Model-based Bridging to Establish Bioequivalence With a Discontinued Reference Listed Product

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Objective

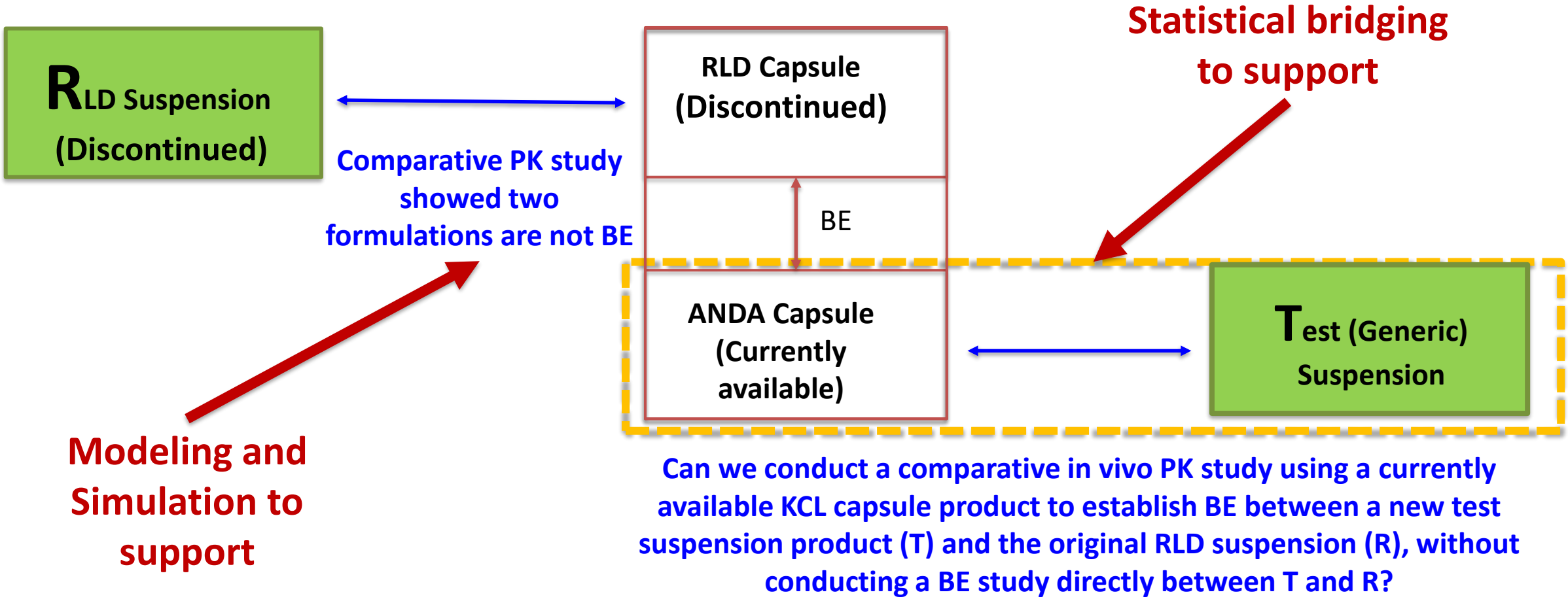
- To provide a potential path for bioequivalence (BE) evaluation using modeling and simulation (M&S) when reference listed drug (RLD) is not available and typical pharmacokinetic (PK) bridging using the reference standard (RS) is not possible.

Modeling and Simulation to Bridge to Unavailable Reference Standard for BE Evaluation

- Ordinarily, FDA selects the RLD as the reference standard
- If FDA cannot select the RLD as the reference standard (e.g., RLD is withdrawn for reasons other than safety or efficacy), FDA may designate one of the generics as reference standard (RS).
- For the unavailable RLD with no approved generics, in certain circumstances, modeling and simulation may be used for scientific bridging.

  Possible examples of the RLD data for scientific bridging
  - Case a: comparative relative bioavailability (BA) study to another product currently available.
  - Case b: limited data in in RLD NDA (available to public) such as relative BA study to standard oral solution.
- Scientific bridging with modeling and simulation may allow BE to be established based on new study and historical data
  - New studies may compare
    - Case a: test product vs. available product
    - Case b: test product vs. standard oral solution
  - Modeling and simulation may be conducted to characterize the historical data and new data to establish BE to RLD with virtual BE.

