STATISTICAL EXPERIENCE AND CHALLENGES IN ASSESSING SIMILARITY OF DISSOLUTION PROFILES, PARTICAL SIZE DISTRIBUTIONS AND API SAMENESS

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This presentation reflects the views of the speaker and should not be construed to represent FDA's view or policy.

OUTLINE

I. INTRODUCTION
II. DISSOLUTION PROFILES COMPARISON
III. COMPARISON OF PARTICLE SIZE DISTRIBUTIONS
IV. COMPARISON OF COMPONENTS OF CONJUGATE ESTROGEN
V. CONCLUSION

I. INTRODUCTION

- In-vitro bioequivalence or similarity may serve as biowaiver for in-vivo bioequivalence.
- In-vitro data often represented as multivariate or repeated measurements.
- Statistical approach to show in-vitro bioequivalence or similarity consists of three steps
  - Define a proper metric of difference or similarity between test and reference products
  - Derive an (unbiased) estimate of the population difference/similarity metric
  - Define a proper margin of equivalence or similarity
- The challenge is to generalize the application

II. DISSOLUTION PROFILES COMPARISON
A. INTRODUCTION

- 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.
- 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.

- Sathe P, Tsong Y, Shah VP (1996a). In Vitro Dissolution Profile Comparison: Statistics, and Analysis, Model Dependent Approach,'' Pharmaceutical Research, 13, 1799–1803.
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- Liu S, Cai X, Shen M, Tsong Y (2022). In vitro dissolution profile comparison using bootstrap bias corrected similarity factor, f_2. In revision for publication in Statistics in Medical Research.

B. 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 $Y_{ij} = (Y_{i1}, \ldots, Y_{in})'$ 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

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

- 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.

C. 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?

D. 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 was shown that $\hat{f}_2$ is a conservative (bias) 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's expansion

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

- 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.
- 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.
- Bootstrap method of the bias-corrected estimate of f_2 (Liu et al, to be published)

$$\hat{f}_2^* = 50 \log\{[1 + \frac{1}{p}\sum_{i=1}^{p}(x_{ti} - x_{ri})^2 - \sum_{i=1}^{p}(s_{ti}^2 + s_{ri}^2)/n]^{-0.5} \times 100\}$$

E. ALTERNATIVE METRICS AND METHODS

- Standardized mean squared distance (Mahalanobis distance) (Tsong et al, 1996, DIJ)

$$D_M = \sqrt{n[(\mu_t - \mu_r)'\Sigma_{pooled}^{-1}(\mu_t - \mu_r)]/2}$$

where $\Sigma_{pooled} = (\Sigma_t + \Sigma_r)/2$ is the covariance matrix pooled across both test and reference products, $\mu_i = (\mu_{i1}, \mu_{i2}, \ldots, \mu_{ip})$, i=t, r is the vector of the mean dissolution of test and reference.

- $\widehat{D_M} = \sqrt{\{n[(\hat{\mu}_t - \hat{\mu}_r)'S_{pooled}^{-1}\,(\hat{\mu}_t - \hat{\mu}_r)]/2\}}$,

  where $\hat{\mu}_t, \hat{\mu}_r$, and S_{pooled} are sample means and sample pooled standard deviation.

- Under the same consideration for f_2, the margin needs to be $\sqrt{n\left[(10)'\Sigma_{pooled}^{-1}(10)\right]/2}$. It needs to be estimated with data

- Modelling approach (Sathe P, Tsong Y, Shah VP (1996a)).
- Best fit model is two-parameter Weibull curve.
- Determine the model for reference.
- Determine the model for test with the same type of model.
- Compare the two parameters of test and reference models.
- How to determine the margin?

