Comparison of *in vitro* Profiles

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General Considerations

Prerequisites of in vitro data:

- All *in vitro* data generated with the same method
- Differences to be taken at the same sampling times
- Differences taken from average values (profiles) with low data variability

Acceptable difference

- Up to 10% average difference in the profiles is assumed to reflect sameness in product performance in patients

f1: „Difference Factor“

- „Proportional to the average difference between two profiles“
- Normalised to percent, acceptance value based on 10% average difference between profiles
- Identical profiles have an f1 value of 0, profiles are considered not different if f1 is between 0 and 15 %

$$f_1 = \left(\frac{\sum |R_n - T_n|}{\sum R_n} \right) \times 100\%$$

f2: „Similarity Factor“

- „Inversely proportional to the average squared difference between two profiles“
- Normalized to percent, acceptance value based on 10% average difference between profiles
- Identical profiles lead to an f2 factor of 100, profiles are considered similar if the f2 value is between 50 and 100

$$f_2 = 50 \log \left\{ \left[1 + 1/N \sum \left(R_n - T_n \right)^2 \right]^{-0.5} \times 100 \right\}$$

Points to remember when calculating the factors

- Profiles need to belong to same curve type
- Average profile based on 12 individual determinations, CV below 10% (up to 20% at early values)
- Only one release value above 85% permissible

- Profiles from rapidly dissolving IR formulations need not be compared by f1 or f2 factors

Regulatory Practice

- Type I (or Level 2) modifications are acceptable if the f1 or f2 criteria are met
- f2 is used more commonly than f1

Pertinent references:

J. Moore and H. Flanner, Pharmaceutical Technology, June 1996, page 64

V. Shah et al., Pharmaceutical Research, **15**, 889-896 (1998)

V. Shah, Dissolution Technologies, August 1999, page 15

J. Polli et al., Pharmaceutical Research, **18**, 734-741