

Advancing Virtual Bioequivalence for Orally Administered Drug Products: Best Practices and Real-World Applications

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Supplementary Materials.

Table S1: Simulated and observed PK parameters and calculated %PE of Molecule 1 for IV and oral capsule administration; Table S2: Simulated and observed PK parameters and calculated %PE of Molecule 1 for two test and one reference formulation from pilot BE study; Table S3: Simulated and observed PK parameters and calculated %PE of Molecule 1 for one test and one reference formulation from pivotal BE study; Table S4: Simulated and observed test/reference C_{max} and AUC ratios and calculated %PE of Molecule 1; Table S5: Population predicted and observed T/R ratios for pivotal RLD & Test in fasting & fed conditions for Molecule 2. Table S6: Upper and lower dissolution specifications dissolution profiles against the pivotal test batch for Molecule 2; Figure S1: Simulated and observed plasma concentration profiles (log scale) after IV administration (A), oral capsule administration (B), test 1 tablet administration in pilot BE study (C), test 2 tablet administration in pilot BE study (D), reference tablet administration in pilot BE study (E), test 1, test 2, and reference tablet administration in pilot BE study (F), test tablet administration in pivotal BE study (G), and reference tablet administration in pivotal BE study (H). Error bars in G and H are standard deviations of observed data.

Table S1. Simulated and observed PK parameters and calculated %PE of Molecule 1 for IV and oral capsule administration.

PK parameter	Metric	IV	Oral capsule
C_{max} (µg/mL)	Observed	0.0024	3.4
	Predicted	0.0023	2.9
	%PE	2.7	14.5
AUC_t (µg*h/mL)	Observed	0.0699	207
	Predicted	0.0752	196
	%PE	-7.6	5.1
T_{max} (h)	Observed	0.23	1.5
	Predicted	0.25	1.9

Table S2. Simulated and observed PK parameters and calculated %PE of Molecule 1 for two test and one reference formulation from pilot BE study.

PK parameter	Metric	Test 1	Test 2	Reference
C_{max} (µg/mL)	Observed	664.5	672.4	702.9
	Predicted	680.8	700.1	725.7
	%PE	-2.5	-4.1	-3.2
AUC_t (µg*h/mL)	Observed	13434	13655	13566
	Predicted	11760	12010	12500
	%PE	12.5	12.0	7.9
T_{max} (h)	Observed	2.0	2.5	2.0
	Predicted	1.7	1.7	1.7

Table S3. Simulated and observed PK parameters and calculated %PE of Molecule 1 for one test and one reference formulation from pivotal BE study.

PK parameter	Metric	Test 1	Reference
C_{max} (µg/mL)	Observed	733.9	674.5
	Predicted	705.9	700.6
	%PE	3.8	-3.9
AUC_t (µg*h/mL)	Observed	14241	13901
	Predicted	12410	12080
	%PE	12.9	13.1
T_{max} (h)	Observed	2.5	2.5
	Predicted	1.8	1.7

Table S4. Simulated and observed test/reference C_{max} and AUC ratios and calculated %PE of Molecule 1.

PK parameter	Metric	Pilot study	Pivotal study
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		Test 1/Reference	Test 2/Reference	Test/Reference
C_{max} ratio	Observed	91.38%	95.66%	108.81%
	Predicted	93.81%	96.48%	100.75%
	%PE	-2.7	-0.9	-8.0
AUC ratio	Observed	93.74	100.66%	102.45%
	Predicted	94.08	96.08%	102.73%
	%PE	-0.4	4.5%	0.3

Table S5. Population predicted and observed T/R ratios for pivotal RLD & Test in fasting & fed conditions for Molecule 2.

PK parameter	Observed	Predicted			Prediction error (%)
Fasting condition					
	T/R ratio	90% confidence interval	T/R ratio	90% confidence interval	
C _{max}	86.57	82.22 - 91.15	89.96	86.35-93.73	3.92
AUC _{inf}	90.86	86.68 - 95.24	91.06	84.26-98.42	0.22
AUC _t	91.29	87.14 - 95.63	90.95	83.31-99.29	0.37
Fed condition					
C _{max}	110.05	104.08 - 116.36	96.68	91.19-102.5	12.15
AUC _{inf}	105.34	101.31 - 109.53	99.12	93.63-104.93	5.90
AUC _t	105.13	101.38 - 109.02	99.23	93.03-105.85	5.61

Table S6: Upper and lower dissolution specifications dissolution profiles against the pivotal test batch for Molecule 2.

