of 3 consecutive full production batches can be performed post-registration, subject to concurrence by the DRA. The report should then be submitted after approval of the product but *prior* to launching / marketing of the product. However, if the product has been marketed in other country / countries, the DRA may request for the validation data of 3 production batches during the registration process.

14. What is the acceptable limit for Cpk?

The guideline states that a Cpk of 1.0, 1.33 and 2.0 represents a 3, 4, 6 sigma respectively. The general rule of thumb is, for a good process under statistical control, Cpk value should be greater than 1.33. If a Cpk value of a process is less than 1.33, the applicant should seek advice from DRA for acceptability.

15. For legacy products which have been historically manufactured at a site, can retrospective validation be used to support process validation?

Retrospective validation may be performed to support process validation for existing **non-sterile** products which are already on the market for some time.

In addition, the following conditions should be met:

- No change in formulation.
- No change in manufacturing process or analytical method.
- No change in equipment or site(s) of manufacturing.
- $CpK \geq 1.33$ (If a $Cpk < 1.33$, the applicant should seek advice from DRA for acceptability) based on 10-20 consecutive batches.

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16. For certain product, premix/pellets/direct compression granules are used in the manufacturing process of the finished product. Should process validation data for the premix/pellets/direct compression granules be submitted together with the process validation data of the product?

The manufacturing process of premix/pellets/direct compression granules must be controlled and validated if the properties of the premix/pellets/direct compression granules have a direct impact on the finished product. Therefore, process validation documents for premix/pellets/direct compression granules should be submitted.