Multivariate Bioequivalence

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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 two patient condition, etc
  - Testing generic formulation against the innovator’s marketed product
Importance of Generics

- 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]

**Drug Market in U.S.**

<table>
<thead>
<tr>
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<th>Generic</th>
<th>Branded</th>
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<tbody>
<tr>
<td>% of prescription[^1]</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>% of expenditure[^2]</td>
<td>16</td>
<td>84</td>
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[^1]: [1]
[^2]: [2]
[^3]: [3]
[^4]: [4]
Multivariate Bioequivalence

- Conventional assessment of bioequivalence based on AUC and $C_{\text{max}}$ comparison

- AUC and $C_{\text{max}}$ 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)
Regulator’s comments:

- “It is impossible to calculate reliable value for $\text{AUC}_{0-\infty}$ in such case. Consequently $\text{AUC}_{0-\infty}$ is just a speculation”.

- “It is possible that the areas could be equivalent without the profiles over time being the same”.

Peculiar profile - Computation of $\text{AUC}_{0-\infty}$ not possible
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 : $D_i \sim MVN_p(\mu, \Sigma)$ where $i = 1,2,\ldots, n (54)$

Objective: To demonstrate equivalence of the entire profile
Hypothesis

$H_0$ Non Bioequivalence
$\mu_j \geq \delta$ or $\mu_j \leq -\delta$ for some $j$

$H_1$ Bioequivalence
$-\delta < \mu_j < \delta$ 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
**Proposed Methods – Profile based Comparison**

### Intuitive Approach

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

Conclude bioequivalence if

$$\max_{j=1\ldots p} |D_j| < c$$

Where, $P(\max_{j=1,2\ldots p} |D_j| < c) \leq \alpha$

under $H_0$

### Quadratic Form

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

Conclude bioequivalence if

$$n\overline{D}^tS^{-1}D < d$$

Where, $P(n\overline{D}^tS^{-1}D < d) \leq \alpha$

under $H_0$
Comparison of Methods - Using Simulation

Parameters needed: \( \mu \), data based \( \Sigma \): Estimate \( S \), \( \mu = k.\delta.E_{1Xp} \)

**INTERPRETATION of PARAMETER \( \mu \)**

- **K = -1**
  - Non-Bioequivalence
  - Chosen \( K \) \( \rightarrow (-2, -1) \)

- **K = 0**
  - Bioequivalence
  - \( (0, \pm 1/3, \pm 1/2, \pm 2/3) \)

- **K = +1**
  - Non-Bioequivalence
  - \( (1,2) \)
Sampling from Multivariate Normal

- With mean $\mu$ and variance-covariance estimate $S$

1. ‘Cholesky decomposition’ of $S=LL'$
2. Vector $Y$ of random numbers from $N(0,1)$
3. $X = \mu + LY$ then $X \sim MVN(\mu, S)$

Call routine ‘CALL CHOL’ -within PROC FCMP
RAND function within PROC FCMP
ARRAY functions within PROC FCMP
%simulation Macro

- \%simulation\( \text{rep} = , \ \text{dscov} = , \ \text{cots1} = , \ \text{cots2} = , \ \text{ns} = , \ \text{nt} = , \ \text{hypval}=, \ \text{path} = \); 

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<td>Required</td>
<td>Estimate of Variance covariance matrix S</td>
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<td>Optional</td>
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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

Power Curve - QTc Profile

Test Procedure: 
- Intuitive Approach
- Quadratic form
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.
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THANK YOU FOR YOUR ATTENTION!