Time (h)	Pivotal Test	Proposed specification	Lower specification	Upper specification
0	0		0	0
0.5	10		0	24
1	17	10-30%	6	31
2	31		20	45
3	44	33-58%	33	58
4	56		45	70
6	76		65	90
8	89	NLT 80%	80	100
10	96		87	100

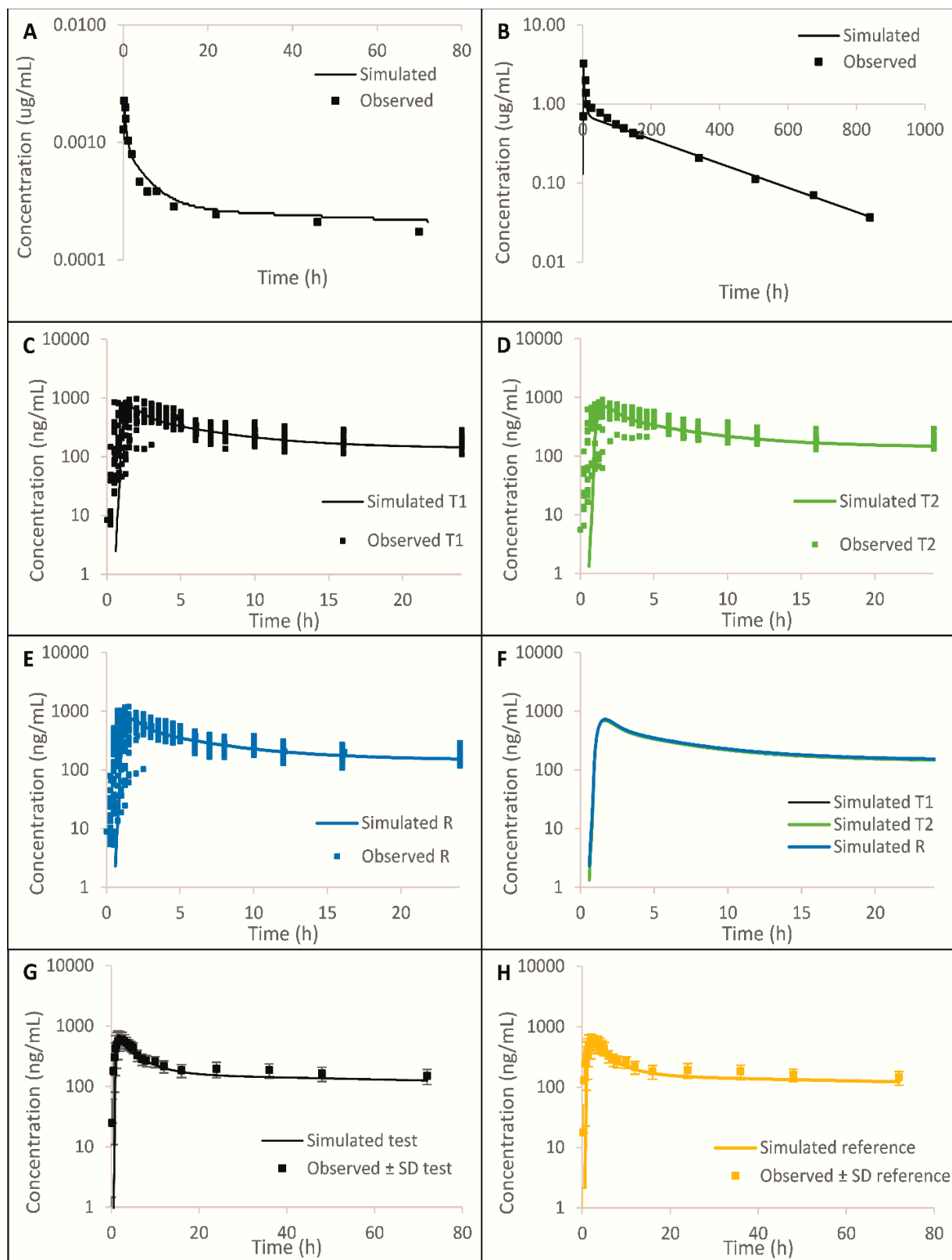


Figure S1. Simulated and observed plasma concentration profiles (log scale) after IV administration (A), oral capsule administration (B), test 1 tablet administration in pilot BE study (C), test 2 tablet administration in pilot BE study (D), reference tablet administration in pilot BE study (E), test 1, test 2, and reference tablet administration in pilot BE study

(F), test tablet administration in pivotal BE study (G), and reference tablet administration in pivotal BE study (H). Error bars in G and H are standard deviations of observed data.