Model-based Scientific Bridging for BE Demonstration with a Discontinued RLD - An Example of Developing a Generic for a Discontinued Potassium Chloride (KCL) Suspension



Can we conduct a comparative in vivo PK study using a currently available KCL capsule product to establish BE between a new test suspension product (T) and the original RLD suspension (R), without conducting a BE study directly between T and R?

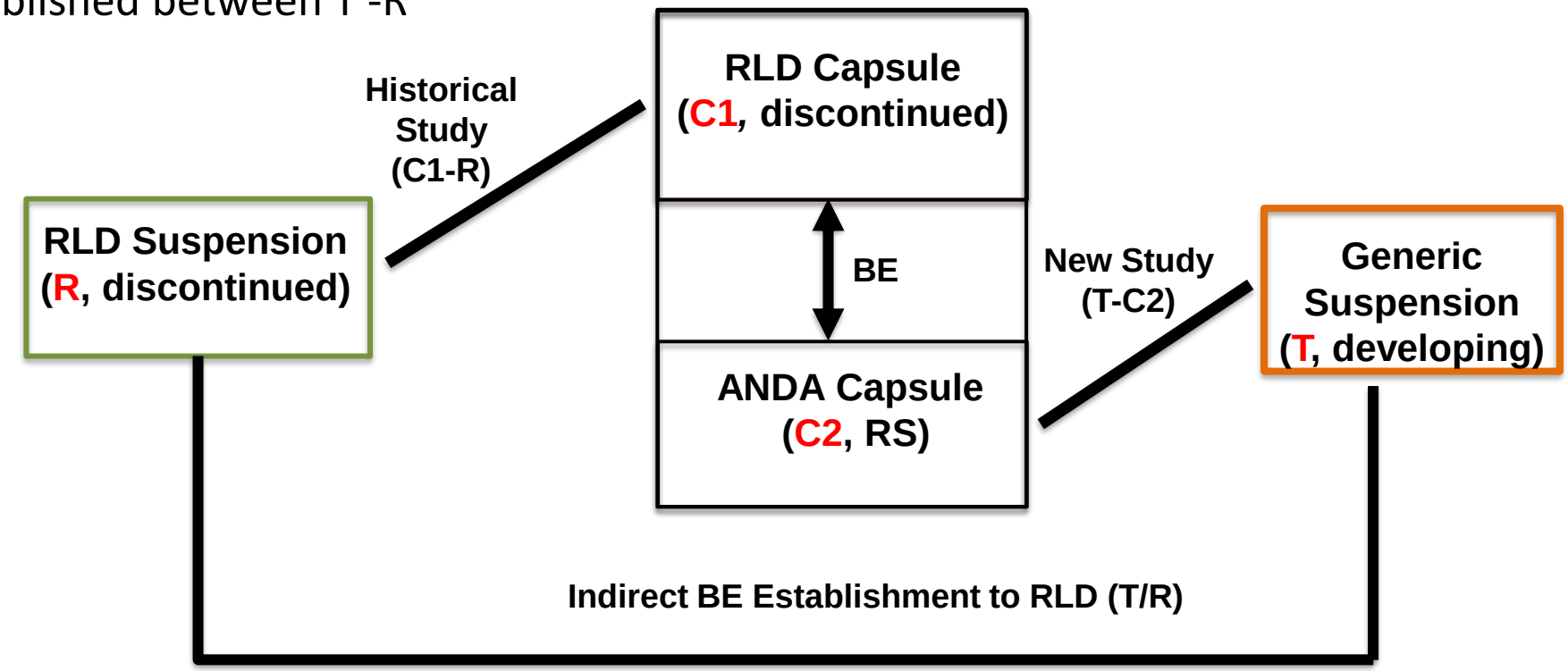
Outline

1. Background
2. Introduction of a hypothetical case of discontinued RLD in BE using KCL ER as an example
    a. Product information and potential PK bridging
3. Model development and validation
4. Model-based bridging with a currently available product as intermediate
5. Conclusion

Strategy to Indirectly Establish BE to Original RLD

Two KCL ER capsule formulations (C1&C2) serve as intermediate standards providing a bridge between T and R in this BE evaluation scheme, T—C2↔C1—R, where

- C1 was bioequivalent to C2 (C2↔C1)
- C1 and R both were discontinued, but C1—R can be informed by historical PK study
- A new PK study is designed to compare T—C2
- BE will be established between T -R



Highlights in Current Product Specific Guidance for Establishing BE for Potassium Products

- Due to potassium homeostasis, plasma concentrations are not suitable for BE.
- Urinary potassium excretion parameters are used for BE:
  - Cumulative urinary excretion amount in 24 hours (**Ae0-24h**)
  - Maximal rate of urinary potassium excretion (**Rmax**).
- Urine sampling scheme: collection intervals at hours 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16, and 16-24 postdosing.
- Baseline excretion of potassium (obtained during the baseline days) should be subtracted from the amount obtained on the drug dosing day to yield the net effect of drug administration[1].

