DISSOLUTION PROFILE SIMILARITY FACTOR, F_2*

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I. INTRODUCTION

- After a drug is approved for commercial marketing, there may be some changes with respect to chemistry, manufacturing, and controls. Before the postchange formulation can be approved for commercial use, its quality and performance need to be demonstrated to show similarity to the prechange formulation. Because drug absorption depends on the dissolved state of drug products, in vitro dissolution testing is believed to provide a rapid assessment of the rate and extent of drug release. As a result, Leeson (1995) suggested that in vitro dissolution testing be used as a substitute for in vivo bioequivalence studies to assess equivalence between the postchange and prechange formulations.

- These postmarketing changes include scale-up, manufacturing site, component and composition and equipment and process changes.
- In 1995, the U.S. FDA published “Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation” (SUPAC–IR).
- Moore JW, Flanner HH (1996) proposed difference factor f_1 and similarity factor f_2 for the comparison of dissolution profiles.
- In 1996, Shah, Tsong and Sathe formed a working group to develop and evaluate methods for the comparison of dissolution profiles.

II. NOTATION AND FORMULA FOR f_2

- Let Y_{ijk} be the observed cumulative percent dissolved for the dosage unit j at sampling time k for formulation i, where k =1, …, n; j =1,...,J; i =T, R. For the same dosage unit, we use the notation $Y_{ij} = (Y_{ij1}, \ldots, Y_{ijn})'$ with mean vector $\mu_i = (\mu_{i1}, \ldots, \mu_{in})$ and covariance matrix Σ_i, where T and R denote postchange and prechange formulation, respectively.
- Let $W = \Sigma(\mu_{Rk} - \mu_{Tk})^2$, then

$$f_2 = 50log[(1 + W/n)^{-\frac{1}{2}} \cdot 100\frac{W}{n}]$$

- The standardized similar factor has a maximum value of 100 when $\mu_{Rk} - \mu_{Tk}$ =0 at all k. A minimum value close to 0 when $\mu_{Rk} - \mu_{Tk}$ = 100 at all k.
- When $\mu_{Rk} - \mu_{Tk}$ = 10 at all k, f_2 =50. SUPAC-IR and SUPAC-MR both suggested to consider profile similar if $f_2 > 50$.
- Moore and Flanner (1996) proposed to use the point estimate of f_2 with $\bar{X}_{Rk}$ and $\bar{X}_{Tk}$ for μ_{Rk} and μ_{Tk} respectly in W for f_2.

III. LIMITATIONS OF f_2 AS PROPOSED BY MOORE AND FLANNER (1996)

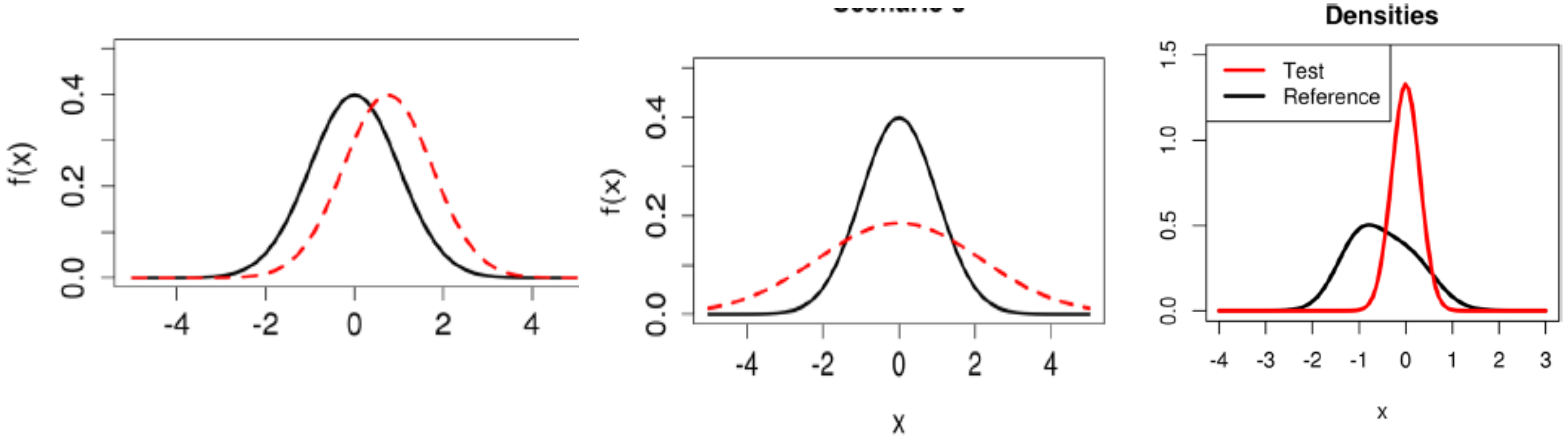
- Used as a deterministic factor instead of an estimate.
- With no restriction on using data in early and late dissolution stages.
- Is f_2=50 a meaningful margin?
- Is there any method to use when the sampling time of two profiles are different?
- Is there any approach with better statistical properties?
- May it be used beyond simple SUPUC change as proposed?
- What we call for profile comparison?

