

Structural and Practical Considerations in the Development of a Parent-Metabolite Model

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Background and Objectives

Issues often exist in parameter estimation of combined pharmacokinetic (PK) models for a parent drug and its metabolites, related to the structural identifiability even with perfect data. For structurally identifiable models, experimental conditions and data availability may cause the model parameters not estimable^[1]. We present a case of PK modeling for Wellbutrin® XL (bupropion XL) and its three main active metabolites, M1, M2 and M3. When orally administered, bupropion was rapidly absorbed and only a small proportion of the dose reached the systemic circulation intact because of high first-pass metabolisms. We investigate the PK of bupropion and its 3 metabolites and, more importantly, use this model as an example to discuss some common issues for modeling oral PK data for parent compound and its metabolites.

Methods

The data used for model building were from a GSK funded Phase I study conducted in healthy Chinese subjects. A total of 16 subjects received bupropion XL 150 mg QD for 5 days, and then the dose was titrated to 300 mg QD from Day 6 to Day 14. Three different model structures were investigated:

- Model without first-pass effect, the parent drug is either eliminated from the system or transformed into the 3 metabolites (Fig 2a);
- 1st-pass effect considered, the dose enters the parent and metabolite compartments simultaneously (Fig. 2b);
- 1st-pass effect considered, a dose apportionment independent of absorption rates with a fraction of dose leading to the parent, and fractions leading to the 3 metabolites as hypothetical metabolite absorption compartments prior to reaching the circulation (Fig 2c).

Some key considerations in the model building procedure are shown in Fig.1. The structural identifiability of these models was analyzed using Laplace transformation approach^[2,3]. Data of bupropion and metabolites were simultaneously fitted using ADVAN5 and FOCE-I methods.

