Permutation Bioequivalence Test under Sparse Sampling and Small Sample Size

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FDA/CDER/OTS/OB

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Outline

- Introduction
- Parametric Approach
- Bootstrap Approach
- Permutation Approach
- A Real Case Example
- Discussion

Introduction

- Bioequivalence Pharmacokinetic Study
  - to determine whether the generic and the reference formulation are equivalent with respect to blood or tissue concentration-time profiles
- Usual Design
  - full concentration-time profile from each subject
- Sparse Sampling/Serial Sampling/Destructive Sampling
  - only one observation from each subject

Statistical Challenge for Sparse Sampling

- One Observation Per Subject
  - Measured at only one time point
  - Conventional statistical methods analyzing full concentration-time profile from each subject are not applicable.
- Small Sample Size
  - Methods based on normal distribution or require relative large sample might not be applicable.

Parametric Approach

- Estimate AUC
  - using mean concentrations at different time points
  - Bailer (1988)
  - Extended by Nedelman (1995) and Yuan (1993)
- Estimate CI
  - the generic to reference ratio
  - Fieller's theorem (1954)

Bailer AJ. 1988. Testing for the equality of area under the curves when using destructive measurement techniques. *J Pharmacokinet Biopharm*, 16, 303
Fieller EC. 1954. Some Problems in Interval Estimation. *Journal of the Royal Statistical Society. Series B (Methodological),* 16:175
Nedelman JR, Gibiansky E, and Lau DT. 1995. Applying Bailer's method for AUC confidence intervals to sparse sampling. *Pharm Res*, 12, 124
Yuan J. 1993. Estimation of variance for AUC in animal studies. *J Pharm Sci*, 82, 761

Bootstrap Approach

- Bootstrap Method
  - resampling mechanism no relying on a specific distribution
  - Efron and Tibshirani (1993)
- Assess AUC parameters
  - using bootstrap method by one-point sampling
  - Takemoto et al (2006)
- Estimate BE
  - by bootstraping subjects at each time point
  - Shen and Machado (2017)

Efron B, Tibshirani RJ. 1993. *An Introduction to the Bootstrap*. Chapman and Hall, London
Takemoto S, Yamaoka K, Nishikawa M, and Takakura Y. 2006. Histogram analysis of pharmacokinetic parameters by bootstrap resampling from one-point sampling data in animal experiments. *Drug metabolism and pharmacokinetics*, 21, 458
Shen M, and Machado SG. 2017. Bioequivalence evaluation of sparse sampling pharmacokinetics data using bootstrap resampling method. *J Biopharm Stat*, 27, 257

Permutation Approach

- Classical hypothesis testing
  - start with assumptions about the underlying distribution and then derive the sampling distribution of the test statistic under H_0.
- Permutation testing
  - generate a distribution by recalculating all possible values of the test statistic under rearrangements of the labels on the observed data points under H_0.
  - Fisher (1935) and Pitman (1937)

Fisher RA. 1935. *The design of Experiments*. Oliver and Boyd, Edingburgh
Pitman EJG. 1937. Significance tests which may be applied to samples from any populations. *J Roy Statist Soc Suppl*, 4, 119

BE Hypotheses

- H_0: $\mu_T / \mu_R \leq \vartheta_1$ or $\mu_T / \mu_R \geq \vartheta_2$ versus H_a: $\vartheta_1 < \mu_T / \mu_R < \vartheta_2$
  - μ_T: population mean of the generic product
  - μ_R: population mean of the reference product
  - Equivalence margins: ϑ_1 and ϑ_2
  - Alternative hypothesis: BE
  - Schuirmann (1987)

Schuirmann DJ. 1987. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm, 15*, 657

Comparison: Bailer and Ruberg (1996)

- Proposed permutation approach
  - For sparse design
  - H_0: no BE
- Bailer and Ruberg (1996)
  - Randomization test for sparse design
  - H_0: no difference
  - Not appropriate for BE test

