

## **Regulatory Basis:**

FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

## **General Discussion**

This document addresses the application of matrices and bracketing strategies to process validation (PV).

Bracketing and matrixing allow a ‘most appropriate challenge’ condition to be defined for a process or drug product family (the same drug product with different dosage strengths). This risk-based approach can allow the validation to be focused on the most challenging circumstances, or “worst cases.” Use of this approach can provide a significant benefit to reduce the overall validation effort. Bracketing or matrixing may be used for validation of Drug Product, Active Pharmaceutical Ingredient and Packaging processes when this approach can be justified.

Bracketing is the assessment of a single parameter or variable by identifying the edge(s) of the range of conditions for the parameter or variable and assessing these during validation to span the possible range of that parameter/variable. Bracketing can be applied to process parameters, multiple pieces of identical equipment, and/or different size considerations for the same product, for instance.

Matrixing involves the assessment of the effect of more than one parameter or variable by using a multi-dimensional matrix to identify the “worst case” conditions for a combination of parameters/variables. These conditions are used during validation of the process, rather than validating all possible combinations.

Matrixing is typically used when there are significant similarities between products in a drug product family (e.g., same product different strengths in the manufacturing stage or different products with similar container closure in the packaging stage).

Examples of variables that might be assessed by bracketing and matrixing include, but are not limited, to:

- Batch size;
- DP dosage strength;
- Identical equipment (e.g. where setup and operating conditions are the same);
- Product packaging, such as where only a minor adjustment in packaging parameters is required to accommodate different bottle heights or dosage counts.

Matrixing across different products may be applied to the packaging validation of the final dosage form, for example to evaluate the packaging of different products in a common packaging presentation. As with other uses of bracketing and matrixing, the risk

## Matrices and Bracketing of Medicinal Products in Process Validation

“Worst case” selections are the lowest and highest dosage strengths (5/10 and 10/40). This would typically mean validating three lots each of the 5/10 and 10/40 dosage strengths, and one lot each of the other dosage strengths (10/10, 10/20, 5/20, and 5/40). This option will better show reproducibility in compressibility of the mixtures since it includes the smallest tablet size with the lowest weight in the tablet of both active ingredients (which has the greatest chance of segregation on the press due to longest run and low active weight) and then the largest tablet with the highest weight of both active ingredients in the tablet (which has the greatest chance of poor press performance due to presence of active). However, this option does not show reproducibility directly on the blend as well as Option 1.

- B.** Factors that might affect the matrixing include, but are not limited to:
- Nature of the formulation;
  - Tablet shape and dimensions (because of potential impact on machine settings and tablet hardness)
  - Compressibility
  - Dissolution characteristics
  - Batch size
  - Equipment used; and
  - Similarity of process parameters across the various blends.
- C.** If two different models of compressing machines will be used during the initial validation, the extent of validation will depend on the history of these machines.

If similar parameters can be used and experience with other products show the machines perform similarly, it may be enough to make lots on one machine without requiring additional validation lots on the other machine. If the history is that the machines perform differently, then it may be necessary to run a three-lot validation study on one machine and run the worst case (for compression) in triplicate on the second machine together with one lot each of all other strengths to confirm the parameters. This assumes that there has been development or qualification work on the machine to establish the parameters.

If machines of the same design are used, it is good practice for the validation study to include at least one lot on each of the machines, but it is not a requirement.

- D.** Evaluating any change should include assessment of the risk to product quality arising from the proposed change. Revalidation may not be necessary if the proposed change poses little risk to product quality. For this example, it is assumed that there is an appreciable risk to product quality because magnesium stearate is a critical component that functions in the mixture as a lubricant and prevents material from sticking in the press. It also impacts the dissolution properties of the formulation because of its lipophilicity. Validation of the source change is therefore considered necessary in this case because of its critical nature