Fig. 1 Model Considerations

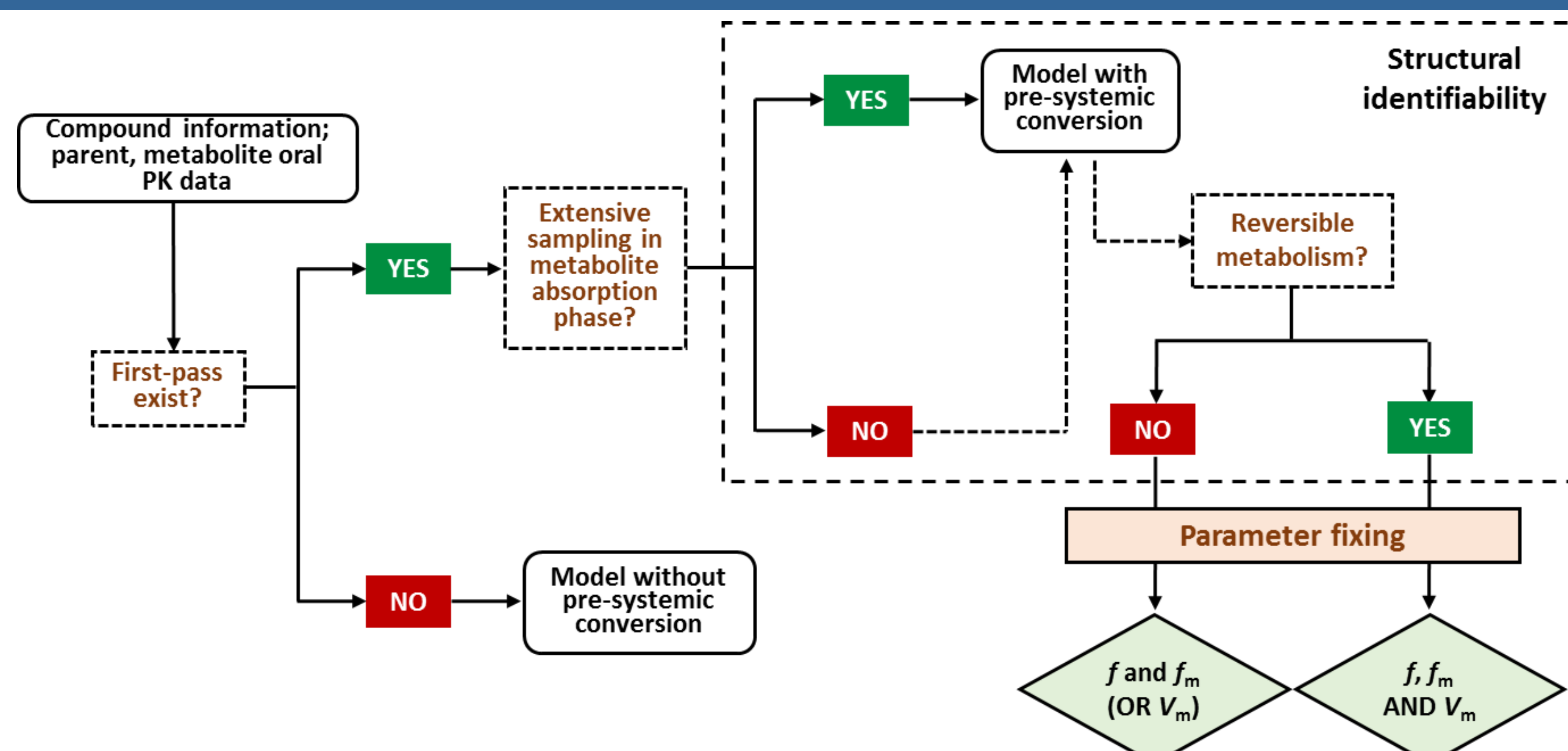