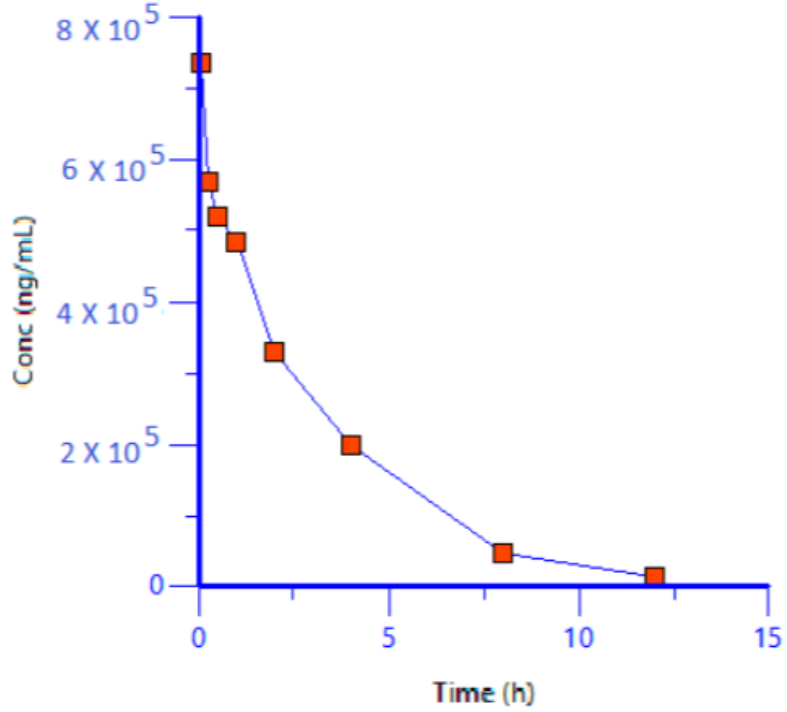
Bailer AJ, and Ruberg SJ. 1996. Randomization tests for assessing the equality of area under curves for studies using destructive sampling. J Appl Toxicol, 16, 391

Permutation Procedures

- Calculate the AUC of each possible combination of concentrations from each time point for each treatment group.
- Calculate generic to reference AUC ratio.
- Calculate 90% Bias-correction CI.
- If the 90% CI is in [80%, 125%], BE is established.

Sodium Ferric Gluconate (SFG) Injection

- Indication: Iron deficiency anemia
  - Reference drug
    - Ferrlecit (Sanofi-Aventis, approved in 1999)
    - First order kinetics with a half life of 2.2h
  - Generic drug:
    - SFG complex (Watson Pharma, approved in 2011)



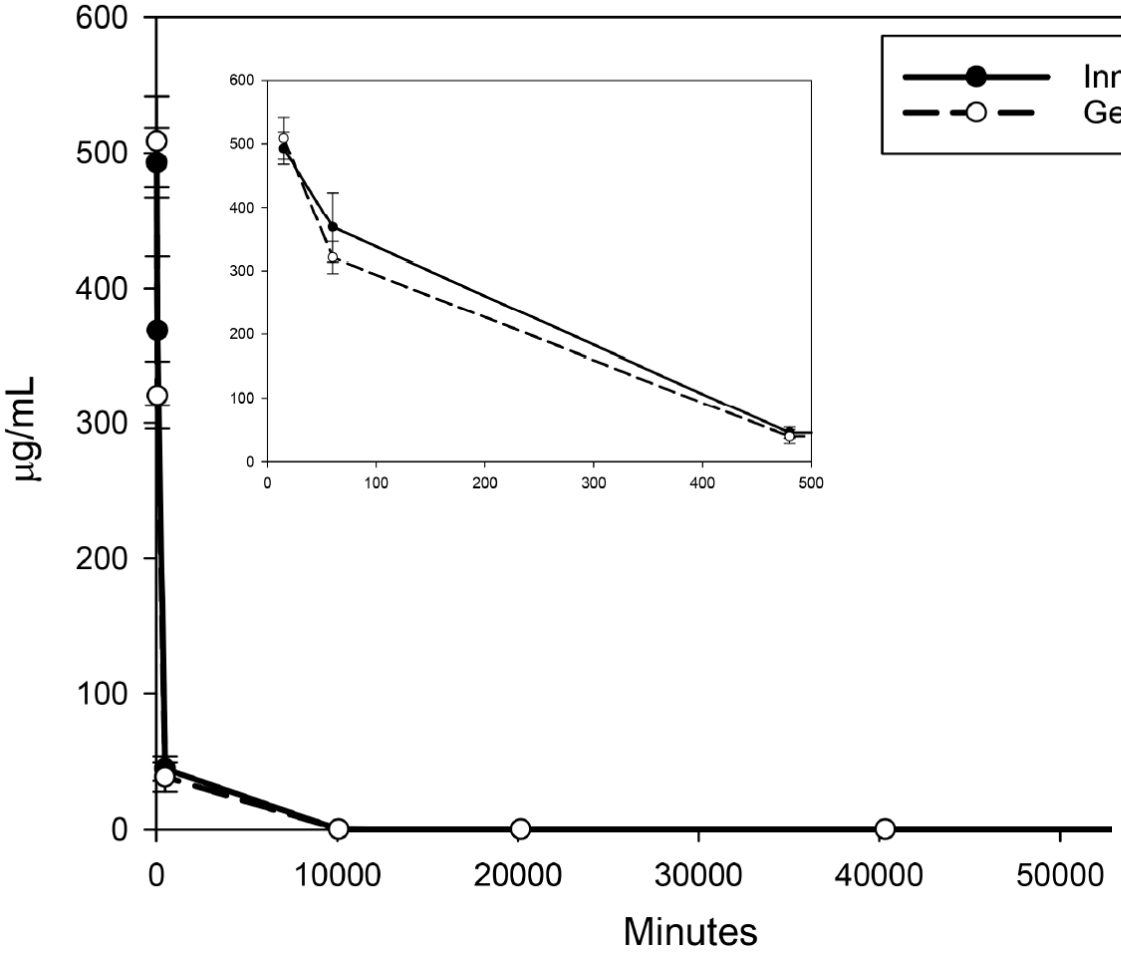
Beekman et al. 2018. Comparative Evaluation of U.S. Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection. Nanomaterials (Basel), 8: 10.
Matta et al. 2018. Determination of Non-Transferrin Bound Iron, Transferrin Bound Iron, Drug Bound Iron and Total Iron in Serum in a Rat Pharmacokinetic Study by Simple Ultrafiltration Inductively Coupled Plasma Mass Spectrometric Detection (UF-ICP-MS). Nanomaterials, 8: 101

