Case Studies: Inadequate Bioequivalence Studies – Regulatory Perspectives

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Outline

- Overview of the regulatory criteria for *in vivo* bioequivalence (BE) studies
- Common BE deficiencies in pharmacokinetic (PK) studies
- Case studies
  - Study design
    - Sampling time insufficient
    - Washing out period insufficient
  - Tlag difference
  - Scaling BE point estimate
- Summary

General Criteria for an Adequate *In Vivo* BE Study

- The subject number should be based on appropriate sample size calculation ($\geq$ 12 for general representive).
- BE evaluation is based on AUCs and Cmax:
  - the 90% confidence interval for the ratio of the test and reference products fall within 80.00-125.00%
- No apparent difference in median t_{max} and Tlag between test and reference products

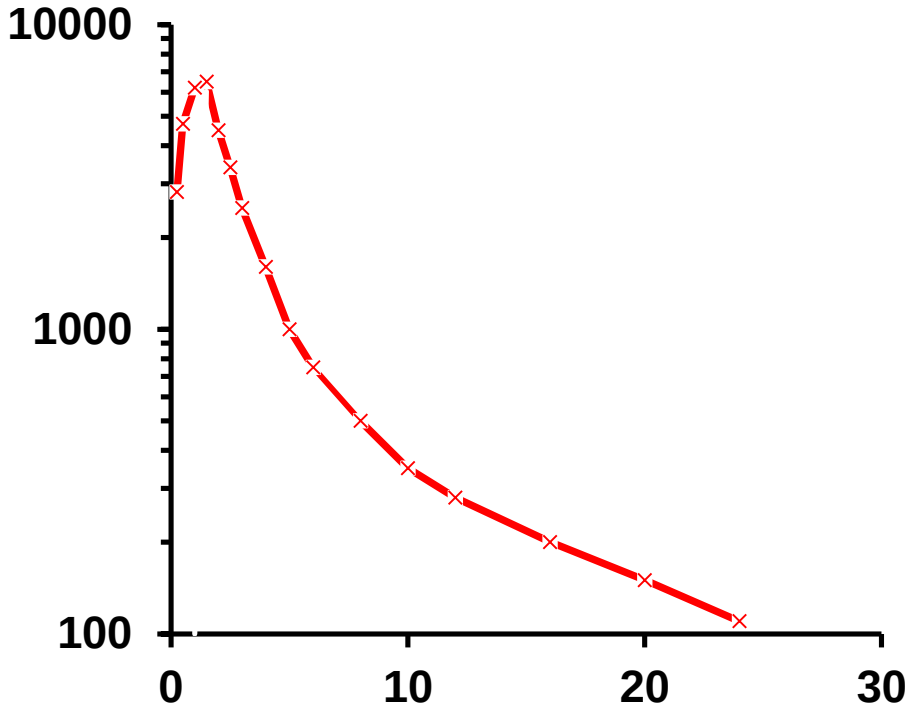
Special Scenarios for BE Criteria

- Narrow therapeutic drugs: reference scaled limit, unscaled average BE and 90% CI of the ratio of the within-subject standard deviation of the T and R is less than or equal to 2.5. (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf)

- Highly variability drugs: reference scaled limit and point estimate of the T/R geometric mean ratio fall within [0.8- 1.25). (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf)

Sampling Times

- Depend on the nature of the drug and the rate of input from the administered dosage form
- The sample collection should ensure that the Cmax and terminal elimination rate constant (Kel) can be estimated accurately (generally 16-18 time points).
- At least three to four samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of λz from linear regression



Study Design Recommendation

- Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (issued in December 2013)

- Recommendations in the product-specific guidance

- Differences from product-specific guidance needs justifications, and the acceptability is evaluated on a case-by-case basis.