[1] FDA Draft Guidance on Potassium Chloride Bioequivalence study for Extended-Release Capsules/Oral.(2011)

The Historical Data Compared between Suspension and Capsule, But not Relevant for PK Difference Characterization

- The published NDA PK Study reported only Mean and SD with no individual data (Melikian, et al., 1988)[1]
- Impossible to establish allowable limits for PK difference between formulations

Day	Period (hr)	R Suspension	C1 Capsule	Solution	Baseline Control
1	0–24	47.5 ± 10.9	46.6 ± 16.0	46.2 ± 12.0	49.4 ± 12.4
2	0–24	49.4 ± 9.0	46.4 ± 8.6	46.7 ± 11.7	48.6 ± 7.6
3	0–24	43.1 ± 6.7	42.6 ± 6.1	42.1 ± 7.6	44.1 ± 8.5
4	0–2	9.0 ± 3.0	8.0 ± 2.5	16.8 ± 5.2	6.6 ± 2.3
4	2–4	9.2 ± 2.6	8.1 ± 2.8	9.4 ± 2.9	4.5 ± 1.5
4	4–6	9.7 ± 3.2	8.5 ± 4.3	7.1 ± 2.5	4.2 ± 1.6
4	6–8	8.7 ± 2.4	8.5 ± 2.8	6.9 ± 2.4	4.8 ± 1.9
4	8–12	12.0 ± 4.5	12.6 ± 3.6	10.7 ± 3.5	9.1 ± 3.7
4	12–24	18.6 ± 5.4	18.3 ± 5.3	18.3 ± 5.8	14.7 ± 5.4
4	0–24	66.6 ± 10.4[ab]	62.8 ± 9.5[b]	69.2 ± 10.0[a]	43.9 ± 8.0[c]
5	0–24	50.7 ± 7.8	51.6 ± 7.0	52.5 ± 9.1	47.3 ± 5.8
4 + 5		117.2 ± 15.6[ab]	114.4 ± 14.03[b]	121.7 ± 15.8[a]	91.2 ± 12.0[c]

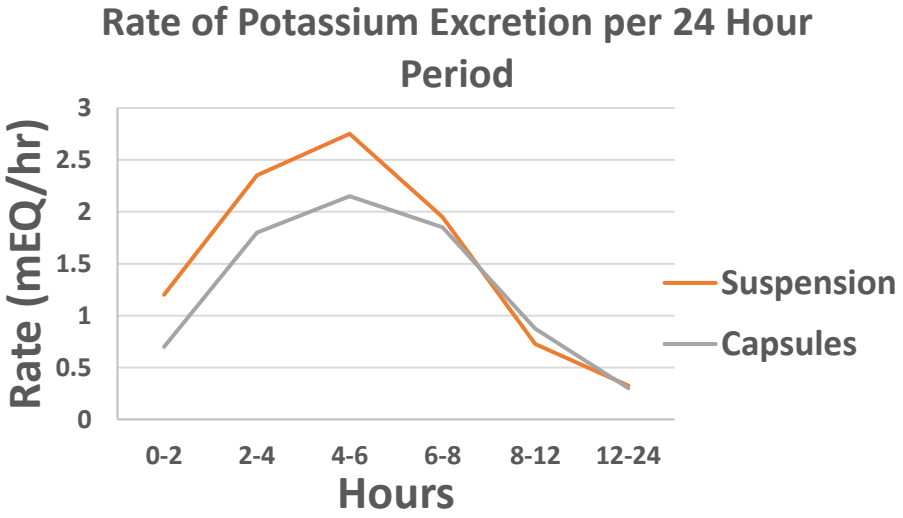
* *Means indexed by the same letter do not differ significantly (P > 0.05).*

Study design: a four-treatment, four-period (4 × 4) crossover study to test relative bioavailability of KCL in ER suspension Micro-KLS and KCL ER capsule Micro-K against KCL solution Kaochlor® S-F, with control group for baseline subtraction.

