Utilizing Physiologically Based Pharmacokinetic Modeling and Virtual Simulation to Evaluate the Sensitivity of Using Parent vs Metabolite as Analytes on Bioequivalence Assessment for Simvastatin

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Purpose

- Typically, parent drug is measured for bioequivalence (BE) assessment because it is more sensitive to detect formulation differences.
- In some cases, metabolite is measured in addition to parent drug because formulation may impact metabolite and parent drug differently and measuring parent drug alone may not detect the formulation differences, especially when metabolite is formed prior to absorption.
- The objective of this study is to investigate and summarize product-specific guidances (PSGs) that recommend measuring metabolites as BE analytes and rationales underlying these recommendations.
- Further, this study aims to use physiologically based pharmacokinetic (PBPK) absorption modeling and virtual BE simulation to evaluate the sensitivity of using parent vs metabolite as analytes on BE assessment. We used simvastatin as a model drug and explore the relevant mechanism since current PSG for simvastatin tablets recommends measuring both parent and metabolite and taking metabolite as supportive data [1].

Methods & Materials

- We searched FDA published PSGs up to August 2022 focusing on oral products and summarized those including metabolites as BE analytes.
- SimCYP™ (Version 20, Certara, Sheffield, UK) software with full PBPK distribution model and Advanced Dissolution, Absorption and Metabolism (ADAM) model was used for developing the PBPK model to describe PK profiles of simvastatin (SV) and its active metabolite simvastatin acid (SVA).
- Metabolite SVA is formed pre-systemically from hydrolysis of SV by carboxylesterase (CES-1). SVA is then absorbed both passively and actively through transporter OATP1B1 to penetrate the hepatocyte sinusoidal membrane [2]. Both SV and SVA are substrates of CYP3A4.
- Physicochemical properties and PK data of SV and SVA in healthy subjects following oral administration of immediate release (IR) tablet of 40 and 80 mg SV were used to develop and validate the PBPK model.
- Sensitivity analyses were conducted to examine the potential impact of excipients (e.g., sodium lauryl sulfate, SLS) on the transporter (OATP1B1)-mediated uptake and subsequent PK profiles of SV and SVA [3].
- To evaluate the sensitivity of SV and SVA as analytes to assess BE between test and reference drugs, simulations were conducted using 100 healthy virtual subjects administered with 80 mg test or reference SV tablets, assuming 76–124% relative bioavailability (BA) in test drugs, compared to the reference drug.

Data & Results

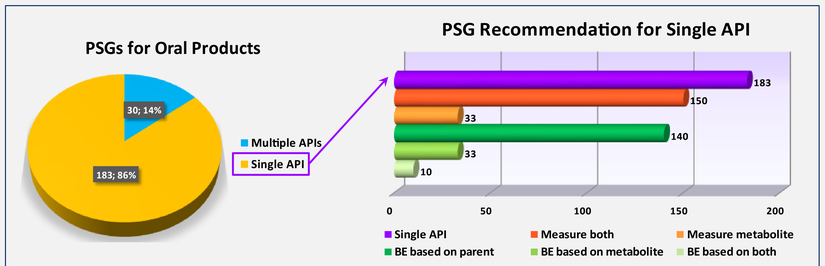

Figure 1. Summary of PSGs for various oral drug products that recommend collecting metabolites as analytes.

- 213 PSGs for various oral dosage forms containing suggestions related to metabolites were extracted; 183 out of 213 total PSGs for a single active pharmaceutical ingredient (API) were filtered out for additional analyses focusing on "Analytes to measure" and "BE based on (90% CI)".
- Among 150 out of 183 PSGs that recommend measuring both parent drug and active metabolite, most PSGs (121/150; 81%) also note that "metabolite data should be submitted as supportive evidence of comparable therapeutic outcome". In addition, another recommendation in 15/150 (10%) PSGs suggest that "if parent drug plasma concentration can be reliably measured and its pharmacokinetic parameters accurately determined, parent drug data should be analyzed using the confidence interval approach; if parent drug data cannot be reliably measured, analyze the metabolite data using the confidence interval approach for BE determination".
- Out of the remaining 33 PSGs, 29 (88%) that recommend measuring metabolite only are those involving parent drugs as prodrugs, which may not be accurately measured. The other four 4 PSGs that recommend BE determination based on metabolite only are possibly due to the rapid metabolism and very low systemic availability of the parent drugs.