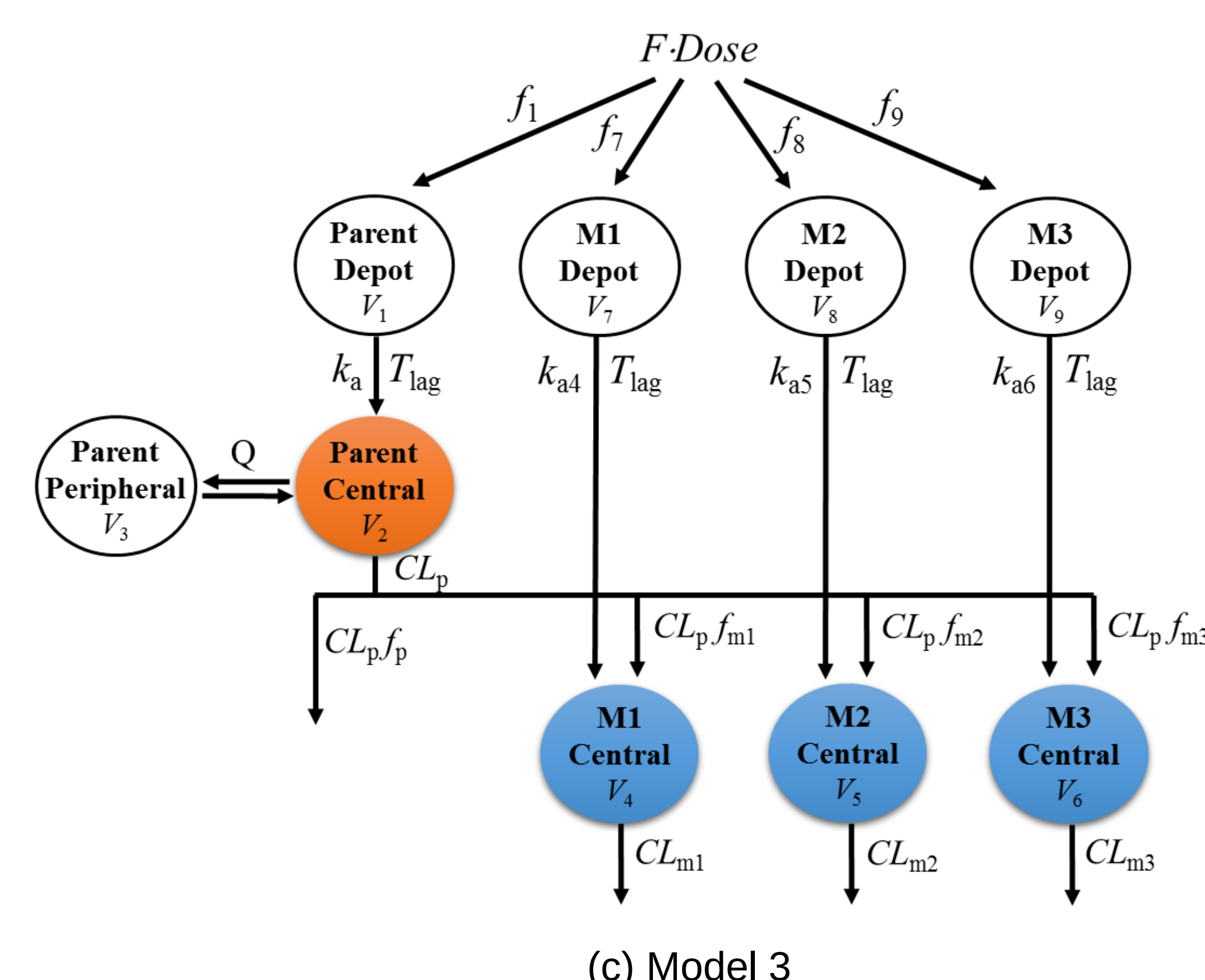