[1] Melikian, et al. Bioavailability of potassium from three dosage forms: suspension, capsule, and solution. J Clin Pharmacol, 1988 Nov;28(11):1046-50

Historical Data Show Suspension is not BE to Capsule

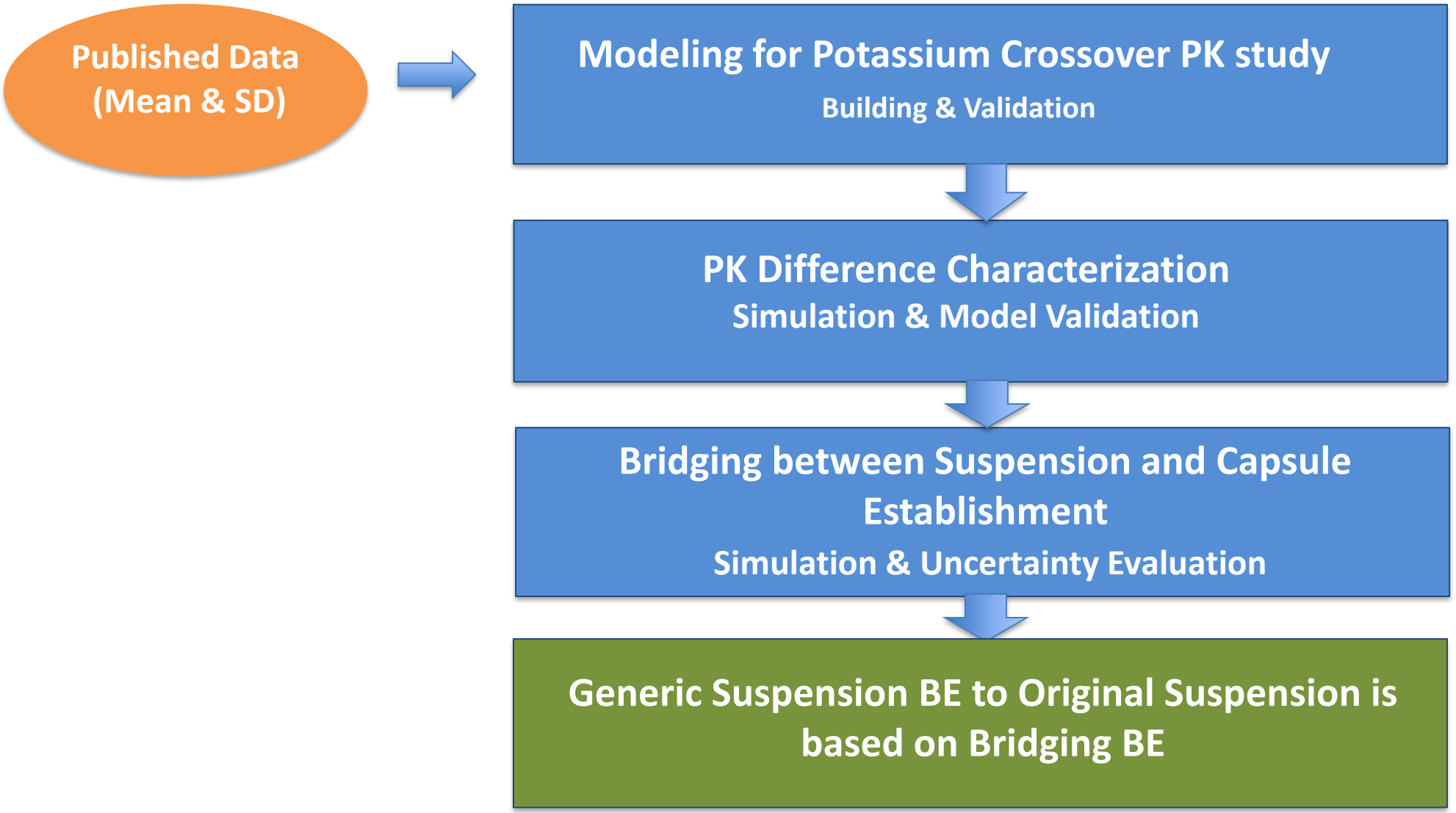
PK endpoint	Ae0-24h	Rmax
R (Suspension)	22.7 (mEq)	2.75 (mEq/hr)
C1 (Capsules)	18.9 (mEq)	2.15 (mEq/hr)
Ratio of C1/R (%)	83.26	78.18



The historical data show that Suspension is not BE to Capsule.

