

Multivariate Bioequivalence

Shital Agawane, Sanjukta Roy

PhUSE 2013

Stream: Statistics and Pharmacokinetics

SP04

Disclaimer

Any views or opinions presented in this presentation are solely those of the author and do not necessarily represent those of the company.

Agenda

- Introduction
 - Bioequivalence
 - Importance of Generics
- Multivariate Bioequivalence and Profile Comparison
 - Hypothesis of Interest
 - Methods
 - Simulation in SAS
 - Power curve
- Multivariate Equivalence

Bioequivalence and its Importance

- FDA defines Bioequivalence as:
- “**the absence of a significant difference in the rate and extent** to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes **available** at the site of drug action when administered at the same molar dose under similar conditions”
- Bioequivalence studies
 - Food effect study
 - Bioavailability under different patient condition, etc
 - Testing generic formulation against the innovator’s marketed product

Importance of Generics

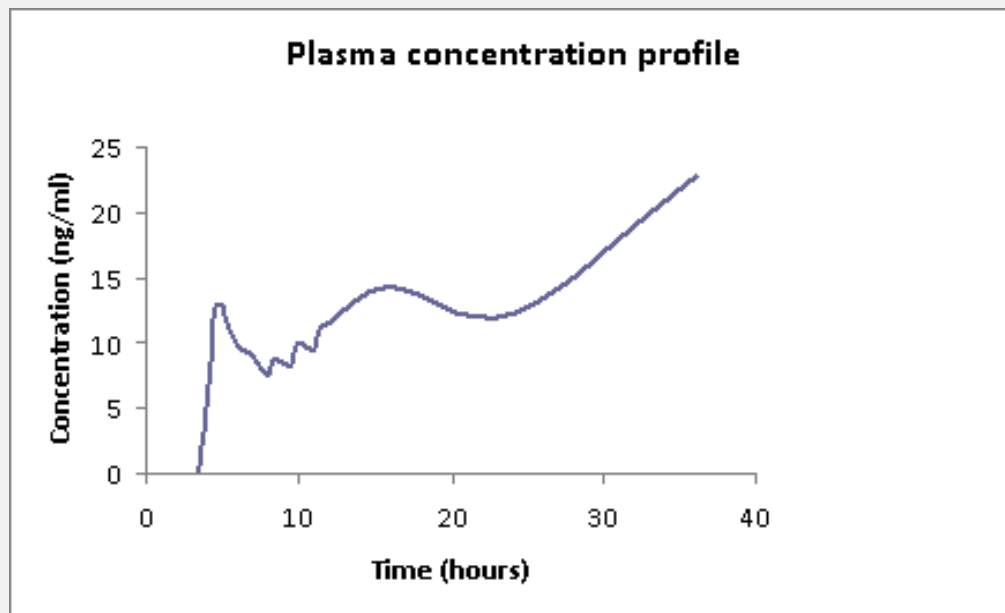
Drug Market in U.S.		
	Generic	Branded
% of prescription ^[1]	80	20
% of expenditure ^[2]	16	84

- The global prescription generic industry < \$50 billion in 2004, > \$80 billion in 2012^[3]
- Generic growth three times higher than the overall growth of drugs^[4]
- A large number of popular drugs come off patent through 2015^[4]

Multivariate Bioequivalence

- Conventional assessment of bioequivalence based on AUC and $C_{\max}$ comparison
- AUC and $C_{\max}$ measured on the same subject, hence related
- Inference drawn separately on these parameters does not take care of the dependency.
- Multivariate approach more reasonable
- First time proposed by Wang et al, in 1999 (Biometrika)

