SUPPLEMENTARY MATERIAL

Supporting information is given in these appendices.

APPENDIX A – ETA PLOTS FOR LITERATURE MODELS

Distribution of posthoc η-values for morphine elimination clearance for the literature models of morphine pharmacokinetics.
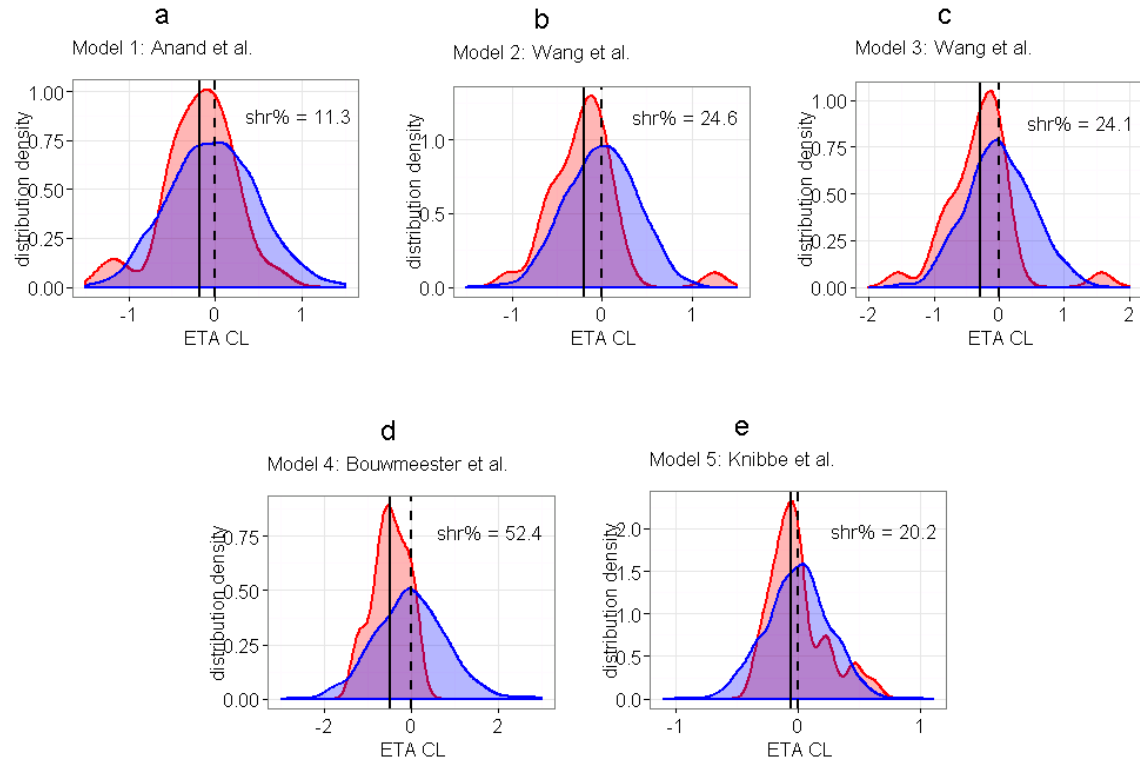

Figure A.1: Distribution densities of between-subject variability (BSV) in clearance ($\eta_{clearance}$) for the five literature models. Red: Individual Empirical Bayesian posthoc $\eta_{clearance}$ values of the new dataset. Blue: The theoretical distribution of η in the dataset based upon the assumption of $N(0,\omega^2)$, where ω^2 is the reported value for clearance BSV for the literature models. The horizontal solid line is the mean of the posthoc distribution, and the horizontal dashed line is 0, which is the mean of the theoretical distribution. η-shrinkage values are shown in plots. a) Model 1 Anand et al., b) Model 2 Wang et al., c) Model 3 Wang et al., d) Model 4 Bouwmeester et al., e) Model 5 Knibbe et al.

