Extrapolation of Pharmacokinetics Bioequivalence to an Alternative Comparator Due to RLD/RS Unavailability

Advancing Generic Drug Development:
Translating Science to Approval 2025 Virtual Workshop

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Learning Objectives

- Discuss an alternative approach for establishing pharmacokinetics (PK) bioequivalence (BE) when the reference listed drug (RLD) or reference standard (RS) is unavailable.
- Analyze case studies that demonstrate the application of using an alternative comparator in BE studies.
- Learn how to calculate BE with this alternative approach through a step-by-step calculation demonstration.

BE Studies With PK Endpoints

To receive approval for an ANDA, an applicant generally must demonstrate among other things, that its proposed drug product is bioequivalent to the reference listed drug (RLD).[3] The FD&C Act provides that a generic drug is bioequivalent to the listed drug if:

> The rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.[4]

For most products, the focus of BE studies is on the release of the drug substance from the drug product into the systemic circulation. During such BE studies, an applicant compares the systemic exposure profile of a test drug product to that of the RLD designated in FDA's *Approved Drug Products with Therapeutic Evaluations* (the Orange Book).[5, 6]

Guidance for Industry, Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (August 2021)

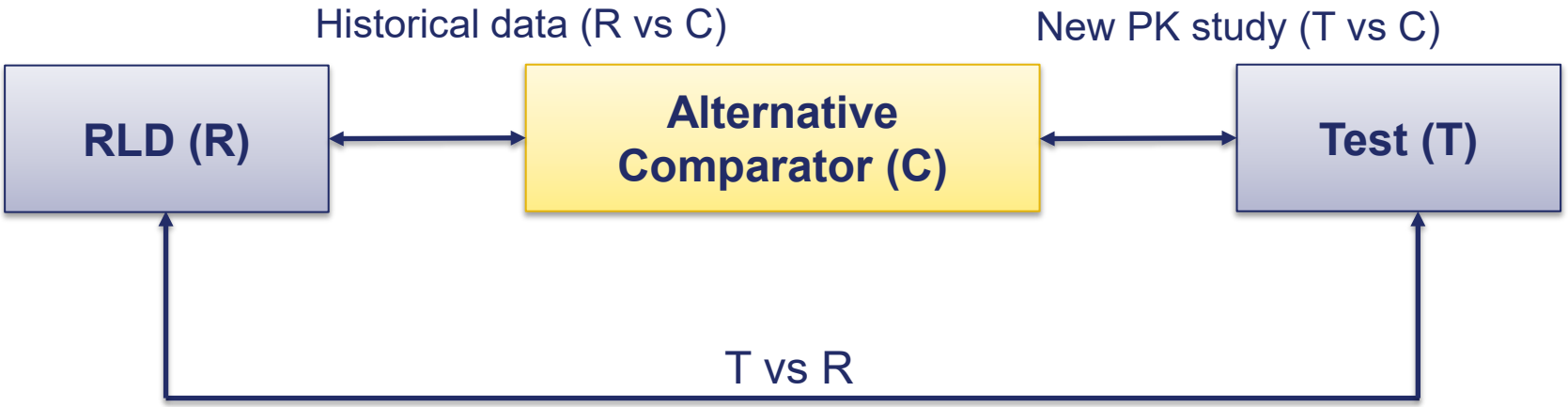
The reference standard (RS) selected by FDA is ordinarily the RLD. If FDA cannot select the RLD as the RS (e.g., RLD is withdrawn for reasons other than safety or efficacy), FDA may designate one of the generics as RS.

Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions (October 2020)

Alternative BE Approach – Extrapolating BE To An Alternative Comparator

- Conduct a relative bioavailability (BA) study with an alternative comparator and establish BE based on comparing the results with historical RLD data.
  - This alternative comparator can be a product with different dosage forms for the same route of administration.
  - Leveraging publicly available bridging studies conducted by the RLD holder during NDA submission.
- An alternative pathway to guide generic applicant interested in developing products when no RLD/RS is available in the market.

Extrapolating BE to An Alternative Comparator



The final BE decision should depend on whether the 90% confidence interval (CI) of the T/R ratio falls within 80.00%-125.00%.