Multivariate Bioequivalence- Need for Profile Comparison

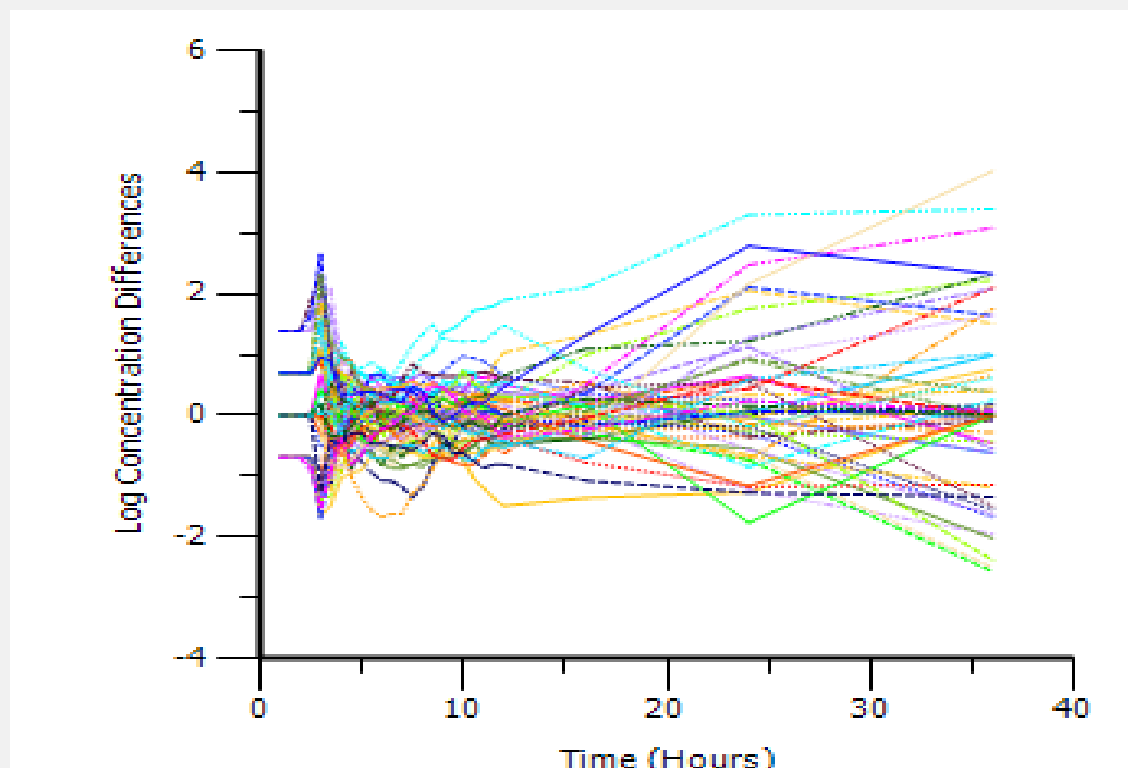


Peculiar profile-
Computation of $AUC_{0-\infty}$
not possible

- Regulator's comments:
 - "It is impossible to calculate reliable value for $AUC_{0-\infty}$ in such case. Consequently $AUC_{0-\infty}$ is just a speculation".
 - "It is possible that the areas could be equivalent without the profiles over time being the same".

Bioequivalence – Plasma Concentration Profile

- Raw Data
 - 2X2 Crossover design, Sample Size – 54, # of Time points – 24



Methodology

54 Subjects



i^{th} Subject ($i=1$ to 54)

X_{iT} (X_{iR}): Natural log transformed concentration vector for test (Reference) drug over 24 time points

$$D_i = X_{iT} - X_{iR}$$

Differences in concentration values for each subject is assumed to follow a (p=) 24 variate normal distribution.

Assumption : $\underline{D}_i \sim MVN_p(\mu, \Sigma)$ where $i = 1, 2, \dots, n$ (54)

Objective: To demonstrate equivalence of the entire profile

Hypothesis

H₀

Non Bioequivalence

$$\mu_j \geq \delta \text{ or } \mu_j \leq -\delta \text{ for some } j$$

vs.

H₁

Bioequivalence

$$-\delta < \mu_j < \delta \text{ for all } j$$

- Conventional BE limits for AUC (test) / AUC (ref), (80%, 125%)
- On log scale BE limits $\pm \ln(1.25)$
- Same measurement at each time point
- Same BE limits

Profile based Comparison

Intuitive Approach

Let $\bar{D}_j$ be the mean difference at time point j

Conclude bioequivalence if

$$\max_{j=1\dots p} |\bar{D}_j| < c$$

Where, $P(\max_{j=1,2\dots p} |\bar{D}_j| < c) \leq \alpha$
under H_0

Quadratic Form

Let $\bar{D}$ be the mean vector of average differences

Conclude bioequivalence if

$$n\bar{D}^t S^{-1} D < d$$

Where, $P(n\bar{D}^t S^{-1} D < d) \leq \alpha$
under H_0

Comparison of Methods - Using Simulation

Parameters needed: μ , data based Σ : Estimate S , $\mu = k \cdot \delta \cdot E_{1xp}$



$K = -1$

$K = 0$

$K = +1$

Non-Bioequivalence

Bioequivalence

Non-Bioequivalence

Chosen $K \longrightarrow (-2, -1)$

$(0, \pm 1/3, \pm 1/2, \pm 2/3)$

$(1, 2)$

Sampling from Multivariate Normal

-With mean μ and variance-covariance estimate S

1. 'Cholesky decomposition' of $S=LL'$



Call routine 'CALL CHOL'
-within PROC FCMP

2. Vector $\underline{Y}$ of random numbers from $N(0, 1)$



RAND function within PROC FCMP

3. $\underline{X} = \underline{\mu} + L\underline{Y}$ then
 $\underline{X} \sim MVN(\underline{\mu}, S)$