- May discuss in control correspondence, pre-ANDA communications

In Vivo BE Study Design

- Standard design: randomized, two-period, two-sequence, single dose cross-over design
- Alternative design: parallel design (substance with very long half-lives) and replicate design (partial and full)

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Common BE deficiencies

- Analytical issues: including pre-study method validation, analytical repeats during the study and incurred sample reanalysis
- Inadequate study design
- Inappropriate statistical approach
- Incomplete SAS Transports files
- Failed to reserve study samples
- Data integrity of the clinical and analytical sites

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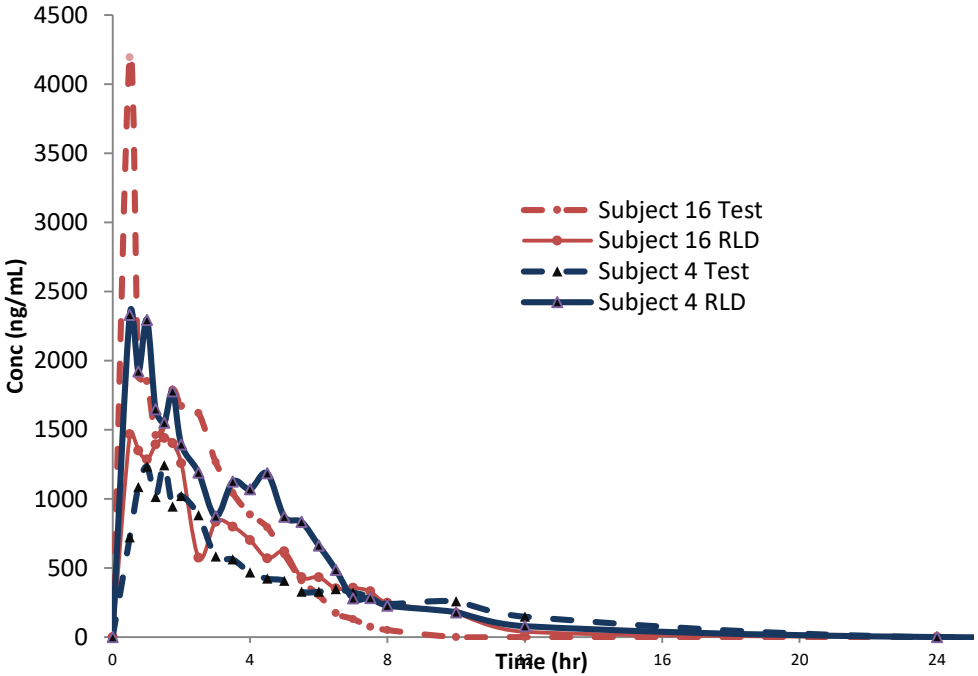
Case #1: Inadequate Study Design

- Used two-way crossover study design instead of fully replicated study design as the Agency recommends for the following categories

Category	Statistical Approach for BE Assessment
Narrow therapeutic Index Drugs (NTIs): Warfarin Sodium Tablets	Reference scaled limit, unscaled average bioequivalence (ABE) and variability comparison
Product with steep exposure-response relationship, but cannot be classified as NTIs: Dabigatran Etexilate Mesylate Capsules	ABE and variability comparison
Some Modified Release Drug products: Methylphenidate HCl ER Tablet	ABE and subject-by-formulation interaction variance

- Variance information can be estimated (e.g., $\sigma_{WR}{}^2$, $\sigma_{WT}{}^2$, $\sigma_D{}^2$)