Distribution of posthoc η-values for metabolite elimination clearance for the literature models of morphine metabolite pharmacokinetics.
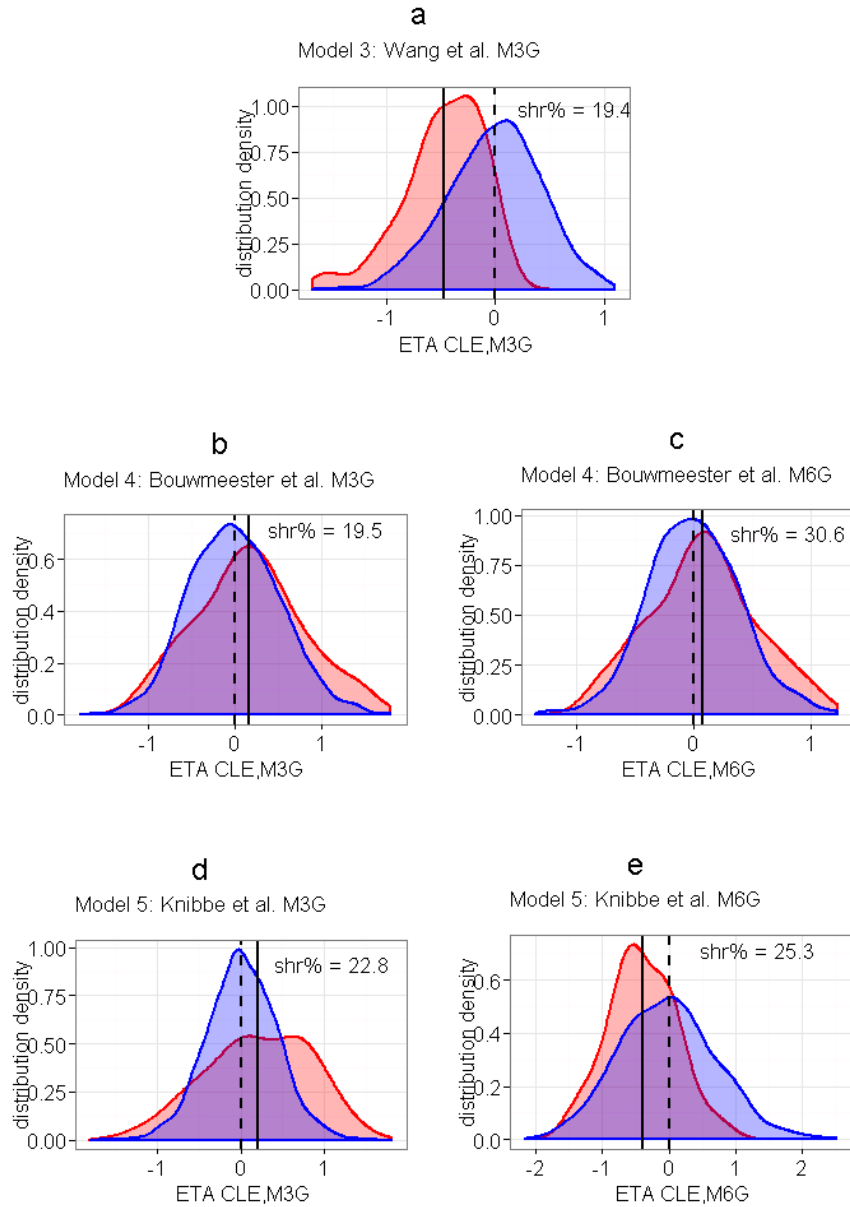

Figure A.2: Distribution densities of between-subject variability (BSV) in clearance (η_{CL}). Red: Individual Empirical Bayesian posthoc η_{CL} values of the new dataset. Blue: The theoretical distribution of η in the dataset based upon the assumption of $N(0,\omega^2)$, where ω^2 is the reported value for clearance BSV for the literature models. The horizontal solid line is the mean of the posthoc distribution, and the horizontal dashed line is 0, which is the mean of the theoretical distribution. η-shrinkage values are shown in plots.

