Evaluation of Multivariate Statistical Distance (MSD) Method for Dissolution Similarity of Highly Variable MR Product
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**Purpose**
To study applicability of MSD for highly variable MR product over traditional f2 value comparison.

**Methods**
Current FDA guidelines suggest that two profiles can be considered similar if f2 is greater than 50 (50–100), which is equivalent to an average difference of 10% at all sampling time points. Multivariate confidence region procedures are recommended by the FDA for comparing dissolution profiles in instances where within-batch variation is greater than 15%. We carried out the dissolution study of BCS class II modified release product of innovator and compared with in house test batches. Product design is matrix coated with enteric polymer thus may give variability in dissolution media. Products were given acid exposure followed by drug release measurement in pH 6.5 buffer. Two different lots of approved products (Biolot and other lot) were evaluated and compared with test product. Dissolution data is analyzed by similarity factor and multivariate statistical method between biolot and test product.

**Results**
The data showed that at earlier time points tablet-to-tablet variability was very high (RSD > 20%), the observed mean difference between two approved products was as high as 16%. Because the f2 criterion does not consider tablet-to-tablet variability at each time point (may or may not formulation related) into the calculation of f2 score, it concludes dissimilar dissolution profile (f2<50) between biolot and test product solely on earlier time point difference. On the other hand, MSD is based on an estimator, which is a weighted average of the mean profile differences at all time points and also considers the variability between approved products concluded similarity in dissolution profile, concluded the similarity in dissolution profile.

**Conclusion**
Thus it is reasonable to use MSD approach where variability is very high in dissolution which may be product design related or dissolution method related.