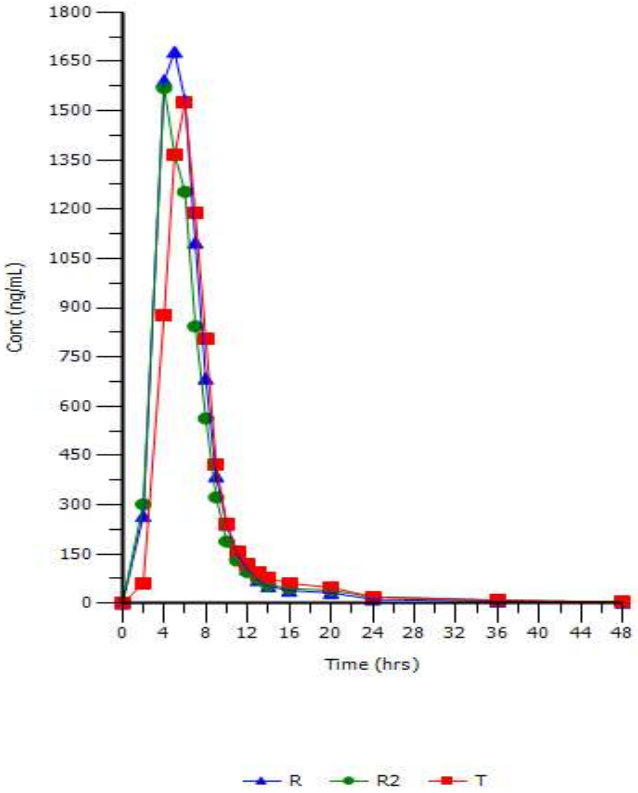
Case #2: Insufficient Sampling Time to Capture Cmax



- Drug A PK information: Tmax = 0.5 hrs
- 41 out of 46 subjects (approximate 89%) had the first time point of Cmax.
- The first point Cmax raises a question about the true Cmax.
- Recommend to collect early time points for assessing early peak concentrations

Sampling times: 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, …….24 hrs

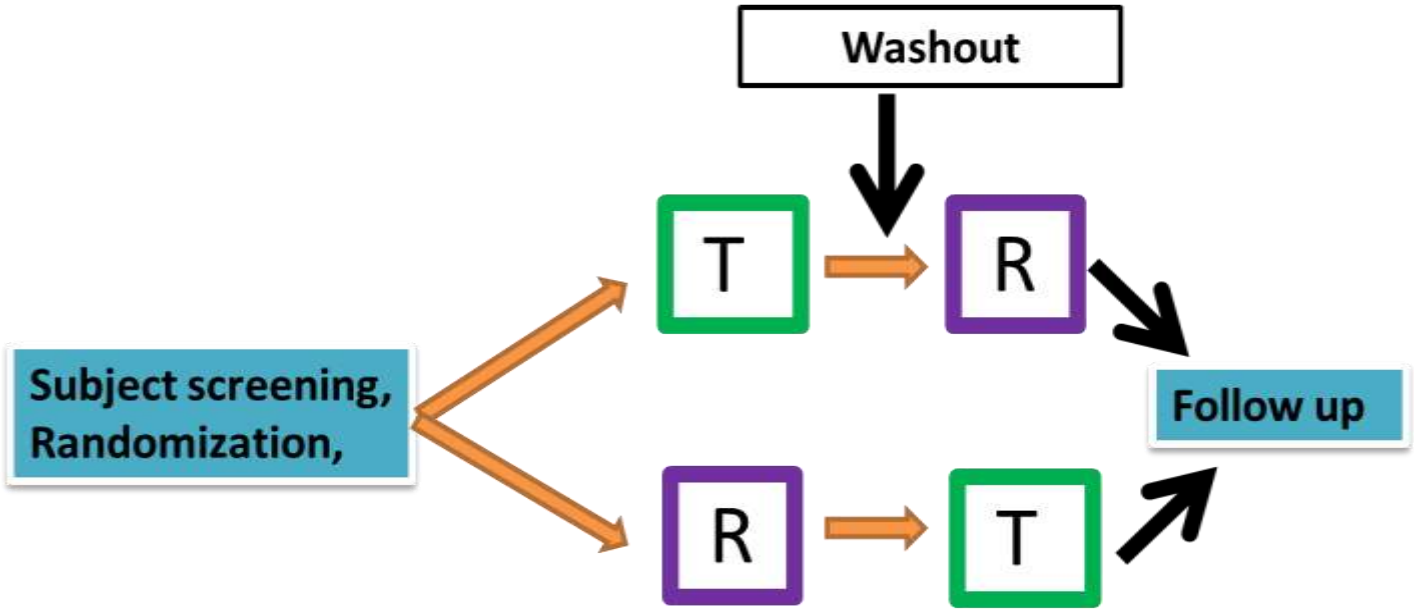
Case #3: Insufficient Sampling Time- at Early pAUC



- Per product specific drug guidance on Drug C, we recommend evaluating pAUC0-3, pAUC3-t, AUC0-t and Cmax. At least four non-zero measurements of concentration are recommended for each partial AUC

- only one 2-hour point in 0-3 hours.