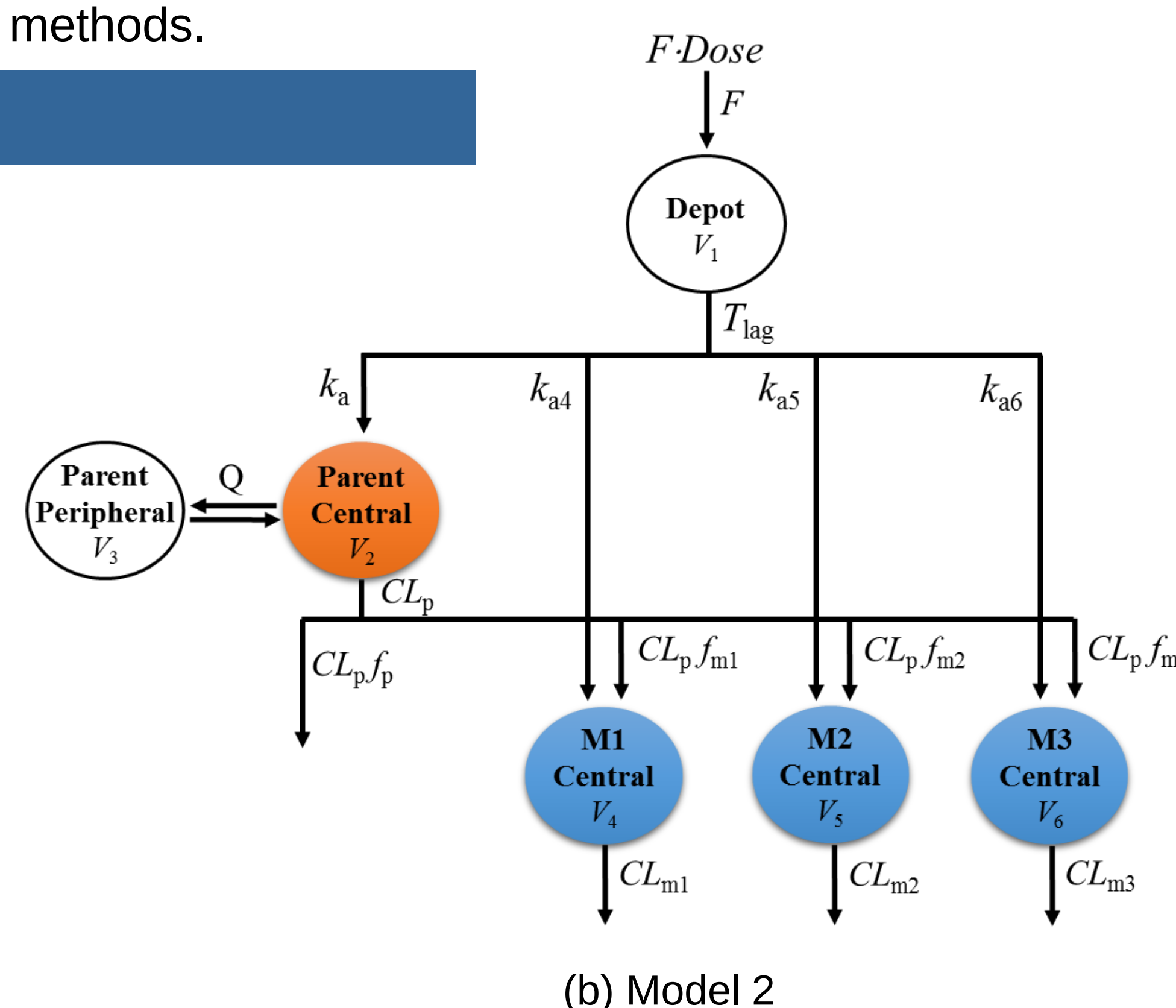
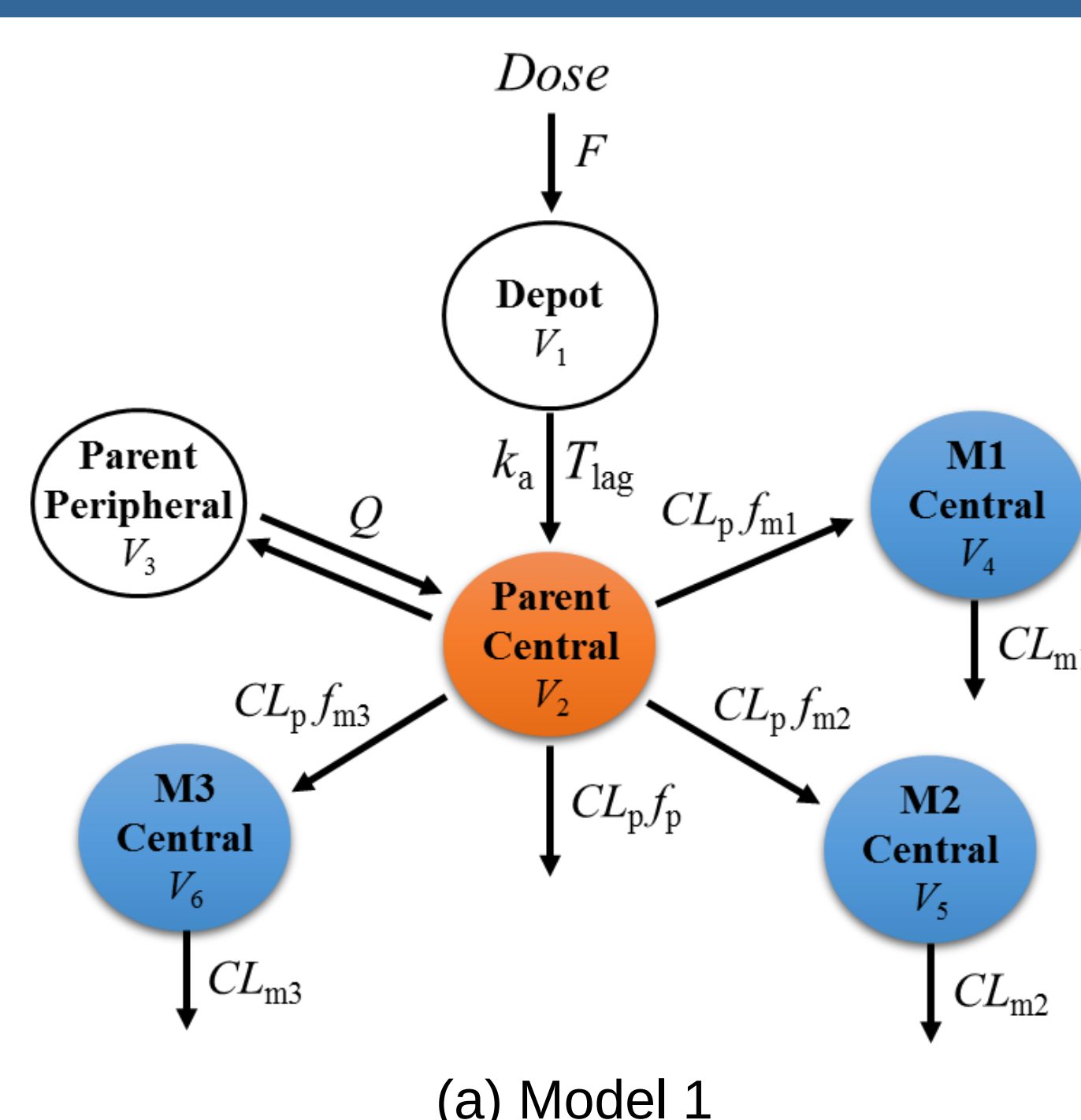


