Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

1 Purpose

The purpose of this document is to provide minimum mandatory requirements in the validation of processes for the commercial manufacture of formulated products to demonstrate the effectiveness and reproducibility of a process and being suitable for the intended purpose. The purpose is also to outline recommendation on how to achieve compliance.

2 Scope and Applicability

This Guideline is applicable to all Operations, functions and departments undertaking work, or providing support services, required to meet Good Manufacturing Practice (GMP) or, in the absence of a GMP standard, International Organization for Standardization (ISO) standards.

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 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.

3.3 Concurrent Validation

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

3.4 Retrospective Validation

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

3.5 Validation Protocol

A written protocol or plan stating how validation, testing and sampling will be conducted, defining roles and responsibilities, and defining acceptance criteria.

3.6 Validation Report

If the validation batches are intended for commercial use, the conditions under which they are prepared and manufactured must comply with the GMP requirements.

5.5.1 Worst Case and Challenge Tests

The process should be challenged by making deliberate changes to demonstrate its robustness and to define its limits of tolerance. In challenging a process to assess its adequacy, the conditions should simulate those that could be encountered during actual production. These tests should be repeated enough times to assure that the results are meaningful and consistent.

Such worst case or challenge tests should preferably be performed prior to manufacture of validation batches. Typically, they are done during the Operational or Performance Qualification stage of a validation program.

5.5.2 Types of Validation

Depending on when the validation is performed in relation to production, it can be prospective, concurrent or retrospective. For new or modified processes, prospective validation must be the default method or approach. The rationale and justification for using concurrent or retrospective validation approach must be documented in the Validation Protocol and in the VMP (if applicable).

5.5.2.1 Prospective Validation

Prospective validation is carried out prior to the commercial distribution of a new product or an existing product made by a new or modified process. It is carried out when a manufacturing process has been established, or following a significant change.

5.5.2.2 Concurrent Validation

Concurrent validation is carried out during routine production of products for sale. In exceptional circumstances it may be acceptable not to complete all validation activities before routine production starts.

Concurrent validation can be performed when the frequency of manufacture is insufficient to satisfy prospective validation requirements. The batches may be individually released, subject to meeting the requirements of the Validation Protocol. There should be sufficient assurance that each batch was thoroughly monitored and tested.

Concurrent validation may also be applied to modified processes and where the product has a short “shelf life”.

5.5.2.3 Retrospective Validation

Retrospective validation must never be used as the general routine approach and can only be considered under unusual circumstances.

retrievable.

The Validation Protocol, describing how the validation activities are to be executed, must be clearly written with defined acceptance criteria. It must be approved by QA, issued in advance of the work and be version controlled.

Where deemed appropriate, rationales and justifications for the scope and strategy should be documented. The validation protocol should include, but not be limited to the following:

Detailed objectives
Process description
List of products/product strengths
List of process, facilities, systems and equipment to use
Summary of critical parameters and activities to evaluate
Number and identity of runs/batches
Release specification/s and list of analytical methods
Acceptance criteria
Proposed in-process controls
Additional testing to be carried out
Sampling plan and testing procedures
Methods for recording and evaluating results
Functions and responsibilities
Proposed timetable

The Validation Report must summaries the raw data and evaluate the work against the acceptance criteria. A clear conclusion needs to be written as to whether the validation has been completed and successful or not. The report should also include a summary of the acceptance criteria to be used in routine manufacture, and conclusions regarding future sampling and revalidation plans..

It should also include a review of deviations, their impact on the results and actions to correct them. Validation protocols and reports must be approved by manufacturing and QA.

5.8 Revalidation Requirements

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

