

# Special Topics

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# $AUC_{0-t}$ | Problem 1

## What if

- The bioanalytical method was sensitive enough to measure *all* concentrations but a sample at the last time point ( $t_{last}$ ) was missing (e.g., vial broken in centrifugation)?
- The bioanalytical method was sensitive enough to measure *most* low concentrations but there were a few values at  $t$  below the LLOQ (lower limit of quantification)?

# $AUC_{0-t}$ | Problem 1

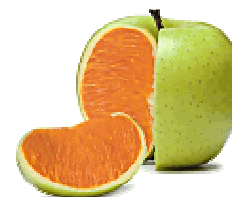
In BE we administer the same molar doses and assume constant inter-occasion clearances. Hence,

$$AUC_{0-t,T} = \frac{f_T \cdot D_T}{CL_T} \text{ and } AUC_{0-t,R} = \frac{f_R \cdot D_R}{CL_R}$$

with  $D_T = D_R$  and  $CL_T = CL_R$  we get  $\frac{f_T}{f_R} = \frac{AUC_{0-t,T}}{AUC_{0-t,R}}$

- Example:  $t_{last}$  for one product is 24 h but due to missingness for the other one occasionally 16 h. If we follow guidelines blindly, the estimate will be biased because

$$\frac{f_T}{f_R} \neq \frac{AUC_{0-16,T}}{AUC_{0-24,R}}$$



# $AUC_{0-t}$ | Problem 1

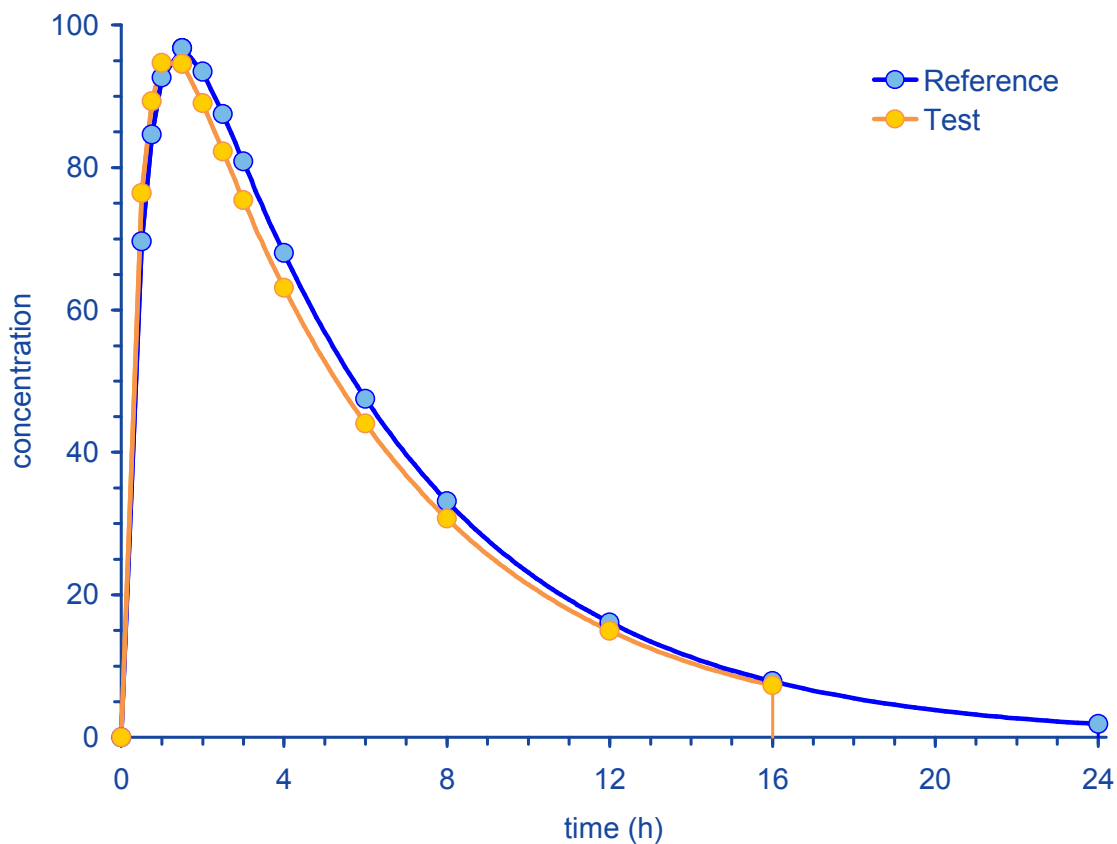
Only if the true relative BA-ratio is *exactly* 1, the chance to observe concentrations at  $t_{last} < LLOQ$  is similar for all treatments and the estimate will be unbiased