Therefore (you can note because of the reasons in slide 8 and 9), publicly available data could not be used for PK BE bridging.

Model-Based PK Bridging and BE Assessment Using Virtual Individual PK profile

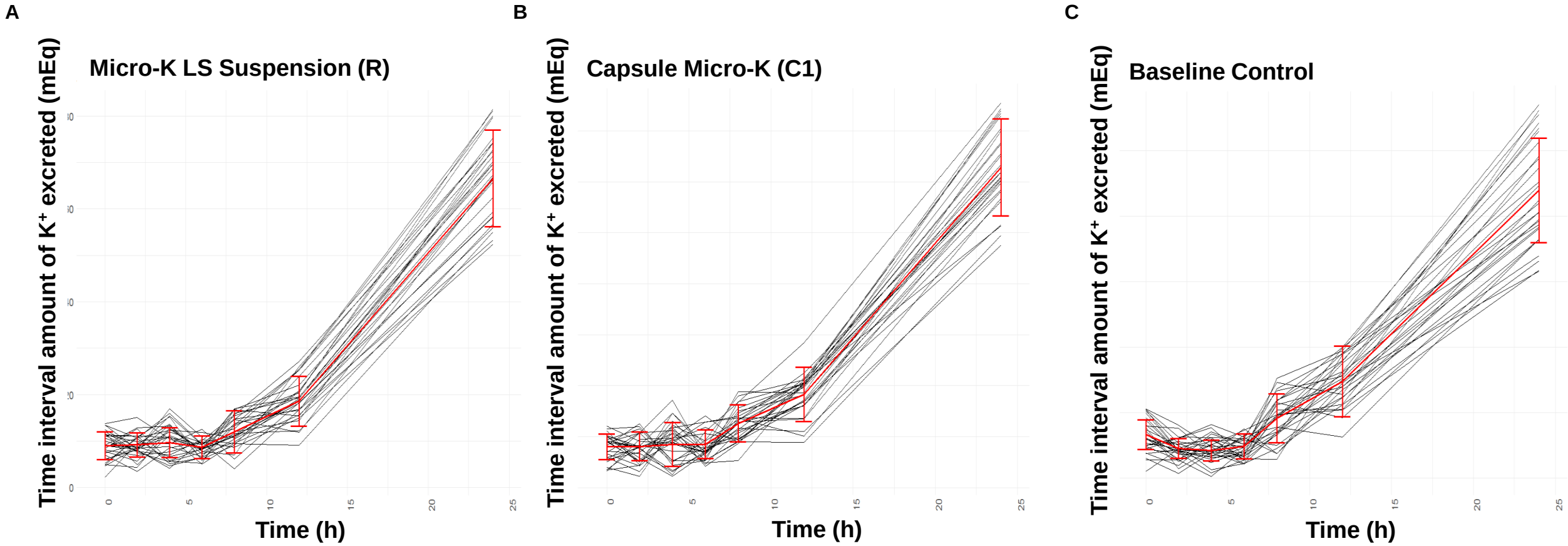


Linear Mixed Effects Model

Linear mixed effects model allows us to simulate individual PK profiles to mimic the historical study

- Directly create correlation matrix using fixed effects and random effects for individual data generation based on mean (±SD) of urine collection in period 0-2h, 2-4h, 4-6h, 6-8h, 8-12h, and 12-24h.
- This approach can capture the correlation across different time points and different dosage forms within the same subject.
- The individual data can be bootstrapped for in vivo study simulation.

