Univariate Bioequivalence

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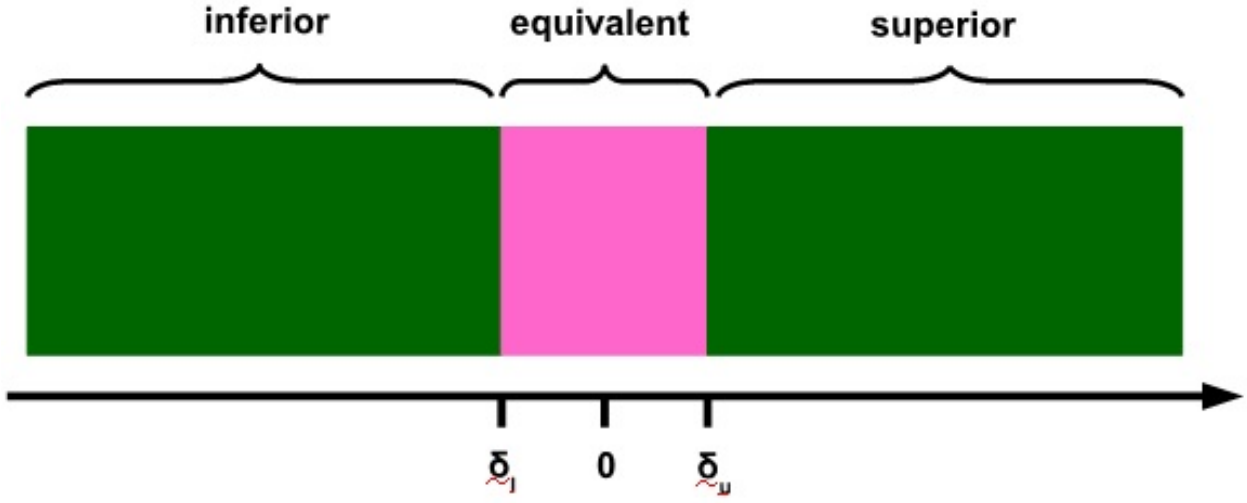
What is bioequivalence?

Equivalence is not equality



Pharmacological question:

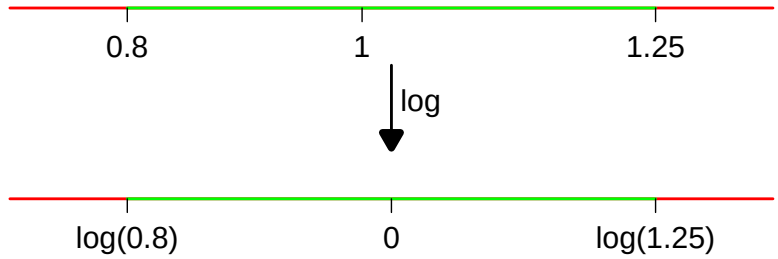
Is test product T equivalent to reference product R in terms of key PK parameters (e.g. AUC_{0-t}, $AUC_{0-\infty}$, C_{max})?

Statistical question:

Is the log-ratio of PK parameters μ^T/μ^R for test and reference within a pre-defined acceptable range $[\Delta_l, \Delta_u]$?

Testing average bioequivalence

A common choice is $\Delta_l = \log(0.8)$ and $\Delta_u = \log(1.25)$ so that the resulting interval $[-0.223, 0.223]$ is symmetric around 0



. . . but why logarithms?

PK parameters like *AUC* and C_{max} are typically assumed to be log-normal and therefore logarithmised

Parameter for analysis: $\theta = \log\left(\frac{\mu^T}{\mu^R}\right) = \log(\mu^T) - \log(\mu^R)$

θ is then assumed to be normal with variance σ^2

Two one-sided tests (TOST)

Standard procedure for average bioequivalence: two one-sided t-tests, each at level α (Schuirmann 1987)

1) Test $H_{01}: \theta \leq \Delta_l$ vs. $H_{A1}: \theta > \Delta_l$ at level α

2) Test $H_{02}: \theta \geq \Delta_u$ vs. $H_{A2}: \theta < \Delta_u$ also at level α

3) Conclude bioequivalence if <u>both</u> H_{01} and H_{02} are rejected

$H_0 \equiv H_{01} \cup H_{02}$

$H_A \equiv H_{A1} \cap H_{A2}: -\Delta < \theta < \Delta$

This procedure controls the type I error rate at level α due to the intersection-union principle (Berger 1982)

A slightly peculiar relationship

The TOST procedure at level α gives the same test decisions as a confidence interval inclusion approach using...