Study Design

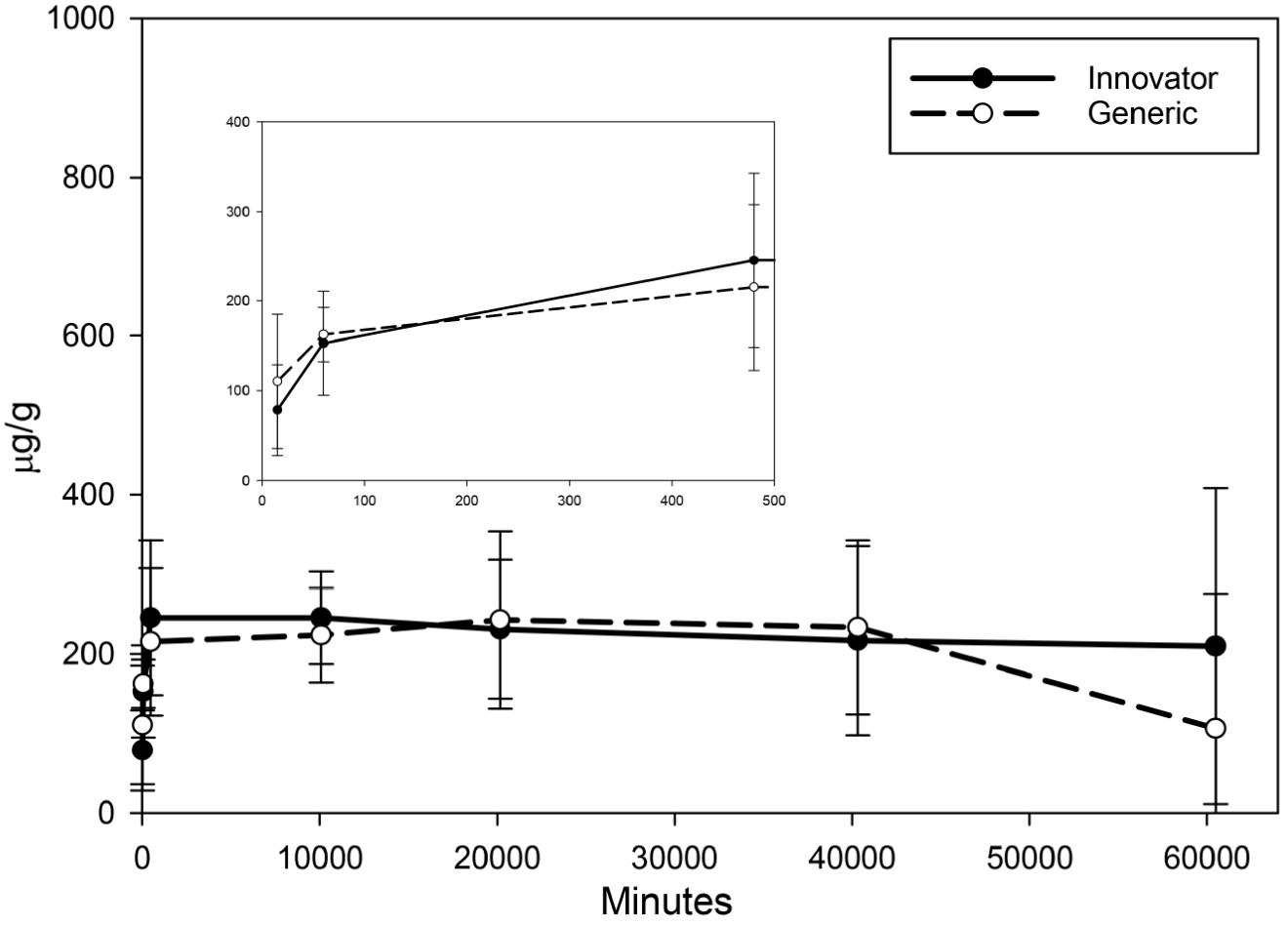
- Three treatment groups
  - Reference drug, Generic drug, Saline
- Six rats for each group at each time point
  - Seven timepoints: 15 min, 1 hr, 8 hrs, 1 wk, 2 wks, 4 wks, and 6 wks.
- Iron Concentration in Eight tissues
  - Serum: delivery
  - Femoral bone marrow: target organ
  - Kidneys, liver, and spleen: uptake/storage
  - Lungs, brain, heart: safety