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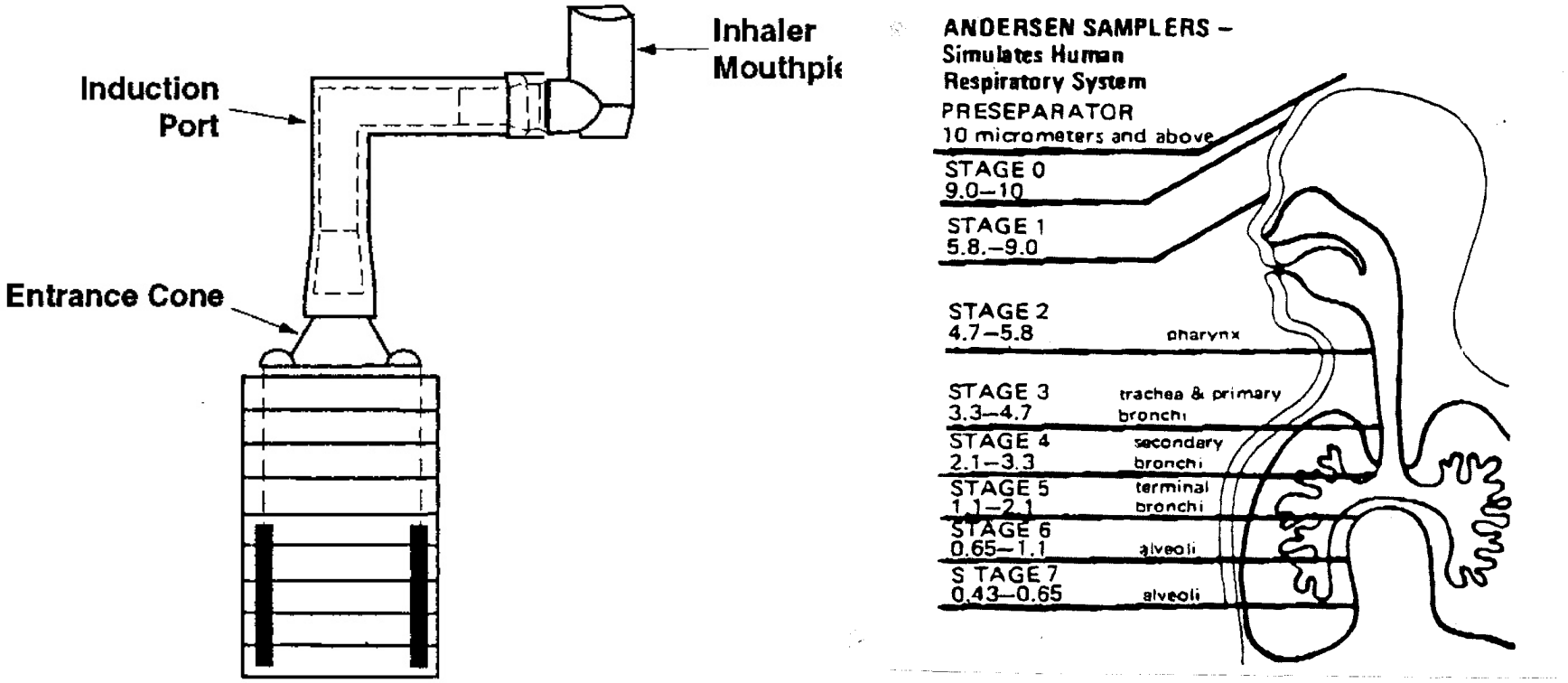
III. PARTICLE SIZE DISTRIBUTION (Anderson Cascade Impactor) PROFILE EQUIVALENCE TEST OF INHALER PRODUCTS



Figures adapted from the USP 26 <601> and Andersen Instruments Operating Manual for 1 ACFM Ambient Particle Sizing Samplers

A. Approach proposed to 2000 Orally Inhaled & Nasal Delivery Drug Products Subcommittee, Advisory Committee of Pharmaceutical Science (Tsong, Shen, Singh & Adams)

- Two-Stage test
  - Test for sameness of total mass (combining mass at all sifting stages).
  - Test for equivalence or similarity of particle size distributions (constrained by the total mass).
- Particle size distribution – constrained by the total mass S

  $X = (X_1, X_2, \ldots, X_K) \sim Multinomial\ (S, P_1, P_2, \ldots, P_K)$

  $\hat{p}_s = \frac{\hat{X}_s}{S}$, s =1, 2, …, K
- Variability = between life stage (beginning, middle, end) + within-lot(between-canister at a given stage)+between-lot
- Assume for 3 lots and 10 observations per lot for test and reference.