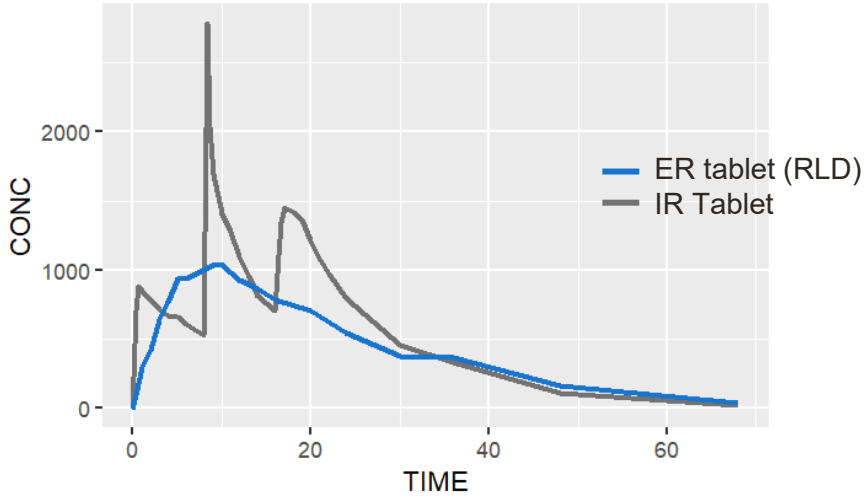
Case #1

- Drug product: oral suspension
- RLD/RS is not available
- The RLD was approved as a New Drug Application (NDA) through the 505(b)(2) pathway. The NDA holder demonstrated its oral suspension **is BE** to the oral tablet product (90% CI fall within 80-125%).
- **BE transitivity:** demonstrating BE between the test product (T) and the oral tablet formulation (serving as the alternative comparator, C) will establish BE transitivity across all three products (R, T, and C) in general.
- BE transitivity is a well-established approach commonly applied when a generic RS is used for in vivo BE comparisons in cases where the RLD has been discontinued from the market.

Case #2

- Drug product: extended release (ER) oral tablet
- RLD/RS is not available
- The RLD was approved as an NDA through the 505(b)(2) pathway. The NDA holder performed a relative BA study that compared its ER tablet to the immediate release (IR) tablet.
- **BE transitivity cannot be directly applied as R is not BE to the alternative comparator (i.e., IR tablet, C). However, the 90% CI of T/R can be extrapolated by leveraging historical and new study data to ultimately determine BE between T and R.**

Available Historical Data



- Two-way crossover PK study
- A single-dose ER tablet vs IR tablet, three times a day
- Following the same total daily dosage, BE between the ER tablet and the IR tablet (administered three times a day) was not demonstrated.

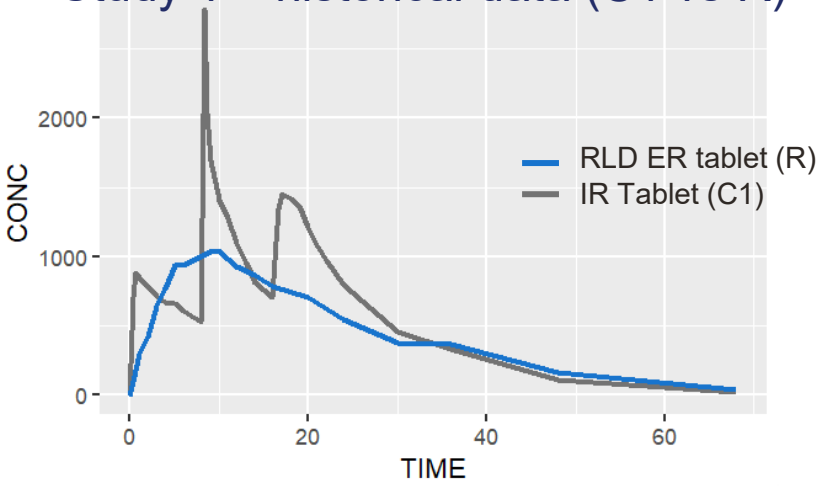
Summary of Statistical Analysis of PK Parameters (IR vs ER)