1) ...either a two-sided $100(1-2\alpha)\%$ interval around $\widehat{\theta}$

$$\left[\widehat{\theta} - SE(\widehat{\theta})t_{1-\alpha,\nu}, \widehat{\theta} + SE(\widehat{\theta})t_{1-\alpha,\nu}\right]$$

where $SE(\widehat{\theta})$ is the standard error of $\widehat{\theta}$, and $t_{1-\alpha,\nu}$ the $100(1-\alpha)\%$ quantile of Student's t-distribution with ν degrees of freedom

2) ...or an "expanded" two-sided $100(1-\alpha)\%$ interval around $\widehat{\theta}$

$$\left[\min\left(0, \widehat{\theta} - SE(\widehat{\theta})t_{1-\alpha,\nu}\right), \max\left(0, \widehat{\theta} + SE(\widehat{\theta})t_{1-\alpha,\nu}\right)\right]$$

In either case bioequivalence may be concluded if and only if the interval lies entirely within $[\Delta_l, \Delta_u]$ (Berger & Hsu 1996)

Case study

Single-dose ticlopidine hydrochloride (250mg active ingredient) administered as a tablet of commercial reference product Tiklid (R) or test formulation (T)

2 x 2 x 2 crossover study with 24 healthy male volunteers randomised to sequence RT or TR (Marzo *et al.* 2002)

AUC_{0-t}, $AUC_{0-\infty}$, C_{max} data in `R` package `jocre` (Pallmann 2017)

Case study

Exercises:

1. Calculate the mean and standard error of the difference (T vs. R) of the logarithms of AUC_{0-t}.
2. Test whether formulations T and R are bioequivalent regarding AUC_{0-t}. Use the TOST procedure at $\alpha = 0.05$ with the conventional [80%, 125%] bioequivalence range.
3. Compute the corresponding 90% confidence interval as well as the 95% “expanded” interval.
4. Translate the point estimate and interval boundaries back to the original scale.

Case study: code & results

```
### Dataset

library(jocre)
data(marzo)
head(marzo, 5)
```

```
##   Volunteer Sequence Cmax_T Cmax_R  AUC_T  AUC_R AUCinf_T AUCinf_R
## 1         1       TR  784.3  878.2 2021.7 2665.2   2131.4   3030.1
## 2         2       RT  304.2  211.7  901.7  685.9   1107.9    798.6
## 3         3       TR  307.3  259.6  741.4  654.0    806.2    696.1
## 4         4       TR  156.7  307.8  475.6  753.7    509.9    833.7
## 5         5       RT  745.6 1036.2 2521.4 2781.9   2784.0   3015.6
```

```
### Differences of logarithms

marzo$logdiffAUC <- log(marzo$AUC_T) - log(marzo$AUC_R)
head(marzo, 5)
```

```
##   Volunteer Sequence Cmax_T Cmax_R  AUC_T  AUC_R AUCinf_T AUCinf_R
## 1         1       TR  784.3  878.2 2021.7 2665.2   2131.4   3030.1
## 2         2       RT  304.2  211.7  901.7  685.9   1107.9    798.6
## 3         3       TR  307.3  259.6  741.4  654.0    806.2    696.1
## 4         4       TR  156.7  307.8  475.6  753.7    509.9    833.7
## 5         5       RT  745.6 1036.2 2521.4 2781.9   2784.0   3015.6
##    logdiffAUC
## 1 -0.27634036
## 2  0.27355003
## 3  0.12543294
## 4 -0.46041725
## 5 -0.09831984
```

Case study: code & results

```
### Mean & SE

mean(marzo$logdiffAUC)

## [1] -0.08027212

exp(mean(marzo$logdiffAUC))

## [1] 0.9228652

sd(marzo$logdiffAUC) / sqrt(nrow(marzo))

## [1] 0.05876836
```

```
### TOST p-values

t.test(x=marzo$logdiffAUC, alternative="less", mu=log(1.25))$p.value

## [1] 1.55846e-05

t.test(x=marzo$logdiffAUC, alternative="greater", mu=log(0.8))$p.value

## [1] 0.01162843
```

Case study: code & results

```
### 90% confidence interval

t.test(x=marzo$logdiffAUC, conf.level=0.9)$conf.int


## [1] -0.1809935  0.0204493
## attr(,"conf.level")
## [1] 0.9


exp(t.test(x=marzo$logdiffAUC, conf.level=0.9)$conf.int)


## [1] 0.8344408 1.0206598
## attr(,"conf.level")
## [1] 0.9


### 95% "expanded" confidence interval: same as 90% interval
```

Literature

Berger RL (1982) Multiparameter hypothesis testing and acceptance sampling. *Technometrics*, **24**(4), 295–300.

Berger RL, Hsu JC (1996) Bioequivalence trials, intersection-union tests and equivalence confidence sets. *Statistical Science*, **11**(4), 283–319.

Jaki T, Pallmann P, Wolfsegger MJ (2013) Estimation in AB/BA crossover trials with application to bioequivalence studies with incomplete and complete data designs. *Statistics in Medicine*, **32**(30), 5469–5483.

Marzo A, Dal Bo L, Rusca A, Zini P (2002) Bioequivalence of ticlopidine hydrochloride administered in single dose to healthy volunteers. *Pharmacological Research*, **46**(5), 401–407.

Pallmann P (2017) `jocre`: joint confidence regions. `R` package version 0.3.3. https://cran.r-project.org/package=jocre

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