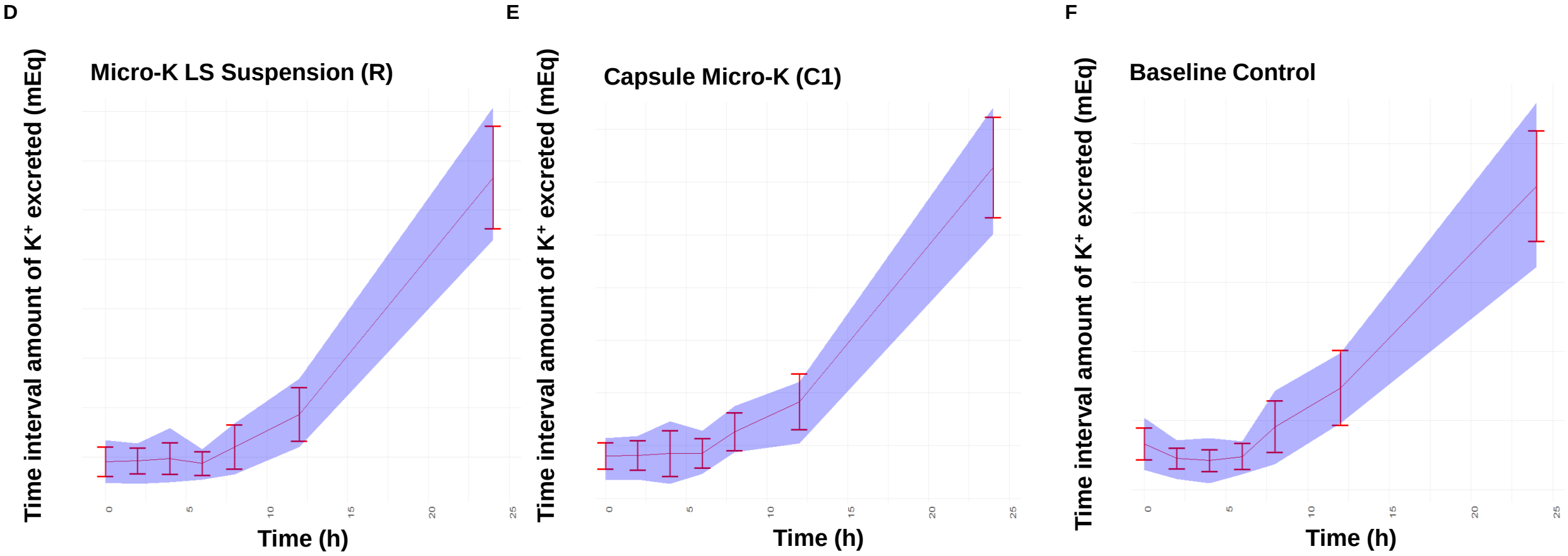
Model allows Simulation of Individual PK Profiles



Red line/bar: Observed mean and SD data

Black line spaghetti plot: simulated individual PK profiles from 28 subjects in one replicate simulation

Model Validation - Simulated PK Profiles are Consistent with the Observed



Shaded areas: confidence intervals at 5th and 95th quantiles from 1000 replicates of simulation

Model Validation by Comparing Arithmetic Mean PK Endpoint Ratios for C1/R between Virtual Data and Publication Data

PK endpoint	Ae0-24h	Rmax
A. Based on virtual Individual data (n=28)		
R	21.98 (mEq)	2.73 (mEq/hr)
C1	18.33 (mEq)	2.14 (mEq/hr)
Ratio of C1/R	83.34%	78.21%
B. Based on observed data from publication (a set of mean vs time intervals)		
R	22.7 (mEq)	2.75 (mEq/hr)
C1	18.9 (mEq)	2.15 (mEq/hr)
Ratio of C1/R	83.26%	78.18%

- Agreement of arithmetic mean ratio for Ae0-24h and Rmax between model-based simulation and the observed mean values.
- Mean ratio of C1/R for Ae0-24h is within [80%,125%], and Rmax is outside of [80%,125%].

Model allows Characterizing PK Difference based on Individual Data

90% CI for Capsule/Suspension Ratio in BE Evaluation Using Simulated Individual PK Profiles

PK endpoint [a]	Ae0-24h	Rmax
90% CI [lower, upper]	[62.39%, 105.90%]	[86.84%, 104.78%]
Point Estimate [b]	81.24%	95.53%

a. PK endpoint estimated using datasets subtracted by baseline.
b. Point Estimate = geometric mean C1/R ratio of lower and upper 90%CI