APPENDIX B – VPC PLOTS FOR LITERATURE MODELS

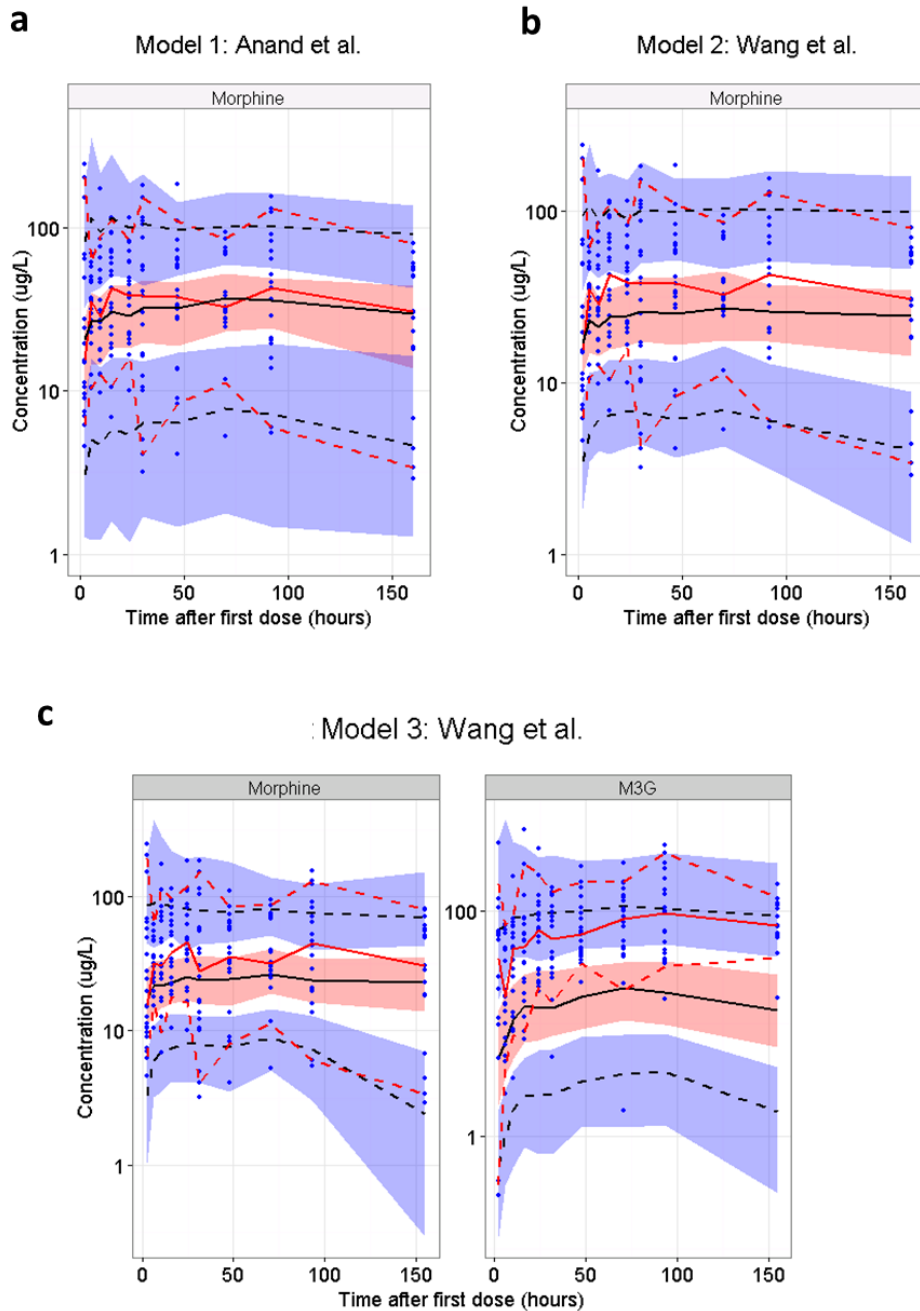VPCs for literature models based on 200 simulations with the current dataset as input.