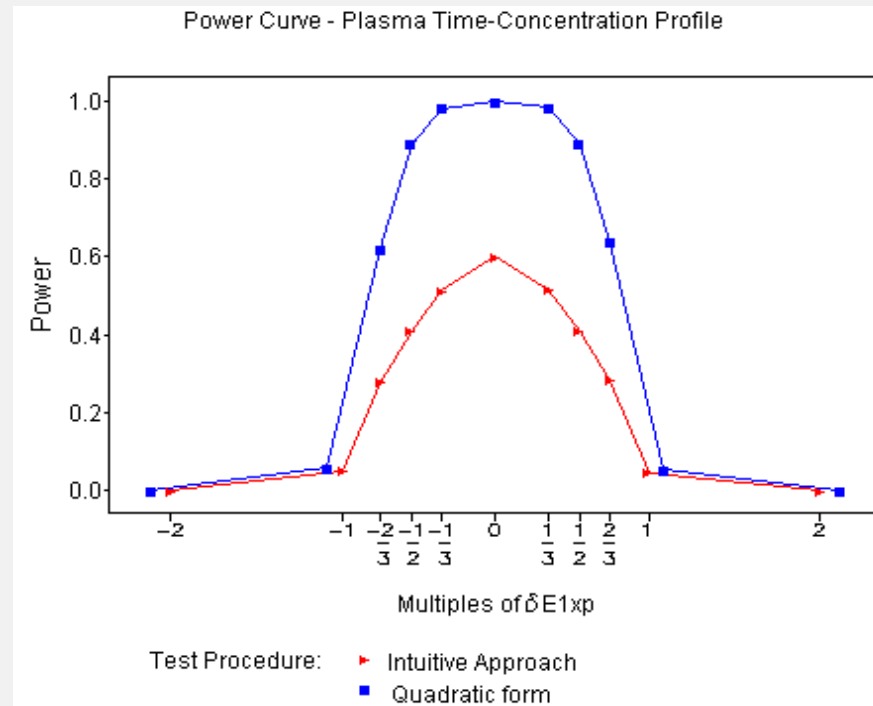
ARRAY functions within PROC FCMP

%simulation Macro

- **%simulation**(rep = , dscov = , cots1 =, cots2 =, ns = , nt = , hypval=, path =);

Parameter	Required/ Optional	Description
rep	Required	Number of Simulations
dscov	Required	Estimate of Variance covariance matrix S
cots1	Optional	Percentile of distribution of Test statistic based on Intuitive Approach
cots2	Optional	Percentile of distribution of Test statistic based on Quadratic Form
ns	Required	Number of Subjects
nt	Required	Number of Time points
hypval	Required	Typical Element of Mean Vector
path	Required	Path to store the output

Power Curve



- Both curves highest at origin, decline progressively on either side
- Quadratic form test is better.

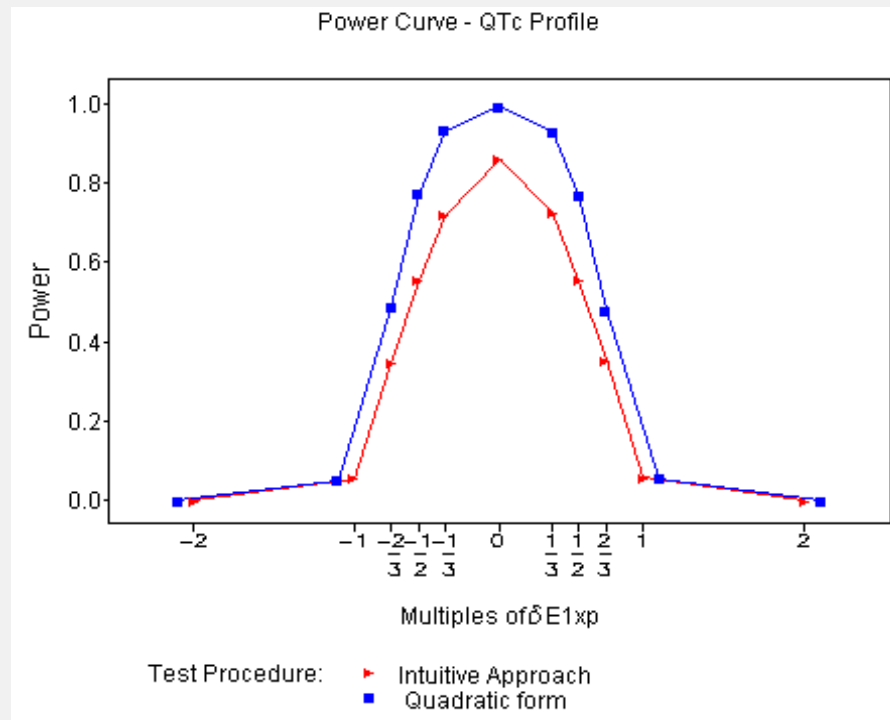
Are these results general?