Equivalence, Similar and Comparable

Equivalence: Difference of means is bounded within the margin

Similar: Overall-shapes difference is bounded within the margin

Comparable: Test quality falls (in high percentage) within the quality rage determined by the reference



IV. STATISTICAL CONSIDERATION FOR f_2

- Let δ_0 be the similar margin, the statistical hypothesis can be expressed as,

  H_0: $f_2 \leq \delta_0$ vs. H_a: $f_2 > \delta_0$

- Let $\hat{f}_2 = 50\log[(1 + \widehat{W}/n)^{-1/2} \cdot 100]$
  with $\widehat{W} = \Sigma(\bar{X}_{\mathrm{Rk}} - \bar{X}_{\mathrm{Tk}})^2$
- The standard error of $\hat{f}_2$ can be determined by bootstrapping method under nonparametric assumption (Shah et al, 1998).
- It is also derived based on multinormal distribution (Ma et al, 2000).
- It was shown that $\hat{f}_2$ is a conservative estimate of f_2.

  $E(\hat{f}_2) = \mathrm{E}\{50\log[(1 + \widehat{W}/n)^{-1/2} \cdot 100]\}$

  $\approx 100 - 25\log(1 + E[\widehat{W}/n])$

  with Taylor'sexpansion

  $< 50log[(1 + W/n)^{-\frac{1}{2}} \cdot 100\frac{W}{n}] = f_2.$

- Shah et al (Pharm. Research, 1998) proposed bias correction.

Limitations of f_2

- The margin δ =50 is derived by assuming $\mu_T - \mu_R$ =10 at all time points.
- The margin δ =50 was determined arbitrary.
- Problem to extend to in-vitro BE in general (Duan et al, 2011).
  - When f_2 is generalized beyond SUPAC, one need to consider multiple batches (say, 3 batches each) of both test and reference products with 12 units per batch.
- f_2 does not imply $\mu_T - \mu_R \leq 10$ at all time points.
- f_2 can be liberal when n (total sampling time points) is large.
- f_2 can be adjusted by covariance structure when using bootstrap method.
- Needs to have the first measurement > 15% and no more than 1 measurement post 85% dissolved.

V. Alternative similarity/difference methods

(Ma et al, 1996) studied the following difference factors

- Weighted mean difference squares $\sum w_k(\mu_{Tk} - \mu_{Rk})^2$
- Weighted absolute differences $\sum w_k|\mu_{Tk} - \mu_{Rk}|$

(Tsong, Sathe and Shah, 2003) discussed other alternative distances

- Maximum $\{|\mu_{Tk} - \mu_{Rk}|\}$
- Mean distance $\Sigma|\mu_{Tk} - \mu_{Rk}|/K$
- Difference of areas under the profiles
  $\sum\{[(\mu_{Tk} + \mu_{T(k-1)}) - (\mu_{Rk} + \mu_{R(k-1)})]\cdot(t_k - t_{k-1})/2\}$
- 1st- and 2nd- order Rescigno indices
- and their weighted versions
- Standardized mean squared distance (Mahalanobis distance) (Tsong et al, 1996, DIJ)

Other alternative approach

- Similar factor f_2 and Mahalanobis distance were proposed for SUPAC in-vitro equivalence when both test and reference profiles were measured at the same time points.
- For the profile comparison with dissolution measurements at different time points, modeling approaches were discussed by Sathe et al (1996, PS) and Tsong (2003). A two parameter Weibull model was recommended in general.

VI. SUMMERY AND CONCLUSION

- Dissolution test is one of the most valuable in vitro tests used to assure the drug product quality.
- Similar dissolution profile is in general considered as an assurance of product sameness and product performance in the presence of scale-up and SUPAC changes.
- However, finding a method to assess similarity between two profiles is not a simple task even though f_2 has been considered the simplest and most widely applicable method for this purpose.
- The statistical properties of f_2 has been studied under normality assumption and nonparametric assumption.
- But its generalization to in-vitro bioequivalence of all drug products is questionable due to the difference in variability and number of measurements from product to product.

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THANK YOU!!!