Beekman et al. 2018. Comparative Evaluation of U.S. Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection. Nanomaterials (Basel), 8: 10.

Serum Iron



Bone Marrow



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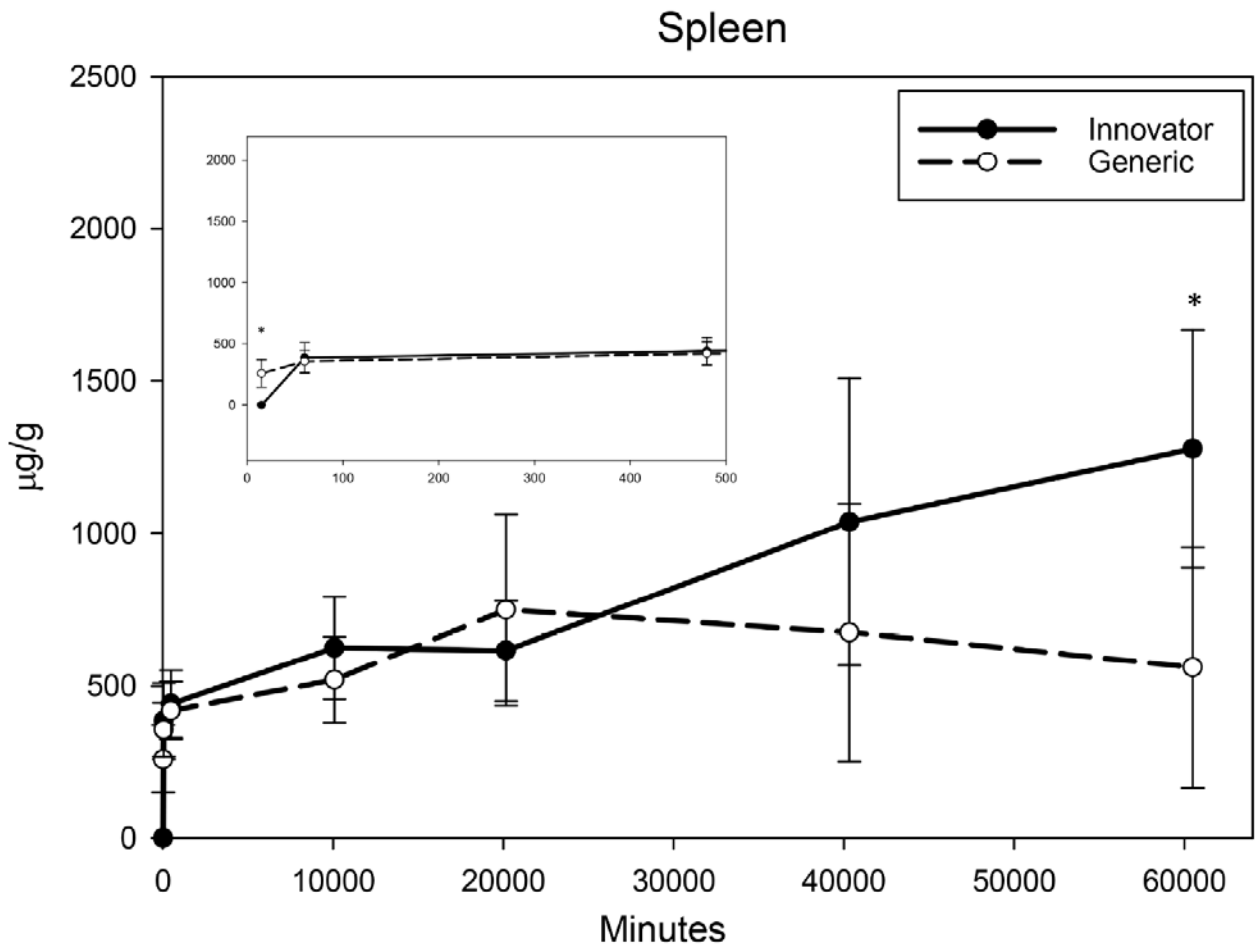

