1 Purpose

The purpose of this document is to provide guidance on the validation of processes for the manufacture of bulk drug i.e. those synthetic stages from introduction of the defined API Starting Materials into the process up to and including the physical processing of the API (Active Pharmaceutical Ingredient).

Validation should extend to those operations determined to be critical to the quality and purity of the API. The validation of stages prior to the API Starting Materials is not mandatory. A risk assessment may deem it necessary.

2 Scope and Applicability

All functions, departments and manufacturing sites or their contractors. The manufacture of intermediates post API starting materials up to and including final API, for onward sale external to the site or for use in site formulated products.

3 Definitions

3.1 Process Validation

Establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

3.2 Validation Protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Note: for process validation , the protocol would identify the number of validation batches.

3.3 API Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

3.4 Critical Parameter

A process parameter that must be controlled within an established range to ensure that the Active Pharmaceutical Ingredient or intermediate will meet specification.

steps from process development and/or historical data and Control (routinely test) other steps. Critical steps are those containing Critical Parameters and/or Critical Activities.

Process validation is therefore required from the first API intermediate stages containing critical steps, through to the stage producing the final API. For consistency of operation, some sites choose to validate all registered stages.

For outsourced registered stages, it is recommended that at least the final outsourced stage be validated, even if it does not contain identified critical steps.

5.2 Types of Validation

New or modified processes should be prospectively validated. In all cases, Process Validation activities should follow a pre ï prepared Validation Protocol which highlights the rationale for the work being carried out and clear acceptance criteria against which the outcome will be assessed.

5.2.1 Prospective Validation

Establishing documented evidence that systems do what they purport to do prior to the commercial distribution of a new product or an existing product made by a new or modified process. This should be based on a pre-planned protocol (normally a minimum of 3 consecutive batches). Prospective process validation is performed when a manufacturing process has been established or following a significant change.

5.2.2 Concurrent Validation

The validation carried out during routine production of products for sale.
In exceptional circumstances it may not be acceptable to complete a prospective validation program before routine production starts. Performed when the frequency of manufacture is insufficient to satisfy prospective validation requirements. Batches may be individually released, subject to meeting the requirements of the protocol. Whilst valid action of the process may not be formally complete during concurrent validation, there should be sufficient assurance that each batch was thoroughly monitored and tested. Concurrent validation may also apply to modified processes and where the product has a short ñshelf lifeò.

5.2.3 Retrospective Validation

The validation of a process for a product that has been marketed based upon accumulated manufacturing, testing and control batch data. It may be used as the basis to support (but not in lieu of) prospective/concurrent validation activities.

5.2.4 Prior to Commercial Process

Process validation activities during product development are the responsibility of

documentation for retention/archiving purposes. It should be retained in a manner that permits traceability and ensures that it is readily retrievable.

Validation Protocols should be clear written programs approved and issued in advance of the work, describing how the validation is to be done - including; detailed objectives, process and equipment to use, critical parameters/activities to evaluate, sampling and testing procedures, number and identify of batches, acceptance criteria and responsibilities.

In addition to the critical parameters, data for the EPR parameters can provide information beneficial during future manufacture.

Validation Reports should summaries the raw data, review deviations, evaluate the work against the acceptance criteria and conclude with a clear conclusion as to the validation status.

Approval of all protocols and reports by manufacturing and QA personnel should be undertaken.

Systems should be in place to provide continued assurance that the validation status is being maintained.

Change control and deviation reporting systems should assess all proposed changes and deviations for potential implications on the validated state, and in each case consider the need for any revalidation. The extent of revalidation may vary with the situation.

A periodic evaluation of the need for revalidation should also be undertaken e.g. by Annual Product Reviews.

5.5 Product Distribution

The manufacturing site undertakes the validation of all APIs and appropriate synthetic stages before product is distributed to the market. See also 5.2.2.

6 Appendices

6.1 Appendix 1 API and Intermediate Sampling and Testing.

B, M, E = Beginning, Middle and End

Note 1: Typically would take top, middle and bottom samples from the discharge process and compare with the blend using pre-defined acceptance criteria, which are based on scientific knowledge and quality attributes of the process. The aim is to minimize variations.

Note 2: Critical process parameters must be operated within their proven acceptable range during validation Critical activities must be carried out correctly.

Batch homogeneity must be proven by analyzing and comparing a minimum of 3 samples (typically beginning, middle and end). One suggested approach is to compare the results (beginning, middle, end and routine), together with their associated analytical variability, such that all ranges should have a value in common with the routine sample. The range can be calculated as the analytical result for the sample +/- method MAD (maximum acceptable deviation). As a minimum this should be done for strength but can also be done for impurity specification limits and other numerical limits.

The impurity profile must be proven to be comparable or better than historical data and, where applicable, the profile demonstrated for batches used in
pivotal clinical and toxicological studies.

For established products the suggested criteria are

- All results within specification
- No new imp >0.1%
- Values for each imp should lie below the historical mean + 3 std deviations
- No two out of three consecutive validation batch results should lie further than 2 std deviations above the historical mean

For new products (where limited batch data exists) suggested criteria are

- All results within spec
- No new impurity > 0.1%
- If sufficient data is available The Upper Control Limit (UCL) for each related substance, calculated using relevant data from process development and data from establishment and Validation, should be no higher than the specification limit, **or** be no higher than the UCL calculated using the relevant data from process development and establishment, whichever is the greater.

Critical in process tests shall pass acceptance criteria

Yields shall be within the predicted range (make an allowance for filter heels where appropriate)