Single dose, Two-treatment, Crossover, Randomized BE study

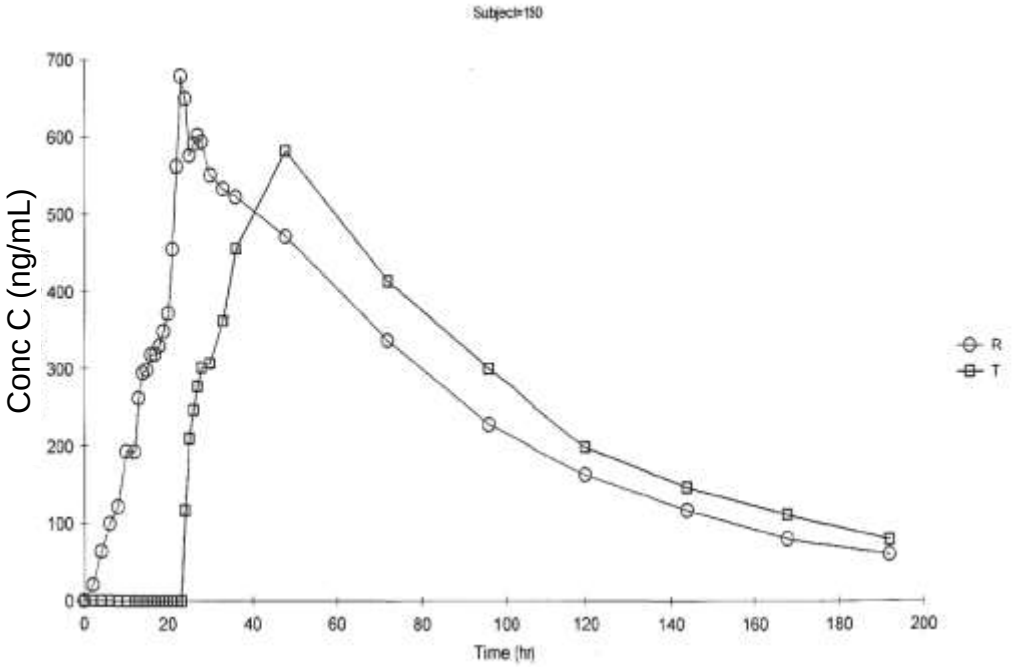


In FDA PK endpoint guidance (issued 2013), an adequate washout period (e.g., more than five-lives of the moieties to be measured), should separate each treatment.

Case #4: Insufficient Washing Out Period

- Drug B PK information: Half-life> 100 hrs. Tmax= 1.5 hrs
- 15 days washout period. 35 out of 44 subjects (79.5%) had pre-dose concentration >5% of their respectively Cmax at period II.
- Only 9 subjects were included in the statistical analysis.
- Among them, 2 subjects from TR sequence and 7 subjects from RT sequence. Indicating a potential imbalance of carry-over effect between the test and reference products.

