Regulatory Basis:

Reference: CFR - Code of Federal Regulations Title 21

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.

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.

Definitions

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.

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.

Concurrent Validation

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

Retrospective Validation

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

Validation Protocol

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

Validation Report

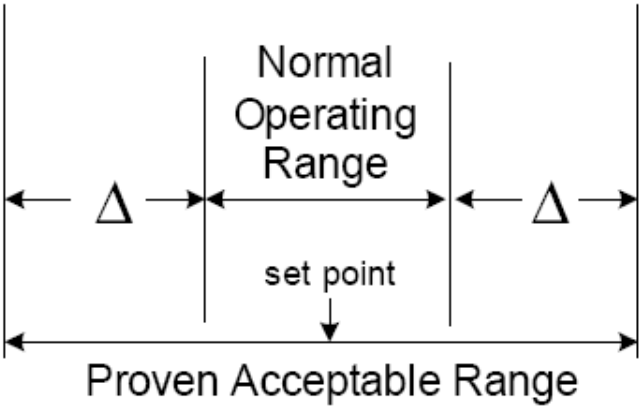
A written report that summarizes the raw data and evaluates the validation work against the acceptance criteria defined in the Validation Protocol. It includes a clear conclusion as to whether the validation has been completed and successful or not.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances,

Figure 1

Figure 1 is a useful reference to understand the critical process parameter ranges.



2. Validation Protocol Contents should include or reference, at least, the following:

- Validation approach to be used (e.g., prospective, concurrent, matrixing, bracketing, retrospective) with justification for approach chosen;
- Brief description of product, including product name, dosage form, and strength where applicable;
- Master manufacturing instructions or Device Master Record (DMR) to be validated;
- Brief description of process with a summary and/or process flow diagram of critical processing steps to be evaluated and critical parameters to be monitored;

  Acceptance criteria for the following:

  - Acceptability (meeting established critical quality attributes and specifications);
  - The number of consecutive successful validation batches/lots needed to show consistent control of the process.
  - Equivalency to existing medicinal products (where applicable) by comparison to previously produced batches/lots (commercial, development, or biobatches).
  - Requirements to conduct homogeneity and hold time studies, if applicable;
- Sampling plan, including type, amount, and number of samples, together with any special sampling or handling requirements.
- Critical process parameters and operating ranges, including justification for these Ranges.
- Calibration of any critical equipment used specifically for the validation studies (e.g., one-time studies on validation batches/lots using portable equipment, measuring equipment);
- Plan for the number of batches/lots to be put on stability, if any; and
- Methods for recording and evaluating results (e.g., statistical analysis).

- Changes to Active Pharmaceutical Ingredients (API) and critical excipients (change in API Site or manufacturer, route of synthesis for APIs, impurity profile, chemical or physical characteristics); and

- Major facility changes (e.g., Site, new aseptic area);

- Changes to major equipment such as size, design, or principle of operation;
- Changes in the acceptable range of a critical process parameter or a planned shift of the NOR that increases the risk of deviation and has the potential to adversely impact product quality;
- New reworking and/or reprocessing procedure;
- Fundamental change to manufacturing process or technology, for example:
  - Batch/lot size;
  - Dry to wet granulation or vice versa;
  - Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave);
- Changes that could affect acceptable microbiological quality of the medicinal product;
- For medical devices, any change that affects form, fit, or function of the device (e.g., material, components, manufacturing or assembly processes, and replacement of equipment); and
- Biopharmaceutical -example(s) such as filtration, concentration or mixing parameters, lengthening maximum hold time, and shipping conditions.

Changes in the process that result in a change in the Regulatory Process Description (RPD) should be addressed through the change management system.

11. Minor Changes may require consideration of revalidation or completion of supplemental studies to support the change. Examples of minor changes include, and are not limited to, the following:

- Changes to equipment with the same design and operating principle;
- Changes, which are unlikely to have measurable impact on product quality or performance, as determined by risk assessment;
- Change within a single Site using the same equipment as previously validated;
- Change in existing code imprint (e.g., changing from numeric to alphanumeric, addition of an ink code imprint, or change to ink used for a solid dosage form where the ink is already used on approved products); and
- Change of imprint by embossing, debossing, or engraving on a solid dosage medicinal product, with the exception of modified release dosage forms.

12. APIs and Excipients used in a validation study should meet all chemical, physical, and microbiological specifications.
Any changes to an API, excipient, carrier vehicle, or to the manufacturing process should be assessed for their potential to affect characteristics of the medicinal product or medical device. Changes determined to affect product quality should be validated, including a comparison to the previously produced batches/lots (e.g., commercial, development, or biobatches).

For changes to the API in medicinal products with multiple strengths, with similar formulations and processes, a worst case matrix approach qualification can be conducted considering a bracket design that covers multiple product strengths.

13. Sterile and Aseptically Filled Medicinal Products and Aseptically Processed Medical Devices include large and small volume parenterals, ophthalmics, and dry powder products. Process validation of such products should include evaluation of the critical steps (e.g., formulation, mixing, filtration, lyophilization, and filling

- Comparison with the previously produced lots (e.g., commercial, clinical, development, or biobatches).

Device Parameters:
- Robustness of Process Capability of component manufacturing and finished device assembly processes demonstrated; and
- Compliance of component(s) to specification including extractables data for components in the medicinal/airway path and in intimate mucosal contact. Validation should be initiated as the result of a component change.

Medicinal/Device Combination Parameters:
- Respirable Fraction of delivered dose.

If validation is being carried out as a result of a change to an existing process, documented justification should be provided in the validation protocol if any of the above applicable parameters are not to be assessed.

15. Metered Dose Inhalers
The validation protocol should include, at a minimum, assessment of the following parameters:
- Moisture content;
- Delivered dose uniformity; this should assess both inter and intra inhaler dose uniformity. The dose uniformity should be assessed from the last nominal shot to exhaustion using three (3) canisters from, at least, two (2) different batches/lots;
- Fine particle dose using a multi-stage impactor or impinger;
- Fill weight or volume and number of dose deliveries from the container;
- Foreign matter including particulates;
- Compliance with finished product specification; and
- Comparison to the previously produced lots (e.g., commercial, clinical, development or biobatches).

Device Parameters:
- Robustness of Process Capability of component manufacturing and finished device assembly processes demonstrated; and
- Compliance of component(s) to specification; including extractables data for components in the medicinal/airway path and in intimate mucosal contact. Validation would be initiated as the result of a component change.

Medicinal/Device Combination Parameters:
- Respirable Fraction of delivered dose.

If validation is being carried out as a result of a change to an existing process, documented justification should be provided in the validation protocol if any of the above applicable parameters are not to be assessed.

16. Oral Solutions and Suspensions include medicinal products such as elixirs, emulsions, solutions, gels, syrups, tinctures, and suspensions.

The process validation protocol for oral solutions and suspensions should include assessment of, at least, the following:
- In-process assay of bulk before filling (where applicable);
- Homogeneity sampling plans should include representative samples from:
  - Throughout the bulk suspension;
  - Top and bottom of solutions, and
  - During the filling operation;
- Rheological properties such as viscosity, thixotropy (where applicable);
- Potency;

- Sample sizes for blend uniformity should be the approximate weight (e.g., 1-3x) of the dosage unit If validation is being carried out as a result of a change to an existing process, documented justification should be provided in the validation protocol if any of the above applicable parameters are not to be assessed.