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

Critical Process Parameters

Critical process parameters (including ranges) and critical quality attributes of the process being validated must be identified and justified. The validation committee is responsible for ensuring that the ranges proposed in the validation protocol for critical process parameters are correct and have supporting documentation included or referenced in the protocol.

Where a change is required to a critical process parameter during the validation study, the effect of the change should be assessed for its impact on the validation study. The change may require restarting the validation study using the new critical process parameter value(s). The previous validation batches shall be evaluated and their disposition documented in the report. The assessment of the impact of the change on the validation study shall be documented in the validation report.

Changes in non-critical process parameters may prove necessary during process validation to improve the performance of the process while ensuring that the process produces products that meet acceptance criteria. Such changes shall be documented and justified in the validation report and evaluated for their impact (individual and cumulative) on the validation exercise.

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

and air-entrainment (foaming) begins at 100 rpm. These are the PAR values (minimum 50 rpm/maximum 100 rpm).

The NOR should not be estimated. It should be supported with data as outlined below. Consideration should first be given to the equipment qualification and the accuracy and precision of the instrument reporting the monitored parameter.

Example 4-Mixing speed NOR, considering calibration
Continuing with the mixing speed example (minimum 50 rpm/maximum 100 rpm), we will assume the calibrated certainty of the measurement of the mix speed is +/-5 rpm. Therefore, the NOR for mixing speed can be no greater than 55 to 95 rpm to allow for the uncertainty of the measurement (i.e. a set point of 55 rpm may provide an actual mix speed of 50 rpm).

The NOR should be centered, where possible, between the PAR limits, but equipment capability and other operating considerations may not permit this ideal to be realized.

Example 5 – Mixing speed; selecting NOR based on PAR
In the mix speed example, we will assume that 100 rpm is the maximum capacity of the mixer. We do not want to run the mixer near capacity so we prefer to select a NOR closer to the lower limit. However, we would also like to establish a buffer or safety factor between the lower PAR and the lower NOR since homogeneity is the most important factor in this step. We will select a NOR of 70-80 rpm with a target of 75 rpm. This provides us the assurance that we are at least 15 rpm (70 rpm – 50 rpm lower limit – 5 rpm uncertainty = 15 rpm) above the lower PAR value and 15 rpm below (100 rpm upper limit – 80 rpm – 5 rpm = 15 rpm) the upper PAR value. In this example, the criticality of the parameter has been reduced since the PAR is large, NOR is small and the parameter is reliably controlled. The NOR for mix speed can be expected to be a robust process parameter.

In practice, it is not always possible to center the NOR due to equipment and/or product-related limitations. However, the concept demonstrated through the examples above remains applicable to all variable parameters.

Additional considerations

Other aspects of process control that are not operational parameters should be evaluated as part of the quality risk assessment. These may influence equipment qualification, method validation and/or additional studies that may be needed because of their importance to product quality. Examples include:

- A performance parameter such as an In-process Control (IPC) that impacts a product CQA, for instance:
  - For an API process, an in-process test performed to insure that a process operation meets a critical quality endpoint; and
  - For a DP process, an in-process test used to prevent diluting of material beyond defined mix characteristics.
- A filtration to remove insoluble particulate matter;
- Environmental condition (e.g., temperature or humidity) that must be controlled because of an impact on a CQA;
- Equipment set points and configurations that are not operational parameters but that may impact on a CQA;
- Processing time limits, if the probable adverse consequence of exceeding a time limit risks unacceptable final product quality, such as:
  - Permitting an excessive reaction time in a synthetic API process when this allows formation of an unacceptable amount of a process impurity not adequately controlled by other means;
  - Delay in the processing of a mixture;
  - Other hold time limits that should be identified to understand process capabilities.

Knowledge of the Proven Acceptable Range (PAR) for a process parameter may be established from:

- Experimentation during laboratory and/or pilot scale development of the process, typically done during development of the process or evaluation of potential process improvements.
- Experience with demonstration batches, historical batches, and/or commercial-scale production batches. Statistical analysis of data may sometimes be used to help establish PAR limits.
- Knowledge acquired from deviations and incidents;
- Experience with PARs in similar processes to make analogous products; or
- Theoretical considerations. For some parameters it may be preferable to document a theoretical rationale why they are expected not to be critical to product quality. The theoretical argument should support a conclusion that the parameter is not critical because the PAR is significantly wider than the normal operating range (NOR) defined for that parameter.

Comparing the Normal Operating Range (NOR) to the PAR is one part of performing a risk assessment of potentially critical process parameters. The comparison will typically reveal one of three general situations:

- The NOR is a significantly smaller range than the PAR (as depicted in Figure 1, where the value of Δ is relatively large). It is typical to conclude such parameters are not critical to product quality if the magnitude of Δ minimizes the risk of exceeding the PAR.

Determination of overall risk:

The overall risk is referred to a quantitative Risk Priority Number (RPN). The RPN is calculated as follows:

RPN = Severity (S) x Frequency (F)

Thresholds for action (or for determining criticality) based on RPN scoring should be agreed upon by reviewers before performing the risk assessment. A sample of action thresholds based on the above scoring strategy is shown below. Justification of values assigned to Severity and Frequency for each evaluated risk should be provided in risk assessments.

Action Thresholds		
Risk category	**Risk factor (RPN)**	**Interpretation**
Intolerable Region: Unacceptable Level of Risk	40 or greater: Intolerable risk	The risk is so severe that it is not tolerable. Refer to Appendix III (explanation of Figure C) for general approaches for reducing risk .
Acceptable Levels of Risk; mitigation recommended (ALARP region)	>24: Risk is tolerable only if reduction is impractical, or costs of mitigation are disproportionate to improvement	Risk in this region are CPPs and should be evaluated bearing in mind the benefits of accepting the risk and the costs or further reduction. Acceptable risk is established on a case-by-case basis.
Acceptable Risk	24 or lower: Negligible risk	The risk is negligible/not CPP, compared with the risk of other hazards that are accepted. Mitigation not necessary, however for business reasons, management may decide to mitigate.

A qualitative classification for risk scoring (low, medium, high) may be used rather than a quantitative scaling. In this event, thresholds for action should still be defined before performing the risk assessment.

