MANUFACTURING & QUALITY AUDIT DIVISION
CENTRE FOR DRUG ADMINISTRATION

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GUIDANCE NOTES ON NON-STERILE PROCESS VALIDATION

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GUIDANCE NOTES

Subject: NON-STERILE PROCESS VALIDATION

1.0 Principle

Process Validation is the means of ensuring, and providing documentary evidence that processes (within their specified design parameters) are capable of repeatedly and reliably producing a finished product of the required quality. The requirements and principles outlined in these recommendations are applicable to the manufacture and packaging of non-sterile pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and re-validation.

2.0 General

2.1 Any manufacturing or packaging process will involve a number of factors that may affect product quality. These factors will be identified during the development of a product and will facilitate process optimisation studies. On completion of development and optimisation, Process Validation provides a structured way of assessing methodically the factors that impact on the final product.

2.2 It would normally be expected that Process Validation be completed prior to the manufacture of finished product that is intended for sale (Prospective Validation). Where this is not possible, it may be necessary to validate processes during routine production (Concurrent Validation). Processes which have been in use for some time should also be validated (Retrospective Validation).

2.3 In theory a validation exercise should only need to be carried out once for any given process. In practice however the process rarely remains static. Changes occur in components (raw materials and packaging materials), equipment is modified and the process environment cannot be assumed to remain as during the initial validation. A regular programme of re-validation is essential.

2.4 The company's policy and approach to Process Validation should be clearly defined.

3.0 Prospective Validation

3.1 During product development the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical factors/parameters that may affect the quality of the finished product.

3.2 A series of experiments should be devised to determine the criticality of these factors. Representatives from Production, QC/QA, Engineering, and in some cases Research and Development will normally be involved in this process. These experiments may incorporate a challenge element to determine the robustness of the process. Such a challenge is generally referred to as a "worst case" exercise. The use of starting materials on the extremes of the specification may indicate the ability of the process to continue producing finished product to the required specification.

3.3 Each experiment should be planned and documented fully in an authorised protocol. This document will have the following elements:

3.3.1 A description of the process,

3.3.2 A description of the experiment,

3.3.3 Details of the equipment/facilities to be used (including measuring/ recording equipment) together with its calibration status,

3.3.4 The variables to be monitored,

3.3.5 The samples to be taken - where, when, how and how many,

3.3.6 The product performance characteristics/attributes to be monitored, together with the test methods,

3.3.7 The acceptable limits ,

3.3.8 Time schedules,

3.3.9 Personnel responsibilities,

3.3.10 Details of methods for recording and evaluating results, including statistical analysis.

3.4 All equipment, the production environment and analytical testing methods to be used should have been fully validated, (Installation/Operational Qualification). Staff taking part in the validation work should have been appropriately trained. In practice, Operational Qualification may be carried out using batches of actual product. This work may also fulfil the requirements of Prospective Validation. This approach to validation should not be adopted as a standard practice however.

3.5 Master Batch Documentation can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

3.6 Using this defined process (including specified components) a series of batches of the final product should be produced. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. In practice, it may take some considerable time to accumulate this data.

3.7 It is preferred that the batches made should be the same size as the intended batch size for full scale production. This may not always be practical due to a shortage of available starting materials and in such cases the effect of the reduced batch size should be considered in the design of the protocol. When full scale production starts, the validity of any assumptions made should be demonstrated.

3.8 During the processing of the batch/run, extensive testing should be performed on the product at various stages. Detailed testing should also be done on the final product and its package.

3.9 The batches/runs under validation should be documented comprehensively. The following items should be included in the validation report:

3.9.1 A description of the process - Batch/Packaging Document, including details of critical steps,

3.9.2 A detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not included reference should be made to the sources used and where it can be found,

3.9.3 Any work done in addition to that specified in the protocol or any deviations from the protocol should be formally noted along with an explanation,

3.9.4 A review and comparison of the results with those expected,

3.9.5 Formal acceptance/rejection of the work by the team/persons designated as being responsible for the validation, after completion of any corrective action or repeated work.

3.10 Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production. These should be incorporated into the Batch Manufacturing or Packaging Record or into appropriate standard operating procedures (SOPs). Limits, frequencies and actions to be taken in the event of the limits being exceeded should be specified.

3.11 If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice and the Marketing Authorisation (if applicable). The premises used should be named on a Manufacturing Authorisation and this Authorisation should allow the manufacture/assembly of the particular type of product. Where appropriate, the batch must be formally certified by the authorised personnel before release.