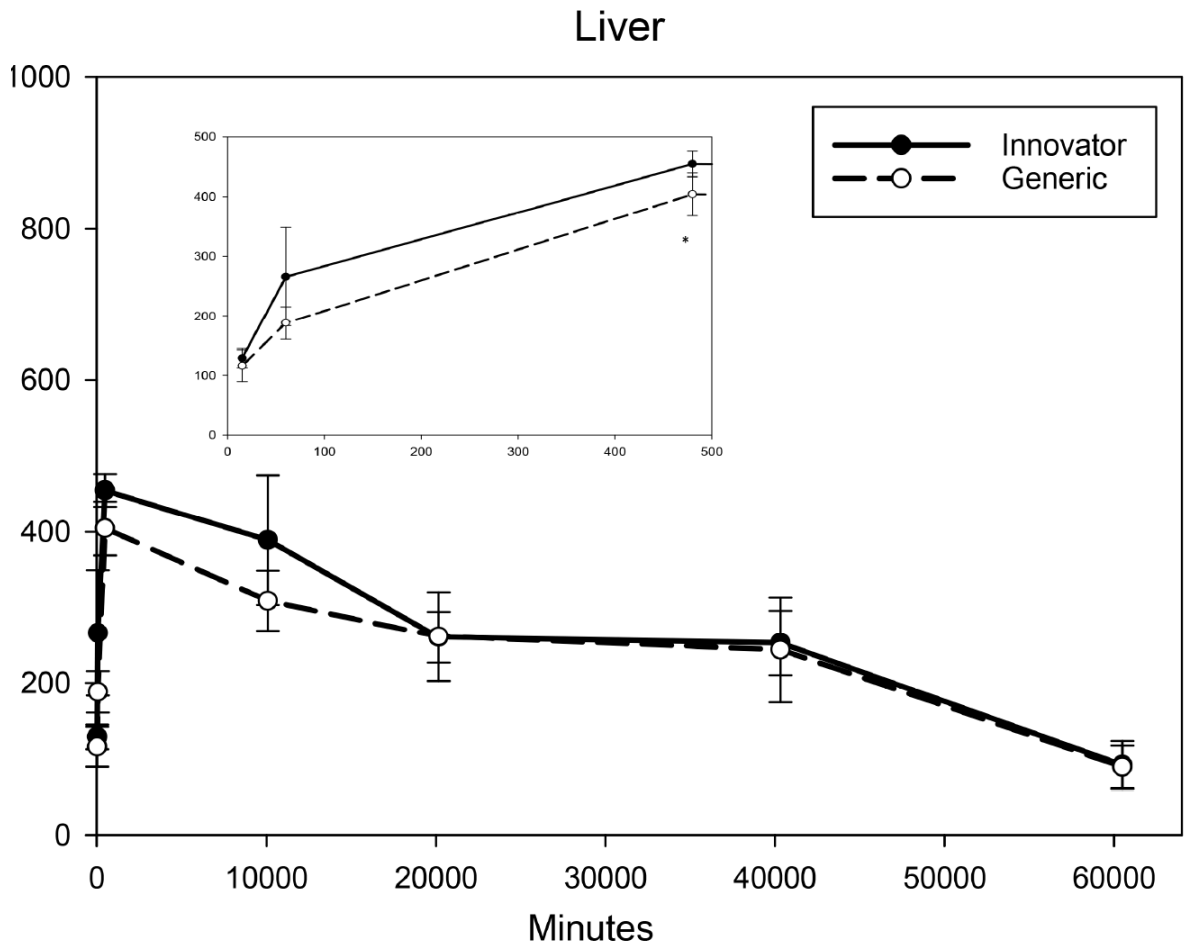