If the true BA-ratio is  $\neq 1$ , the estimate will be biased away from one (*i.e.*, the difference between treatments will be exaggerated)

- Regulators don't care because the patient's risk is not affected and the chance to demonstrate BE decreases
- Applicants should care since the producer's risk of failure increases

# AUC<sub>0-t</sub> | Problem 1

AUCt (R) 683, AUCt (T) 618, T/R 90.4%, bias -4.87%



# AUC<sub>0-t</sub> | Solutions

## Impute missings or BQLs by their estimates

- Requires reliable estimate of  $\lambda_z$
- Implemented only in the current release of Phoenix/WinNonlin
- In other software or ‘by hand’ according to

$$C_t = e^{\log(\hat{C}_0) - \hat{\lambda}_z \cdot t}$$

## Compare AUCs in each subject where *both* treatments showed concentrations $\geq$ LLOQ\*

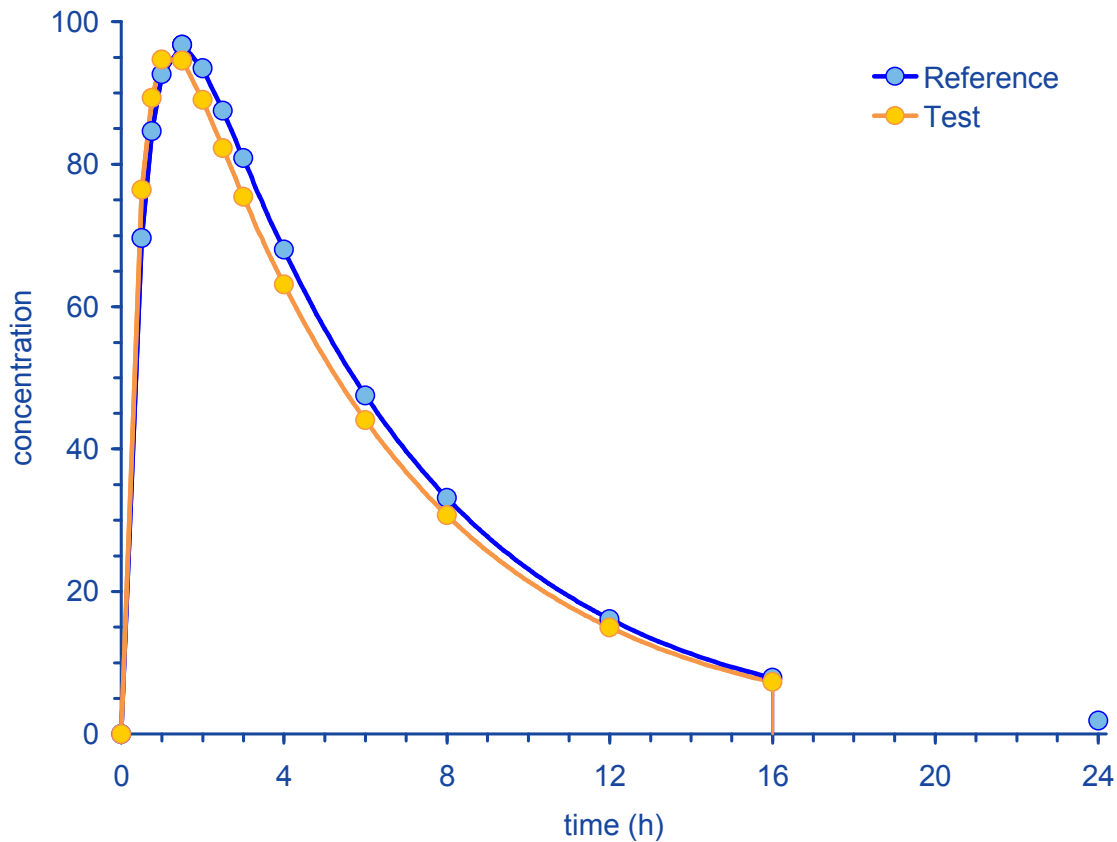
- Example:  $t_{last,T} = 16$  h,  $t_{last,R} = 24$  h,  $t_{last}$  (Common) = 16 h