Fig. 2 Model Structures



Results and Conclusion

From the structural identifiability analysis for model 1, parameters k_a , CL_p/F , Q/F , V_2/F and V_3/F can be globally identified, while in model 2, none of the parameters can be identified. In model 3, only the absorption rates for the parent and all the metabolites are identifiable. However, model 3 was selected for further investigation based on mechanism.

To have a structural identifiable model, the fractions of the parent converted to metabolites within circulation and the proportions of compounds reaching circulation after absorption need to be fixed to the proportions determined from the observed peak molar concentrations (12.84%, 59.52%, 23.81% and 3.83% for bupropion, M1, M2 and M3). The model performance with results presented in Table 1 and Fig. 3.

In conclusion, we believe a proper balance between mechanistic complexity of the model and amount of data has to be reached for modeling parent-metabolite data.

Table 1. Parameter Estimates							
Parameter	Estimate	%RSE	%CV	Parameter	Estimate	%RSE	%CV
k_a (h^{-1})	0.536	11.5	--	CL_{m2} (L/h)	6.46	8.7	32.3
CL_p (L/h)	28.2	3.9	12.49	V_5 (L)	225	17.8	--
V_2 (L)	318	7.1	--	k_{a5} (h^{-1})	0.169	20.4	--
Q (L/h)	8.9	14.8	--	CL_{m3} (L/h)	5.84	6.3	23
V_3 (L)	177	10.2	37.15	V_6 (L)	257	7.1	--
T_{lag} (h)	1.79	2.9	9.59	k_{a6} (h^{-1})	0.137	13.8	--
CL_{m1} (L/h)	8.52	8.2	31.62	f_1	0.128 (fix)	f_9	0.038 (fix)
V_4 (L)	260	14.1	--	f_7	0.594 (fix)	--	--
k_{a4} (h^{-1})	0.17	22.2	--	f_8	0.238 (fix)	--	--
Residual variability							
σ^2_{prop} (par)	0.121	14.4	--	σ^2_{add} (par)	10.7	31	--
σ^2_{prop} (M1)	0.044	30.8	--	σ^2_{add} (M1)	28400	40.1	--
σ^2_{prop} (M2)	0.02	32.2	--	σ^2_{add} (M2)	20700	36.4	--
σ^2_{prop} (M3)	0.021	24	--	σ^2_{add} (M3)	192	36.2	--

Note: CL_p , CL_{m1} - CL_{m3} , V_2 - V_6 represent apparent clearance ($CL_p/F/f_1$, $CL_{m1}/F/f_7$, $CL_{m2}/F/f_8$, $CL_{m3}/F/f_9$) and apparent volumes of distribution ($V_2/F/f_1$, $V_3/F/f_1$, $V_4/F/f_7$, $V_5/F/f_8$, $V_6/F/f_9$). CL and V are absolute terms of parent drug; interactions of residual errors are not included

Reference

- [1] Bertrand, Julie, et al. "Development of a complex parent-metabolite joint population pharmacokinetic model." *The AAPS journal* 13.3 (2011): 390-404.
- [2] Evans, Neil D., et al. "An identifiability analysis of a parent-metabolite pharmacokinetic model for ivabradine." *Journal of pharmacokinetics and pharmacodynamics* 28.1 (2001): 93-105.
- [3] Cheung, SY Amy, James WT Yates, and Leon Aarons. "Structural identifiability of parallel pharmacokinetic experiments as constrained systems." *IFAC Proceedings Volumes* 39.18 (2006): 99-104.

Fig. 3 Visual Predictive Check