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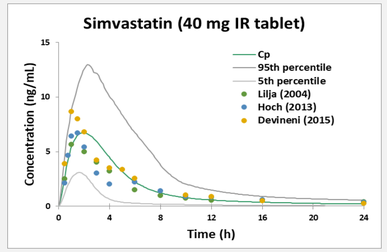
Data & Results Cont.



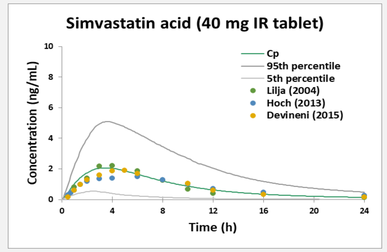


Figure 2. Representative observed and simulated PK profiles for parent drug (SV) and its primary metabolite (SVA) in healthy subjects using developed PBPK absorption model [4–6].

Table 1. PBPK absorption modeling and simulation results for parent drug (SV) and metabolite (SVA) in healthy subjects following administration with single-dose 40 or 80 mg IR tablets of SV.

Study	Dose (mg)	SV prediction error (%)			SVA prediction error (%)		
		C_{max}	AUC_t	AUC_{inf}	C_{max}	AUC_t	AUC_{inf}
Model development							
Lilja (2004) [4]	40	0	-19.9	–	15.4	-5.9	–
Hoch (2013) [5]	40	9.6	-11.8	-19.2	-20	-5.4	18.7
Devineni (2015) [6]	40	15.6	9.5	-2.8	-3.3	-3.7	-2.9
Model validation							
Teng (2013) [7]	80	-1.3	**33.7**	-2.7	14	14.1	**29.6**
Reference drug	80	17.8	19.2	-20.6	8.6	16	15.4
Test drug	80	6.4	24.4	-10.4	10.7	23.5	**25.7**

Most PK parameters can be reasonably predicted using developed PBPK absorption model with prediction error (PE) of ≤25%.

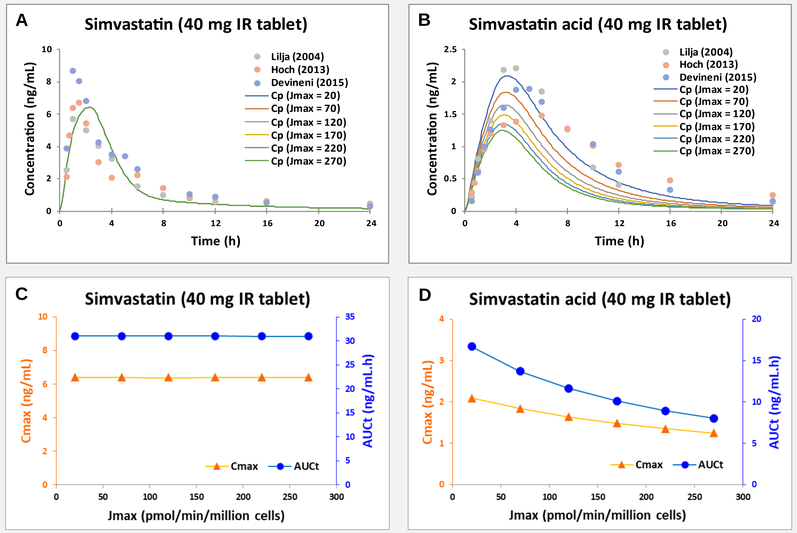


Figure 3. Sensitivity analyses in PK profiles of parent drug (SV) and metabolite (SVA) [4–6] (A, B) and PK parameters C_{max} and AUC_t (C, D) that incorporate maximal substrate-mediated transporter uptake rate for OATP1B1 (J_{max}) into PBPK absorption model. Results indicate that if certain excipients contained in the drug formulation inhibit transporter activity, it may result in decreased clearance and increased systemic exposure of SVA, potentially causing bioinequivalence (BIE) for SVA if test and reference drugs contain different excipients. In contrast, as SV is not a substrate of OATP1B1, our simulation suggests that excipients affecting OATP1B1 will not impact PK of SV.