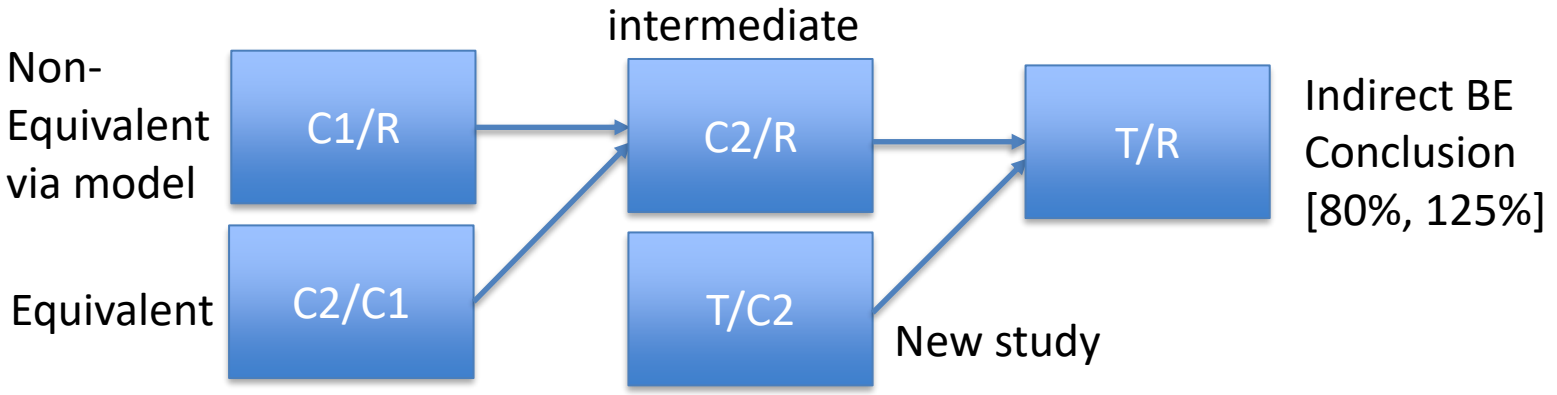
Note: BE analysis based on virtual logarithmic individual data (n=28), C1/R

The model-based BE assessment provided 90% CI for C1/R ratio:

- Rmax meets BE, but Ae0-24 does not meet BE.
- Capsule/Suspension is not BE but model characterizes the PK difference.
- Based on PK difference, we will determine BE between RLD and test suspension.

BE Bridging Process

- Rmax is BE and can be directly 'transited' based on BE between ANDA capsule (C2) and to new test suspension (T):
  - Rmax is BE between R and C1. Based on BE transitivity. [1,2]
  - If C2 and T are BE, then T and R are BE.
- For Ae0-24, Liu[3] provided theoretical support for bridging BE.
  - Model helped us to characterize PK difference between C1/R.
  - C1 is BE to C2 and we can assume that we can use same PK difference between C1/R as C2/R.
  - Our new study is C2/T. Using the published method by Liu for bridging BE studies, C2/R and C2/T can be translated to T/R allowing us to use conventional BE limits of 80-125.



[1] Anderson S, Hauck WW. The transitivity of bioequivalence testing: potential for drift. Int J Clin Pharmacol Ther 34 369-374. (1996)
[2] Gwaza L, et al. Influence of point estimates and study power of bioequivalence studies on establishing bioequivalence between generics by adjusted indirect comparisons. Eur J Clin Pharmacol 71 1083-1089. (2015)
[3] Liu JP. Bridging bioequivalence studies. J Biopharm Stat 14 857-867. (2004)

Examples of BE Bridging Analysis for Ae0-24 by Varying Sample Size and Mean Square Error (MSE)

	C1 vs. R				C2 vs. T						T vs. R			
No.	Sample size	Lower bound 90% CI	Upper bound 90% CI	*MSE*	**Sample size**	Lower bound 90% CI	Upper bound 90% CI	Point Estimate %	***MSE***	Power	Lower bound 90% CI	Upper bound 90% CI	Point Estimate %	*MSE*
1	28	62.39	105.9	0.16832	28	110	140	124.10	0.03499	0.9555	82.13	123.89	100.87	0.10169
2					28	95	162.1	124.10	0.17175	0.2326	77.32	131.59	100.87	0.17007
5					36	110	140	124.10	0.04577	0.9548	82.70	123.03	100.87	0.10708
6					36	95	162.1	124.10	0.22468	0.2267	77.15	131.89	100.87	0.19654

90% CI will be varied depending on variability (i.e., MSE) and sample size, given the BE results of 90% CI of [62.39%, 105.9%] between C1 and R.

Conclusions

- Model-based bridging BE may provide a solution for generic drug development when RLD and RS are unavailable.
- Linear mixed effect model can restore individuals PK profiles for crossover BE study using mean and SD values from historical data.

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