  N=30 per product.

- Randomly select observations of one test canister, and two reference canister to form (T, R, R') triplets.
- Profile distance between (T and R &R') and (R and R') are defined by Chi-square metric.

$$d_{TRR'} = \sum_i \frac{\left[p_{T_i} - \frac{1}{2}\left(p_{R_i} + p_{R'_i}\right)\right]^2}{p_{T_i} + \frac{1}{2}\left(p_{R_i} + p_{R'_i}\right)}$$

$$d_{RR'} = \sum_i \frac{\left(p_{R_i} - p_{R'_i}\right)^2}{\frac{1}{2}\left(p_{R_i} + p_{R'_i}\right)}$$

Ratio of chi-squares is defined by

$$rd = \frac{d_{TRR'}}{d_{RR'}}$$

- Define RD as the expectation of rd.

The mean RD test is defined as:

$$H_0: RD \geq \theta_{BE} \; v.s. \; H_a: RD < \theta_{BE}$$

To reject H_0, the 95% upper confidence bound (Bootstraped) for rd, rd_{95}, is less than θ_{BE}

- With n=30, the total number of triplets is 30x30x29/2=13050 triplets.
- Randomly sampling without replacement of M (≥ 30) triplets for test. Repeat sampling for 200 times for bootstrap to determine rd_{95}.
- How to determine θ_{BE}?
- Based on a simulation study using available Anderson Cascade Impactor data of 10 Albuterol MDI lots with 100 canisters per lot, we propose θ_{BE}=7.66.

Extended researches on equivalence test of particle size distribution profiles

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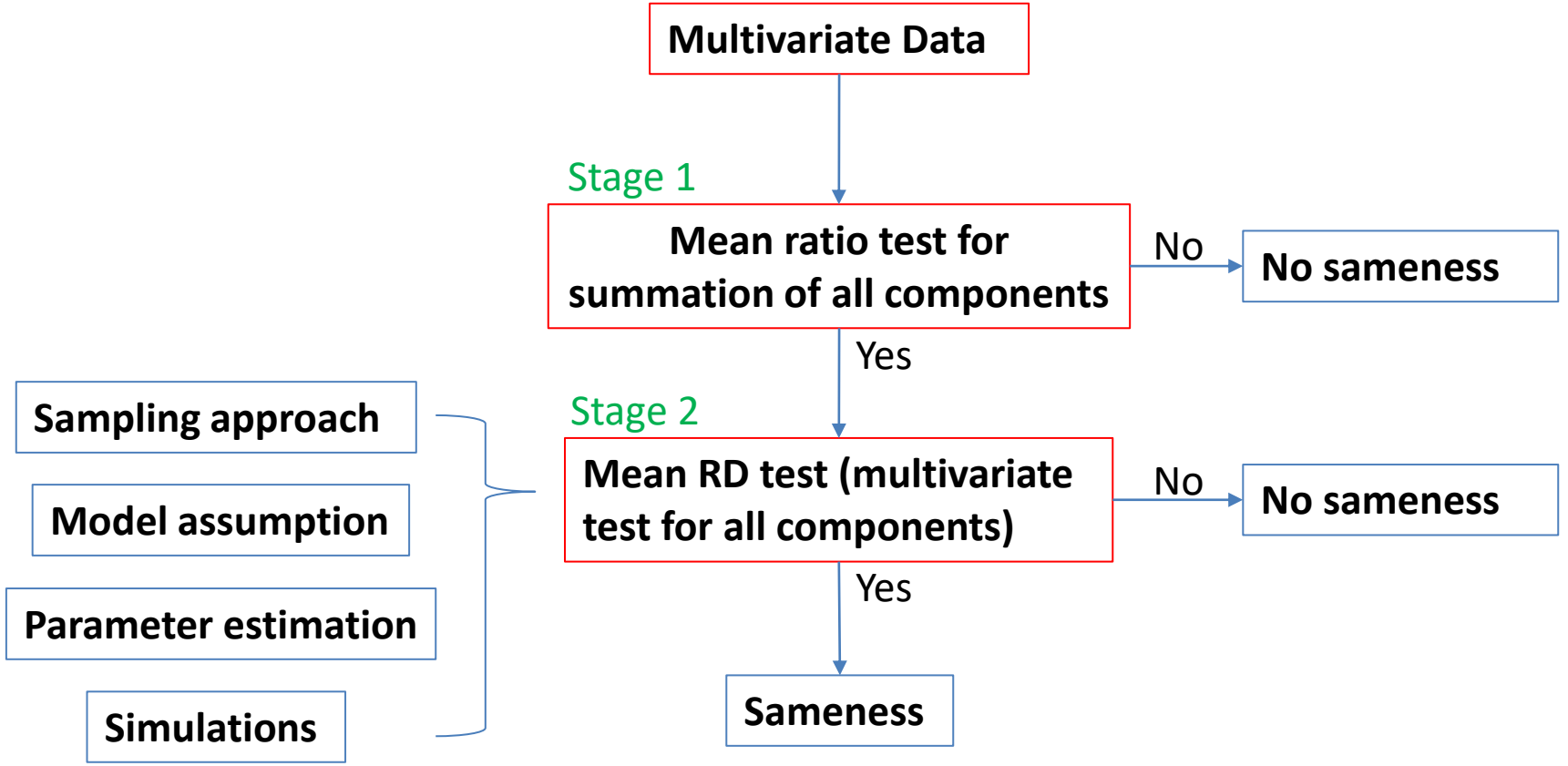
IV. Developing a Statistical Approach to Facilitate Sameness Assessment of Complex Heterogenous Active Pharmaceutical Ingredients (Weng Y-T, Hu M, Zhao L, Wang C, Shen M, Gong X)