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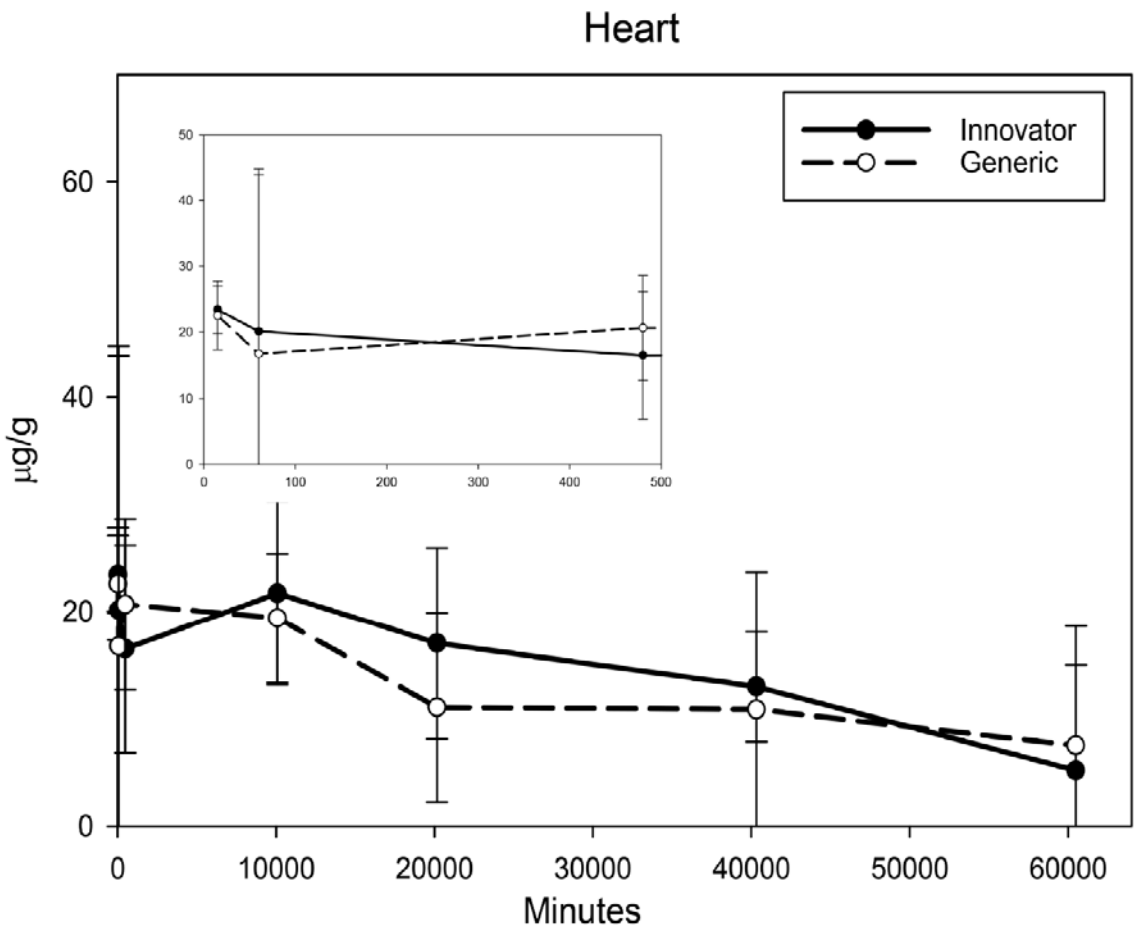