$$\frac{f_T}{f_R} = \frac{AUC_{0-16,T}}{AUC_{0-16,R}}$$

\* Fisher D, Kramer W, Burmeister Getz E. *Evaluation of a Scenario in Which Estimates of Bioequivalence Are Biased and a Proposed Solution:  $t_{last}$  (Common)*. Clin Pharm. 2016;56(7):794–800. [doi:10.1002/jcph.663](https://doi.org/10.1002/jcph.663). [Open access](#).

# $AUC_{0-t}$ | Solution

AUCt.comm (R) 650, AUCt.comm (T) 618, T/R 95.0%, bias 0.00%



# $AUC_{0-t}$ | Problem 2

## What if

- a substantial number of samples in the late part of a profile is missing?
- Such a case might happen if a subject drops out from a study
- $AUC_{0-t(\text{common})}$  will not necessarily help because according to most GLs a 'reliable estimate' of the extent of absorption is given if  $AUC_{t-\infty}$  is  $\leq 20\%$  of  $AUC_{0-\infty}$
- However, regulations  $\neq$  science
  - For IR products ( $k_a \gg k_e$ ) already at  $2 \times t_{max}$  absorption is practically complete (93.75%); at  $4 \times t_{max}$  99.61% are already absorbed\*
  - In the late part of the profile distribution / elimination prevails – which is drug-specific and not relevant for detecting differences between treatments

\* Scheerans C, Derendorf H, Kloft C. *Proposal for a Standardised Identification of the Mono-Exponential Terminal Phase for Orally Administered Drugs*. Biopharm Drug Dispos. 2008;29(3):145–57. [doi:10.1002/bdd.596](https://doi.org/10.1002/bdd.596).



# $AUC_{0-t}$ | Solution

## EMA BE-GL Section 4.1.8 (2010)

- Subjects should not be excluded from the statistical analysis if  $AUC_{(0-t)}$  covers less than 80% of  $AUC_{(0-\infty)}$ , but if the percentage is less than 80% in more than 20% of the observations then the validity of the study may need to be discussed.
  - For optimistic ones
    - Cross fingers and prepare for the discussion
  - For very brave ones
    - Give a justification in the protocol that absorption is already complete even at very early time points
    - Use  $AUC_{0-t(common)}$
  - For brave ones
    - As above but state in the protocol a limit for the earliest acceptable truncation time; if earlier, exclude the subject from the comparison of  $AUCs$

# AUC<sub>0-t</sub> | Solution

## EMA BE-GL Section 4.1.8 (2010)

- For wavy ones
  - Exclude the subject from the comparison of *AUCs* but – if  $C_{max}$  is well defined (e.g., a couple of decreasing concentrations after  $t_{max}$ ) – keep the subject in the comparison of  $C_{max}$
  - Rationale
    - » In general the variability of  $C_{max}$  is substantially higher than the one of *AUC* and therefore, likely the study was powered for  $C_{max}$
    - » Although power to show BE will slightly decrease for *AUC*, the overall power of the study will not be affected
- Prolonged (aka sustained) release formulations
  - By their biopharmaceutical design (flip-flop PK:  $k_a \leq k_e$ ) the *late part* of the profile represents *absorption*
  - Exclude the subject from the comparison of *AUCs*

