

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

A written report that summarizes the raw data and evaluates the validation work against the acceptance criteria defined in the Validation Protocol. It includes a clear conclusion as to whether the validation has been completed and successful or not.

for example about the behavior and the physical and chemical properties of the drug substance, the composition and the manufacturing process, to be able to clearly define the critical process parameters and controls. Collection of process monitoring data during the process development can provide useful information to enhance process understanding. The evaluation of the process during this phase should provide proof of feasibility of the process at the commercial scale.

The site that will manufacture the product should be involved during the process development phase, prior to Technology Transfer, to gain knowledge about the product and the process, as well as around scale-up and commercial scale manufacture.

5.4.1 Setting the Manufacturing Process to Work

When a new or modified product or process is being established there is invariably a period of experimental manufacture during which processing conditions may be adjusted until optimization of the process is achieved. This experimental setting to work should be carried out in accordance with a protocol that should specify the objectives, methods and criteria for completion of the work.

When all experimental work has been successfully completed and the product or process can be considered established, validation is ready to begin.

5.5 Validation of Commercial Process

The Process Validation must ensure by testing that a process is capable of repeatedly and reliably produce a formulated product of the required quality.

Information from R&D must be used to identify the critical process parameters to be tested during Process Validation in order to ensure batch reproducibility.

A risk assessment approach should be used to determine the scope and extent of validation.

A predefined number of validation batches (also called conformance batches) should be manufactured to demonstrate that, under normal conditions and defined ranges of operating parameters, the commercial scale process appears to make an acceptable product. It should normally cover the manufacture of at least three consecutive batches of material.

Validation should be performed under conditions to be used for routine manufacture. The batch size should be the same as or representative of the intended commercial scale batches.

Sampling and testing should be carried out to ensure compliance with the most stringent requirements.

Retrospective validation can only be 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.

Retrospective validation is part of a validation process for a product already in distribution based upon accumulated production, testing and control data. It includes a review of key historical data including analytical results, processes used and equipment used during a relevant period of review.

It may be used as a basis to support (but not in lieu of) prospective/concurrent validation activities.

5.5.3 Matrix or Family Approach to Process Validation

The general principle is to validate a manufacturing process and the 'same' process can typically be used for several related products. Rather than to develop a plan for each product manufactured by a process, it can be possible to develop a plan for that process instead.

There are two general principles that could be applied. 'Matrix approach' generally means a plan to conduct process validation on different strengths of the same product.

'Family approach' describes a plan to conduct process validation on different, but similar products.

Either approach must demonstrate that the process is consistent for all the strengths or products involved. The plan should be designed to evaluate all likely sources of variation in the products manufactured by the process.

Each plan should be evaluated on a case-by-case basis. For significant differences in equipment or process this approach would not be applicable and render each strength or product to be validated separately.

5.6 Timing of Process Validation

Process validation must be completed, evaluated, documented and approved before commercial distribution.

It is normally not expected that process validation be completed at the time of submission of a new product application to authorities. However, where the manufacturing process utilizes a non-standard method of manufacture, data demonstrating the validity of that method should be submitted in the EU marketing authorization dossier. These data should be submitted from all sites where production is intended to take place.

5.7 Validation Documentation

All documentation and raw data generated during validation activities is considered GMP documentation for retention/archiving purposes. It must be retained in a manner that permits traceability and ensures that it is readily