

(the average sum of squares) difference in mean cumulative percentage dissolved between the test and reference formulations over all sampling time points. That is,

$$f_2 = 50 \log \left\{ \left[1 + \frac{Q}{n} \right]^{-0.5} 100 \right\}, \quad (8.4)$$

where

$$Q = \sum_{t=1}^n (\mu_{R_t} - \mu_{T_t})^2,$$

and \log denotes the logarithm based on 10.

On the other hand, the difference factor is the sum of the absolute difference in mean cumulative percentage dissolved between the test and reference formulations divided by the sum of the mean cumulative dissolved of the reference formulation.

$$f_1 = \frac{\sum_{t=1}^n |\mu_{R_t} - \mu_{T_t}|}{\sum_{t=1}^n \mu_{R_t}} \quad (8.5)$$

It should be noted that the definitions of f_1 and f_2 provided by Moore and Flanner (1996) and in the SUPAC and guidance on dissolution testing are not clear as to whether they are defined based on the population means or the sample averages. However, following the traditional statistical inference with ability for evaluation of error probability, we define both f_1 and f_2 based on the population mean dissolution rates. It follows that f_1 and f_2 are population parameters for the assessment of similarity of dissolution profiles between the test and reference formulations.

The use of the f_2 similarity factor has been discussed and criticized by many researchers (e.g., Liu et al., 1997; Shah et al., 1998; Ma et al., 1999). Chow and Shao (2002) pointed out two main problems in using the f_2 similarity factor for assessing similarity between the dissolution profiles of two drug products. The first problem is its lack of statistical justification. Since f_2 is a statistic and, thus, a random variable, $P(f_2 > 50)$ may be quite large when the two dissolution profiles are not similar. However, $P(f_2 > 50)$ can be very small when the two dissolution profiles are similar. Suppose that the expected value $E(f_2)$ exists and that we can find a 95% lower confidence bound for $E(f_2)$. Then, a reasonable modification to the f_2 similarity factor approach is to replace f_2 with the 95% lower confidence bound for $E(f_2)$. The second problem with using the f_2 similarity factor is that the f_2 similarity factor assesses neither local similarity nor global similarity, owing to the use of the average of the dissolution data.