	GMR	90%CI	Sample size
Cmax	2.51	217.66-290.49	23
AUC(0-t)	1.24	113.25-134.83	23

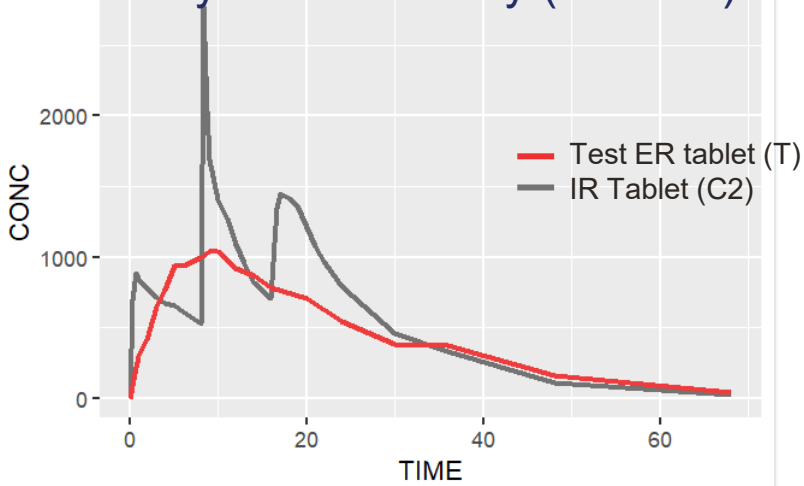
GMR- geometric mean ratio

Extrapolating BE Using IR Tablet As Alternative Comparator

Study 1 – historical data (C1 vs R)



Study 2 – new study (T vs C2)



- The alternative approach utilizes the relative difference, i.e., the geometric mean ratio (GMR) between two dosage forms (ER vs. IR).
- 90% CI for T vs R will be extrapolated based on their relative ratios compared to the IR tablet (i.e., T vs. C2 and C1 vs. R)

Statistical Analysis Method - Calculating Point Estimator

- Study 1 and 2 need to be conducted in a similar manner that satisfy the constancy assumption.
- An unbiased point estimator of the log-transformed geometric mean ratio of T/R (θ_{T_R}) can be calculated as

$$\hat{\theta}_{T\_R} = \hat{\theta}_{T\_C2} + \hat{\theta}_{C1\_R}, \qquad \textbf{Equation (1)}$$

where

$\hat{\theta}_{T\_C2}$ = estimate of log-transformed geometric mean ratio of **T** vs. **C2** from Study 2,
$\hat{\theta}_{C1\_R}$ = estimate of log-transformed geometric mean ratio of **C1** vs. **R** from Study 1.

Statistical Analysis Method - Calculating 90% CI

- Based on the testing results of equality of intra-subject variances between T and C2 and between C1 and R using an F test, calculate 90% CI of θ_{T_R} under either the homogeneous or heterogeneous assumption
- The following shows the equation of calculating 90% CI under the homogeneous variance assumption

$$\hat{\theta}_{T\_R} \pm t_{(0.95,\, df_{T\_R})} \times SE_p \,,$$

where $\hat{\theta}_{T\_R}$ is obtained from Equation **(1)**, and the standard error of $\hat{\theta}_{T\_R}$ and degrees of freedom under homogeneity (SE_p and df_{T_R}) can be calculated as

$$SE_p = \sqrt{MSE_p \times \frac{1}{2}\left(\frac{1}{n_{T\_C2,1}} + \frac{1}{n_{T\_C2,2}} + \frac{1}{n_{C1\_R,1}} + \frac{1}{n_{C1\_R,2}}\right)} \,,$$

$$df_{T\_R} = df_{T\_C2} + df_{C1\_R} \,,$$

SE = standard error
MSE = mean squared error
df = degrees of freedom
n1 =number of subjects in sequence 1
n2 =number of subjects in sequence 2

Statistical Analysis Method - Calculating 90% CI (cont.)

where

$$MSE_p = \frac{df_{T\_C2} \times MSE_{T\_C2} + df_{C1\_R} \times MSE_{C1\_R}}{df_{T\_C2} + df_{C1\_R}}$$

is the pooled mean squared error,

$n_{T\_C2,1}$ = number of subjects in sequence 1 from the study that compares **T** and **C2**,

$n_{T\_C2,2}$ = number of subjects in sequence 2 from the study that compares **T** and **C2**,

$n_{C1\_R,1}$ = number of subjects in sequence 1 from the study that compares **C1** and **R**,

$n_{C1\_R,2}$ = number of subjects in sequence 2 from the study that compares **C1** and **R**.

- 90% CI can also be calculated under the heterogeneous variance assumption depending on the results of the F test
  - 90% CI calculation under heterogeneous variance assumption are not shown in this presentation.