4.0 Concurrent Validation

4.1 In certain circumstances it may not be possible to complete a validation programme before routine production starts. In these cases it will be known in advance that the finished product will be for sale or supply.

Circumstances where this is likely are, for example, when a process is being transferred to a third party contract manufacturer/assembler.

4.2 In addition there are many instances when it is appropriate to validate a process during routine production. Such instances are, for example, where the product is a different strength of a previously validated product, a different tablet shape or where the process is well understood.

4.3 It is important in these cases however, that the premises and equipment to be used have been validated previously and that the decision to carry out Concurrent Validation is made by appropriately authorised people.

4.4 Documentation requirements are the same as specified for Prospective Validation and the testing to be carried out in-process and on the finished product will be as specified in approved protocols. The completed protocols and reports should be reviewed and approved before product is released for sale or supply.

5.0 Retrospective Validation

5.1 There are many processes in routine use in many companies that have not undergone a formally documented validation process.

5.2 Validation of these processes is possible, using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. The steps involved in this type of validation still require the preparation of a protocol, the reporting of the results of the data review, leading to a conclusion and recommendation.

5.3 This type of validation exercise is only acceptable for well established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

5.4 The source of data for this validation may include batch documents, process control charts, maintenance log books, records of personnel changes, process capability studies (reflected in a CpK), finished product data, including trend cards, and storage stability results.

6.0 Re-validation

6.1 Re-validation provides the evidence that changes in a process and/or the process environment, introduced either intentionally or unintentionally, do not adversely affect process characteristics and product quality.

6.2 There are two basic categories of re-validation:

6.2.1 Re-validation in cases of known change (including transfer of processes from one company to another or from one site to another),

6.2.2 Periodic re-validation carried out at scheduled intervals.

6.3 A system should be in place (refer to Validation Master Plan requirements) to ensure both situations are addressed. Documentation requirements will be the same as for the initial validation of the process, and in many cases similar protocols can be employed.

6.4 The definition of what constitutes a change to a process or process environment needs to be agreed. Guidance on this is given below.

6.5 The need for periodic re-validation of non-sterile processes is considered to be a lower priority than for sterile processes. In the case of standard processes on conventional equipment a data review similar to what would be required for Retrospective Validation may provide an adequate assurance that the process continues under control. In addition the following points should also be considered:

6.5.1 The occurrence of any changes in the master formula, methods or starting material manufacturer,

6.5.2 Equipment calibrations carried out according to the established programme,

6.5.3 Preventative maintenance carried out according to the programme,

6.5.4 Standard operating procedures (SOPs) up to date and being followed,

6.5.5 Cleaning and hygiene programme still appropriate,

6.5.6 Unplanned changes or maintenance to equipment or instruments.

7.0 Change Control

7.1 Change control is an important element in any Quality Assurance system. Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or support system operation.

7.2 All changes should be formally requested, documented and accepted by representatives of Production, QC/QA, R&D, Engineering and Regulatory Affairs as appropriate. The likely impact (risk assessment) of the change on the product should be evaluated and the need for, and the extent of re-validation discussed. The change control system should ensure that all notified or requested changes are satisfactorily investigated, documented and authorised.

7.3 Products made by processes subjected to changes should not be released for sale without full awareness and consideration of the change by the responsible personnel.

7.4 Changes that are likely to require re-validation are as follows:

7.4.1 Changes of raw materials (physical properties such as density, viscosity, particle size distribution may affect the process or product),

7.4.2 Change of starting material manufacturer,

7.4.3 Changes of packaging material (e.g. substituting plastic for glass),

7.4.4 Changes in the process (e.g. mixing times, drying temperatures),

7.4.5 Changes in the equipment (e.g. addition of automatic detection systems). Changes of equipment which involve the replacement of equipment on a 'like for like' basis would not normally require a re-validation,

7.4.6 Production area and support system changes (e.g. rearrangement of areas, new water treatment method),

7.4.7 Transfer of processes to another site,

7.4.8 Unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).

8.0 References

PIC/S document PI 006-1: Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation.

END OF DOCUMENT

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REVISION HISTORY

Rev No.	DCC Ref No.	Author	Date of Revision	Remarks of Revision
001	-	-	01 Jan 2000	New.
002	-	-	03 Aug 2001	Change of organisation name
003	-	Terrance Ong	09 Dec 2002	Update document format.
004	211	Terrance Ong	01 Mar 2004	1) Change 3D HSA logo to 2D HSA logo. 2) Change Centre name to Centre for Drug Administration 3) Detached Revision History from Guidance Notes.
005	259	Terrance Ong	06 Sep 2004	1) Re-located Revision History to the main document.