Case #5: Tlag Difference



Test: Tlag= 24 hrs
Ref= Tlag= 2 hrs

- Drug C: indicated for adjunctive therapy for primary generalized tonic-clonic seizures and partial-onset seizure with or without secondary generalization.
- PK information: Tmax= 4-11 hrs; half-life= 24 hrs
- Tlag values are consistently longer for the test product than for the reference product
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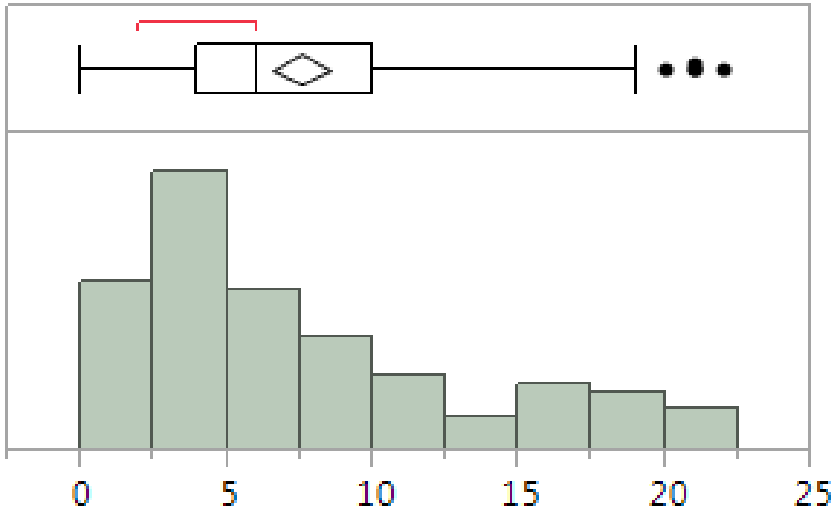
Tlag Difference