Example: Step-by-Step Calculation

	n (n1, n2)	GMR (θ, original scale)	90%CI (original scale)	θ (log-scale)	MSE
Study 1 C1/R (AUCt) Historical data	23 (11,12)	1.24	113.25-134.83	0.2116	0.0295
Study 2 T/C2 (AUCt) New study*	23 (11,12)	0.81	74.17-88.30	-0.2116	0.0295

*a hypothetical case example

n = total number of subjects
n1 = number of subject in sequence 1
n2 =number of subjects in sequence 2
MSE = mean squared error

Example: Step-by-Step Calculation

Calculate geometric mean ratio of **T/R** (θ_{T_R})

	n (n1, n2)	θ (log-scale)
Study 1 C1/R (AUCt) Historical data	23 (11,12)	0.2116
Study 2 T/C2 (AUCt) New study	23 (11,12)	-0.2116

→

	θ (log-scale)	θ (original scale)
T/R	0	1

$$\hat{\theta}_{T\_R} = \hat{\theta}_{T\_C2} + \hat{\theta}_{C1\_R}, \qquad \textbf{Equation (1)}$$

Example: Step-by-Step Calculation

Test the equality of intra-subject variances between **T** and **C2** and between **C1** and **R** using an F test

	n (n1, n2)	MSE
Study 1 C1/R (AUCt) Historical data	23 (11,12)	0.0295
Study 2 T/C2 (AUCt) New study	23 (11,12)	0.0295

95% CI of $\sigma^2_{T\_C2}/\ \sigma^2_{T\_C2}$ is 0.4152-2.4086.

Because this 95% CI contains 1, we consider variances of two populations from study 1 and 2 are equal.

Calculate the 95% CI of $\sigma^2_{T\ C2}/\sigma^2_{C1\ R}$ as

$$\left[\frac{MSE_{T\_C2}/MSE_{C1\_R}}{F_{(0.975,\, df_{T\_C2},\, df_{C1\_R})}}, \frac{MSE_{T\_C2}/MSE_{C1\_R}}{F_{(0.025,\, df_{T\_C2},\, df_{C1\_R})}}\right].$$

Example: Step-by-Step Calculation

Calculate 90% CI of **T/R** (θ_{T_R})

	n (n1, n2)	θ (log-scale)	MSE
Study 1 C1/R (AUCt) Historical data	23 (11,12)	0.2116	0.0295
Study 2 T/C2 (AUCt) New study	23 (11,12)	-0.2116	0.0295
T/R	-	0	-

$$\hat{\theta}_{T\_R} \pm t_{(0.95,\, df_{T\_R})} \times SE_p \,,$$

where $\hat{\theta}_{T\_R}$ is obtained from Equation **(1)**, and the standard error of $\hat{\theta}_{T\_R}$ and degrees of freedom under homogeneity (SE_p and df_{T_R}) can be calculated as

$$SE_p = \sqrt{MSE_p \times \frac{1}{2}\left(\frac{1}{n_{T\_C2,1}} + \frac{1}{n_{T\_C2,2}} + \frac{1}{n_{C1\_R,1}} + \frac{1}{n_{C1\_R,2}}\right)},$$

$$df_{T\ R} = df_{T\ C2} + df_{C1\ R},$$

where MSE_p is the pooled mean squared error

$$MSE_p = \frac{df_{T\_C2} \times MSE_{T\_C2} + df_{C1\_R} \times MSE_{C1\_R}}{df_{T\_C2} + df_{C1\_R}}$$

90% CI of **T/R** is 88.64 – 112.81 (original scale)

BE between T and R is demonstrated

Summary

- We demonstrated an alternative approach for establishing BE through an alternative comparator (e.g., a product with a different dosage form for the same route of administration).
- The 90% CI for T/R will be extrapolated based on their relative PK ratios of both products compared to the alternative comparator. BE will be concluded if the extrapolated 90% CI for the T/R ratio falls within the acceptance criteria of 80.00%-125.00%.
- This approach provided an alternative method to guide generic applicant interested in developing products when no RLD/RS is available in the market.
- We strongly encourage applicants to engage in early communication with the FDA during product development (e.g., Model-Integrated Evidence Industry Meeting Pilot) if considering this alternative approach for demonstrating BE.

Model-Integrated Evidence (MIE) Industry Meeting Pilot

Launched on October 1st, 2023

The pilot program allows enhanced scientific communications on a broad range of quantitative methods and modeling techniques to address generic drug development issues or questions that are either out of the scope of or cannot be sufficiently addressed by the existing pre-ANDA and ANDA scientific meetings. E.g.,

- Common modeling issues across multiple products
- Complex modeling approaches for non-complex products

A dedicated regulatory platform for interactions on MIE

- To foster early and focused interactions between industry and FDA on MIE approaches for establishing bioequivalence (BE) in generic drug development

MIE Industry Meeting Pilot Between FDA and Generic Drug Applicants

MIE Pilot Program General Principles document

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Questions?

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