Data & Results Cont.

Table 2. Virtual BE simulations conducted in 100 healthy virtual individuals administered with 80 mg test (T) or reference (R) SV tablets to investigate sensitivity of using parent drug SV (P) vs metabolite SVA (M) as analytes on BE assessment. Where test drugs were assumed with relative BA ranging 76–124%, corresponding to 61–99 mg, compared to the reference drug.

	T/R ratios for parent drug (SV)			T/R ratios for metabolite (SVA)		
	C_{max}	AUC_t	AUC_{inf}	C_{max}	AUC_t	AUC_{inf}
T with 124% BA (99 mg)	121.0 [120.3, 121.6]	119.6 [119.1, 120.2]	114.8 [113.0, 116.7]	120.7 [120.1, 121.2]	119.9 [119.4, 120.5]	117.9 [117.1, 118.6]
T with 110% BA (88 mg)	108.7 [108.3, 109.0]	108.3 [107.9, 108.6]	105.6 [104.0, 107.3]	108.7 [108.5, 109.0]	108.4 [108.1, 108.7]	107.5 [107.2, 107.9]
T with 90% BA (72 mg)	91.2 [90.9, 91.6]	91.6 [91.3, 91.9]	91.0 [87.6, 94.5]	91.2 [90.9, 91.6]	91.5 [91.1, 91.8]	92.3 [91.9, 92.7]
T with 76% BA (61 mg)	**78.6** [**78.1**, **79.1**]	**79.7** [**79.1**, 80.3]	80.6 [**76.8**, 84.6]	**78.7** [**78.2**, **79.2**]	**79.4** [**78.8**, **79.9**]	81.5 [80.7, 82.4]

Point estimate of T/R ratio [90% CI]. Failed BE tests were determined and marked as **red** when estimated % T/R ratio falls outside 80–125%.

- PBPK absorption model incorporating transporter-involved absorption and enzyme-mediated metabolism adequately describes pharmacometrics of SV and SVA in healthy subjects administered with 40 mg IR tablets of SV with PE of ≤25% for PK parameters C_{max}, AUC_t, and AUC_{inf} (Figure 2 and Table 1).
- The PBPK model was properly validated using approved application data of reference and test drugs with PE estimates in C_{max} and AUC_t ranging 6.4–24.4% and 8.6–23.5% for SV and SVA, respectively (Table 1).
- The sensitivity analyses suggest that when the test drug contains certain excipients (e.g., SLS) affecting transporter activity that the reference drug does not contain or contain at different level, SVA as analyte is more sensitive to show drug exposure differences due to change in transporter (OATP1B1)-mediated uptake and subsequent PK of SVA, potentially resulting in BIE, as compared to SV (Figure 3).
- Given the excipient-associated transporter effect is not considered, virtual BE simulation shows that SV and SVA have similar sensitivity to detect BIE in C_{max} (SV vs SVA: 78.6 vs 78.7%) and AUC_t (79.7 vs 79.4%) when reducing relative BA to 76% (corresponding to 61 mg) in test drugs, compared to the reference drug of 80 mg SV (Table 2).

Conclusion & Significance

- The majority of PSGs published by the FDA for a single API (>80%) that recommend measuring on both parent and metabolite also recommend submitting metabolite as supportive data for BE assessment.
- The developed PBPK absorption model can reasonably describe PK profiles of SV and SVA in healthy subjects administered with IR tablets of SV.
- PBPK modeling and virtual simulation of SV suggest that using metabolite (SVA) as analyte may give a chance to detect formulation effect under special condition when certain excipient could change clearance of the metabolite (e.g., by changing transporter uptake).
- This study further demonstrates the need to include metabolite as supportive information on BE assessment in some cases.

References

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Acknowledgements

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