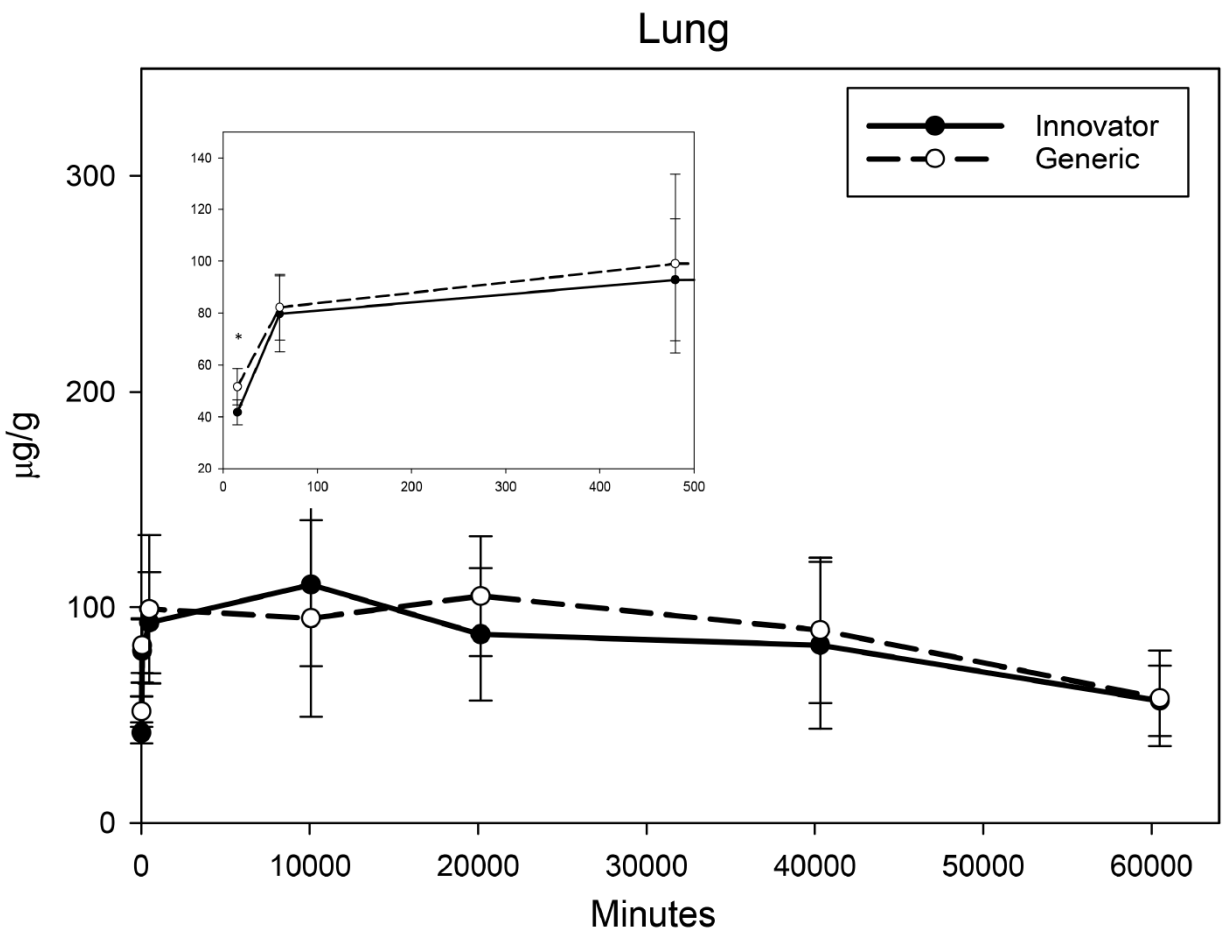

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Results

- Parametric vs. Permutation
  - Agreement (6/8)
    - BE: Brain, Heart, Kidney and Liver
    - Not conclusive: Blood, Spleen
  - Disagreement (2/8)
    - Bone Marrow and lung
    - BE by parametric
    - Not conclusive by permutation
- Bootstrap vs. Permutation

Approach Comparison

- Parametric
  - Easy to implement, but require normal distribution.
- Bootstrap
  - Distribution free, but require relatively large sample size
- Permutation
  - Distribution free, suitable to small sample size

Conclusion

- The proposed permutation approach may be used as part of evidence to support bioequivalence evaluation with pharmacokinetic data under sparse sampling and small sample size because no distribution assumption is needed.

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