# Special Case: Truncated AUC

## Truncated $AUC$ instead of $AUC_{0-t}$ as the primary PK metric

- EMA
  - $AUC_{0-72h}$  acceptable for all IR products
  - Stated as the method of choice in all product-specific guidances
  - *Not necessary* to extrapolate and show that 80% of  $AUC_{0-\infty}$  are covered
  - Absorption is practically complete after  $2-4 \times t_{max}$ 
    - A truncation time of 72 hours is very conservative and based on the observation in clinical studies that within three days any formulation has left the GIT
  - Problematic for controlled release products
    - $AUC_{0-\infty}$  is additionally required
    - A reliable estimate of  $\lambda_z$  is mandatory; might need longer sampling, since the late part of the profile represents absorption
    - However, once the formulation leaves the absorption window (or the GIT) expect a rapid decrease in concentrations; don't use them to estimate  $\lambda_z$

# Dose Linearity and Proportionality

## Various models exist

- The most simple one (dose proportionality) is employing conventional BE (90% CI) of dose-normalized PK metrics

- Some authorities ask for a Bonferroni-adjustment due to the multiple tests
- Comparing only two dose-levels cannot detect a deviation from dose proportionality

tests	$\alpha$	$p_{\alpha=0.05}$	$\alpha_{adj}$	% CI	$p_{\alpha,adj}$
1	0.050	5.00%	0.0500	90.00	5.00%
2	0.050	9.75%	0.0250	95.00	4.94%
3	0.050	14.26%	0.0167	96.67	4.92%
4	0.050	18.55%	0.0125	97.50	4.91%
5	0.050	22.62%	0.0100	98.00	4.90%

- For assessing dose linearity commonly the ‘power-model’ is used

$$E(Y | x) = a \cdot x^b$$

$$\log(E(Y | x)) = \log(a) + b \cdot \log(x)$$

where  $Y$  is a PK response ( $AUC$ ,  $C_{max}$ ),  $x$  the dose,  $a > 0$ , and  $b \neq 0$

# Dose Linearity and Proportionality

## Various models exist

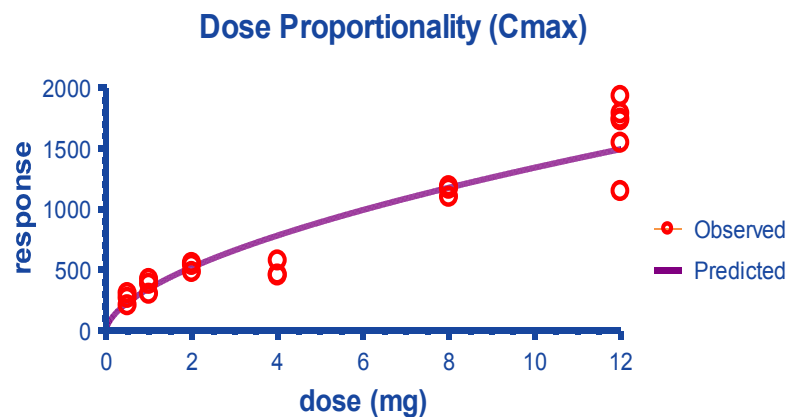
- ‘Power-model’
  - The first form requires software for nonlinear regression
  - The second (linearized) form is a simple linear regression
  - The model is evaluated by examining the 95% confidence interval  $[L, U]$  of the exponent  $b$  for departure from one
  - Decision criteria
 

– if $0.75 < L < 1.0 < 1.25$	no departure from dose linearity
– if $1.0 < L < U < 1.25$ or $0.75 < L < U < 1.0$	slight departure from dose linearity, but no practical significance from dose linearity
– if $L > 1.25$ or $U < 0.75$	reject hypothesis of dose linearity

# Dose Linearity and Proportionality

## Various models exist

- ‘Power-model’
  - Example: FIM biological, six dose levels,  $C_{max}$ 
    - $b$  0.587 (95% CI: 0.471 – 0.704)
    - CV 7.25%, correlation 0.9446
    - Since  $U < 0.75$ , deviation from dose linearity



# Special Topics

**Thank You!**  
*Open Questions?*



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