Background

Sameness of Active Pharmaceutical Ingredient (API) serves as an important component of pharmaceutical equivalence (PE) assessment for generic products. API sameness assessment can be challenging, especially for drug products with complex API.

- API with heterogenous chemical structures and/or heterogenous mixtures
- Often involves analytical methods that generate multivariate data representing detected multi-component mixture, e.g., by liquid chromatography–mass spectrometry (LC-MS)

B. Proposed Two-stage Approach



*: Adapted from Weber et al., 2015

Stage 1: Mean Ratio Test

- Define μ_T, μ_R as mean sum of area percent of multiple components of interest of two products.

The mean ratio test is defined as:

$$H_0: {}^{\mu_T}/_{\mu_R} \geq 1.1^* \; or \; {}^{\mu_T}/_{\mu_R} \leq 0.9^* \; v.s. \; H_a: 0.9 < {}^{\mu_T}/_{\mu_R} < 1.1$$

**: can be justified from case to case*

- This test is similar to the average bioequivalence test.

Stage 2: Measure of RD

- Used in FDA's guidance on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (June 1999)

$$rd = \frac{d_{TRR'}}{d_{RR'}}$$

$$d_{TRR'} = \sum_i \frac{\left[p_{T_i} - \frac{1}{2}\left(p_{R_i} + p_{R'_i}\right)\right]^2}{p_{T_i} + \frac{1}{2}\left(p_{R_i} + p_{R'_i}\right)}$$

$$d_{RR'} = \sum_i \frac{\left(p_{R_i} - p_{R'_i}\right)^2}{\frac{1}{2}\left(p_{R_i} + p_{R'_i}\right)}$$

Stage 2: Mean RD Test

- Define RD as the expectation of the distribution of rd.

The mean RD test is defined as:

$$H_0: RD \geq \theta_{BE} \; v.s. \; H_a: RD < \theta_{BE}$$

- To reject H_0, the 95% upper confidence bound for rd, rd_{95}, is less than θ_{BE}

V. CONCLUSION

- In-vitro data often represented as multivariate or repeated measurement.
- Statistical approach to show in-vitro bioequivalence or similarity consists of three steps
  - Define a proper metric of difference or similarity between test and reference
  - Derive an (unbiased) estimate of the population difference/similarity metric
  - Define a proper margin of equivalence or similarity
- However, the challenge is to generalize the application.

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THANK YOU!!!