Testing for Equivalence

- PD Endpoint (1)

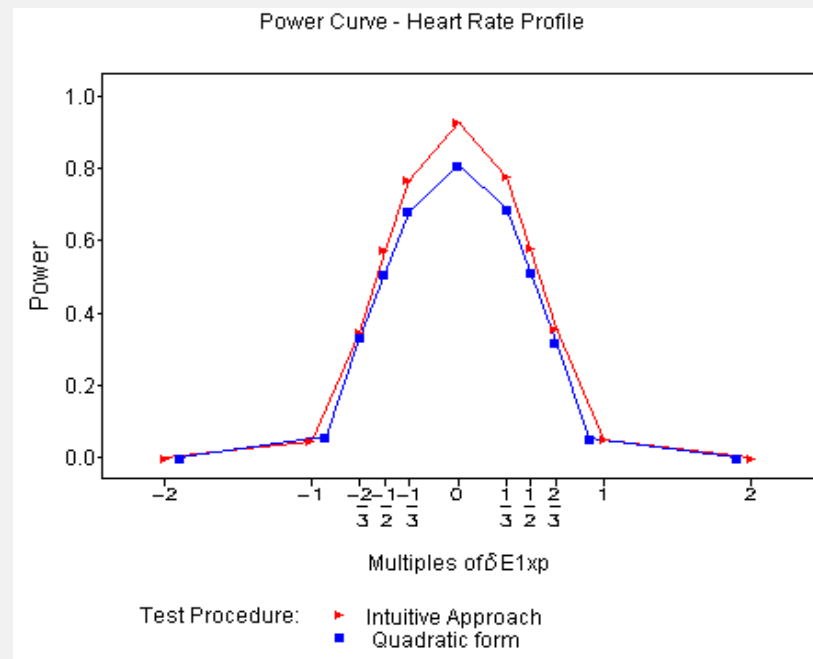
- Endpoint: QTc
- Raw data: 28 subjects, 18 time points
- Equivalence boundary: 5 milliseconds



Testing for Equivalence

- PD Endpoint (2)

- Endpoint: Heart Rate
- Raw data: 28 subjects, 18 time points
- Equivalence boundary: 5 beats per minute



For two out of three cases the quadratic form test gives high power

Conclusions

- We can bypass the intractable multivariate mathematics using simulation approach.
- The test based on quadratic form better than intuitive test.
- Dependency of variance covariance structure on results can be explored further.

References

- [1] FDA, “Facts about Generic Drugs”,
<http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm>
- [2] Long D. 2003 Year in Review: Trends, Issues, Forecasts, 2004, [http://www.worstpills.org/public/page.cfm?op_id=47#fn2].
- [3] Hardin, David, December 2010, “*Gaining Market Share In The Generic Drug Industry Through Acquisitions And Partnerships*”,
[\[http://thomsonreuters.com/products/ip-science/04_013/newport-deals.pdf\]](http://thomsonreuters.com/products/ip-science/04_013/newport-deals.pdf).
- [4] Bera, Ajoy & Mukherjee, Ashish, “*The Importance Of Generic Drugs In India*”, [<http://www.iipcbcs.com/files/2106-22.pdf>]
- Wang W., DasGupta,A. and Hwang, J. T. 1999, “*Statistical Tests for Multivariate Bioequivalence*”, *Biometrika*, 86, 2, pp. 395-402.
- The FCMP Procedure – Guide, SAS Publishing
- Guidance for Industry– Bioavailability and Bioequivalence studies for Orally Administered Drug Products – General Consideration, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research March 2003,
- Mauger, Chinchilli 2000, “*Profile Similarity in Bioequivalence Trials*”, *Sankhya The Indian Journal of Statistics*, 62, 1, pp. 149-161



Contact Author:

Shital Agawane

shital.agawane@cytel.com

Sanjukta Roy

sanjukta.roy@cytel.com

THANK YOU FOR YOUR ATTENTION!