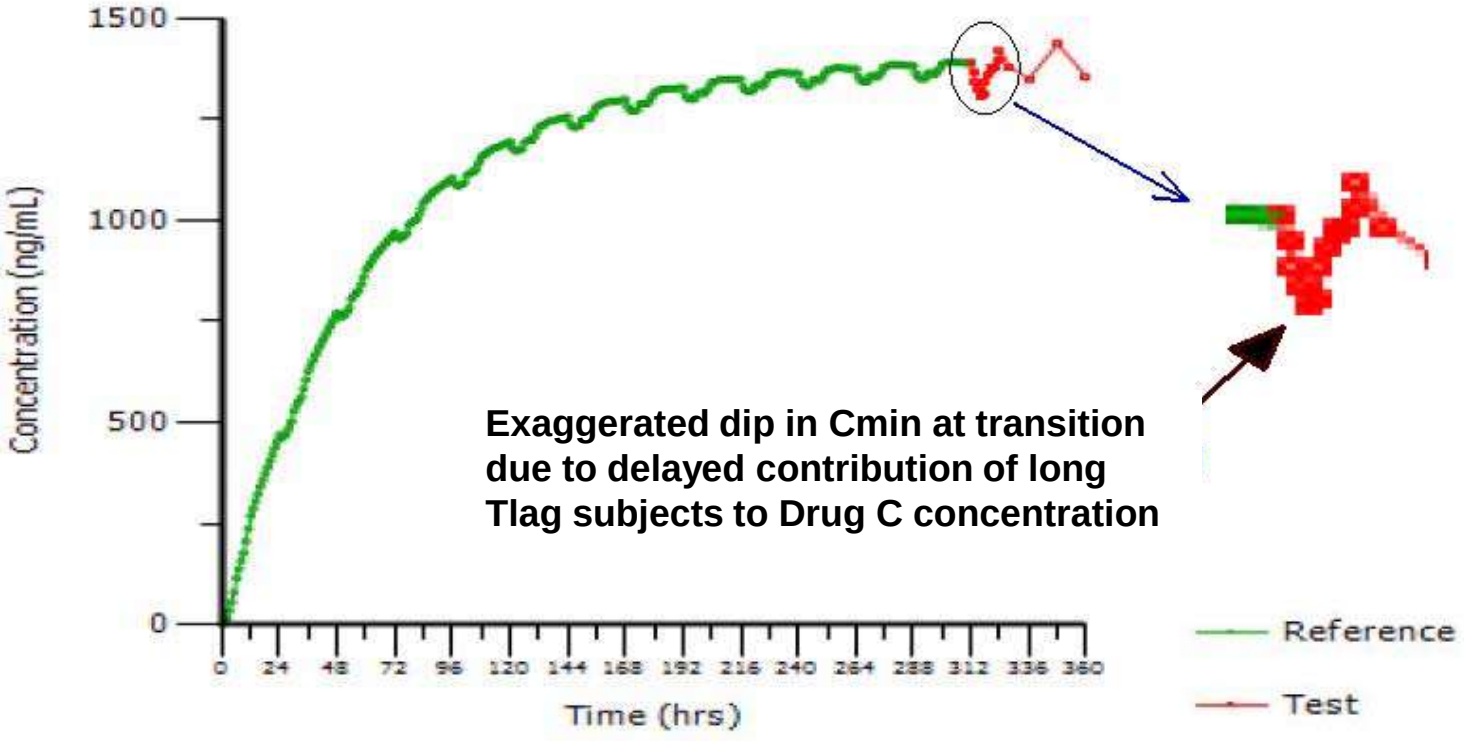
Distribution of Tlag Difference



Quartile	Difference of Tlag (hr)
minimum	0
1st Q	4
2nd Q (median)	6
3rd Q	10
maximum	22

Tlag	N	%
≥ 6 hour	67	54.5
≥ 8 hour	47	38.2
≥ 10 hour	33	26.8
≥ 12 hour	27	21.9
≥ 15 hour	20	16.2

Simulated Translation from R to T Product at Steady State

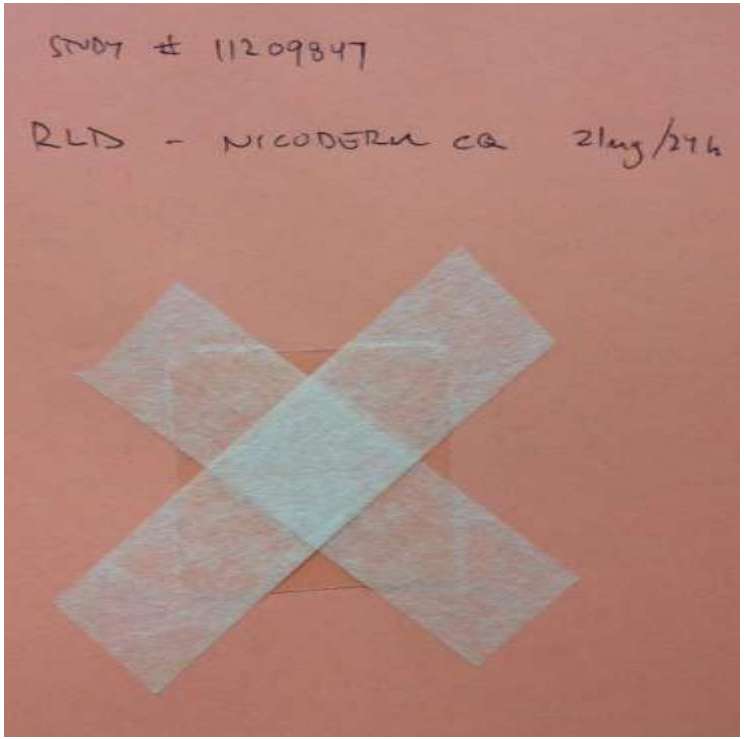


Tlag Difference

- After consult with clinical division for prolong Tlag issue, the patients may experience sub-therapeutic Drug D levels when dosed for the naïve patients with the test product or when switching from the reference product to the proposed test product.

- The test product may not be therapeutically equivalent to the reference product.

Case #6: Inadequate Study Design- Adhesive Tape



- Per product specific guidance on Nicotine TDS, overlay should avoid throughout the study.
- Adhesive tape was applied for the entire BE study duration and covered 75% of the patch edges.
- Application of tape could produce changes 1) the local temperature of the skin; 2) moisture trapped under the patch; and 3) nicotine evaporation rate

Case #7: Unacceptable Reference-scaled Approach BE Study

PK Parameter	S_{wr}	Approach	95% upper CI bound	Point Estimate
AUC0-t	0.732	Scaled	-0.177	1.31
AUCi	0.623	Scaled	-0.189	1.27
Cmax	0.671	Scaled	-0.0875	1.31

N= 43 subjects, 4-way crossover fed BE study

Summary

- Understand pharmacokinetic property of the drug product
- Use the product-specific guidance and PK endpoint guidance
- Justify difference from product specific guidance with adequate and scientifically sound justification

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