- 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 of using this strategy for the potential products encompassed by the matrixing plan should be considered, documented and approved.
The use of bracketing/matrixing for the validation of a manufacturing process across different products should be approached with caution because of the risk of overlooking other possible affects of the change. Use of this type of bracketing/matrixing requires a good understanding of the processes involved and the risks being assumed. For example, in the evaluation of a change of a critical material for different products, the excipient interactions, critical process parameters and critical quality attributes (CQAs) are not necessarily the same for each product. The effect of the change in the CQAs may be different for each product. A product sensitive to the change may experience a failure in a CQA (e.g. dissolution) while in a case of a product not sensitive to
the change, it may experience no effect at all in its CQAs.

To obtain the maximum benefit with minimum risk from bracketing and matrices, it is necessary to have a well-developed understanding of the impact of critical process parameters on critical quality attributes. There should be a documented and justified rationale that explains why one set of test conditions (e.g., manufacturing process, product presentation, etc.) is representative of one or more related test conditions. Typically, the rationale is addressed by selecting parameters and/or products that represent the edges of a range or “worst case” of allowable conditions. The rationale and justification for the bracketing/matrixing strategy to be used in validating a process should be provided in the validation protocol, or in another document referenced in the protocol.

Depending on the circumstances, prospective and concurrent validation approaches may be used for validating a process using bracketing or matrixing. If a concurrent approach is used, an interim report provides a summary of the results obtained for a product batch, in order to justify the validation and release of one of the product presentations within the bracket/matrix. This approach may also assist in approving the manufacturing and/or release of additional batches of a particular presentation. At the completion of the validation, the validation report will address all batches.

At present, some regulatory authorities may not accept the use of bracketing or matrixing for validation. Japan, for example, currently requires that all combinations be validated.

The following examples include possible matrixing/bracketing approaches. There may be other acceptable approaches.

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 to the formulation. Given experience with the product's blend ratios and dosage strengths and the manufacturing process, the matrixing strategy described for validation (see answer A in this example) can be used.

Example 3: Bracketing and Matrixing for a DP packaging process
A new product will be transferred from one manufacturing site to another. The product is a capsule dosage form. A common blend is used to prepare five different dosage strengths. The packaging presentations and capsule sizes are shown in Table 2:

Table 2: Bracketing and Matrixing for a DP packaging process

Table 2			
Dosage	**Capsule size**	**Capsule fill weight**	**30-count bottle**
120 mg	2	80 mg	80 cc
180 mg	2	120 mg	80 cc
240 mg	0	160 mg	90 cc
360 mg	0	240 mg	90 cc
420 mg	00	280 mg	120cc

Define a bracketing and matrixing strategy for the process and packaging validation that defines which dosages and how many of each should be included in the validation study.

ANSWERS for Example 3
Process Validation Strategy:
This example is one of matrixing because we have a solid dosage form compounded in various dosages with similar overall shape and size using a common blend. The challenge in the encapsulation stage is to be able to fill consistently the different capsule sizes at the specified weight.

The "worst case" extremes are 120 mg (lowest weight) and 420 mg (highest weight). A typical strategy would be to include three lots each of the worst case dosage weights, and one lot each of the dosages that fall between these extremes. Capsule size and capsule fill

