means a range of strengths with similar, but not identical, basic composition such that the ratio of the active ingredient to excipients remains relatively constant throughout the range, allowing for addition or deletion of colorant or flavoring, for example. Where the strength and the container size and/or fill quantity of a drug product vary, a bracketing design may be applicable with the necessary justification.

A bracketing design should always include the extremes of the intended commercial sizes and/or strengths. However, if the extremes are not truly the worst-case selections based on strengths, container sizes, and/or fill quantities, use of a bracketing design is not appropriate. Where the amount of the active ingredient changes, whereas the amount of each excipient or the total weight of the dosage unit remains constant, bracketing may not be applicable unless justified.

If the market demands require discontinuing either the lowest or the highest bracket extreme and marketing of the intermediate sizes or fill quantities are still needed, the post-ANDA approval commitment to conduct ongoing stability at the extremes of the bracketing should be maintained.

Before implementing a bracketing design, its effect on shelf-life verification should be assessed. If the stability of the extremes is shown to be different, the intermediate packages should not be assumed to be more stable than the least stable extreme. In other words, the shelf-life of the intermediate packages should not exceed that for the least stable extreme of the bracket.

A bracketing design from the guidance Q1D is illustrated in the following table to demonstrate the concept behind bracketing [22]. This example is based on a product available in three strengths and three container sizes. For the selected combination of batches, the postapproval stability program should require testing at all time points to assure that the results continue to meet all stability-related specifications.

Example of a bracketing design:

		Strength								
		50 mg			75 mg			100 mg		
Batch		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Container size	15 cc	T	T	T				T	T	T
	100 cc									
	500 cc	T	T	T				T	T	T

T = test sample at all time points specified in the post approval commitment.

An intended bracketing design should be included in the stability testing protocol of the ANDA application. If the ANDA application does not contain the bracketing design, a supplemental application and approval will be required before implementation of the design for stability studies of routine production batches.

Matrixing

The CDER has also accepted the ICH guidance on matrixing, which is another type of a reduced design based on different principles [5,22]. In a matrixing design, a fraction