Figure B.1: Visual Predictive Check of the literature models of morphine and metabolites PK. The observed data are represented by blue symbols, a red solid line (median), and red dashed lines (5th and 95th percentiles). The red shaded area represents the 95% empirical confidence interval around the predicted median (black solid line), and the blue shaded areas represents represents the 95% empirical confidence interval around the 5th and 95th percentiles (black dashed lines) of the predictions. Data were binned into 10 groups. a) VPC for Model 1, Anand et al., b) VPC for Model 2, Wang et al., c) VPCs for Model 3, Wang et al.,
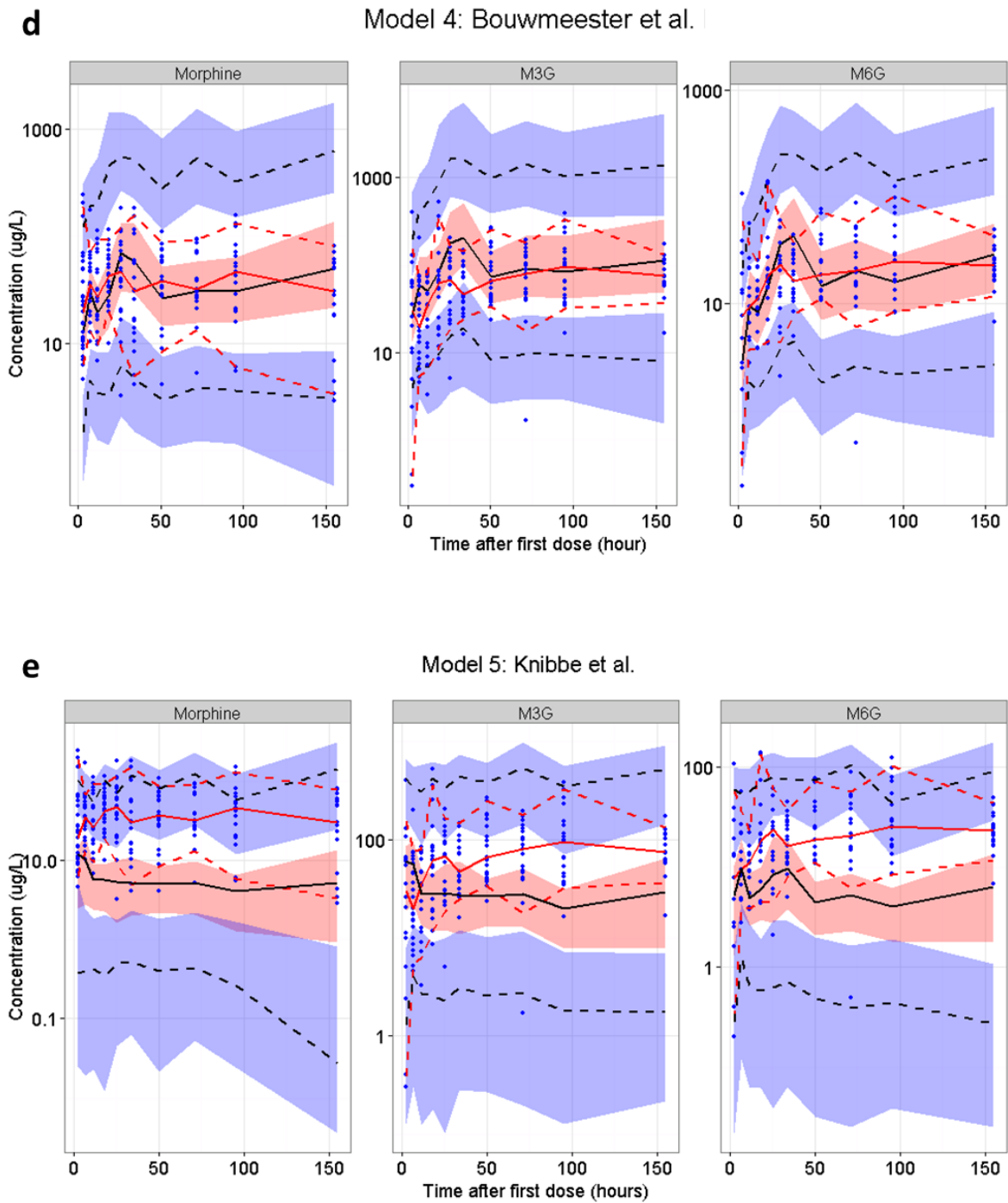
Figure B.2 continued: d) VPCs for Model 4, Bouwmeester et al., e) VPCs for Model 5, Knibbe et al.

APPENDIX C – ETA PLOT FOR PK META MODEL

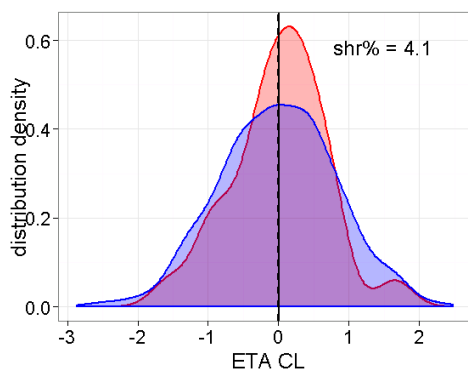**Figure C.1: Distribution densities of between-subject variability (BSV) in morphine clearance ($\eta_{clearance}$) for the meta-model. Red: Individual Empirical Bayesian posthoc $\eta_{clearance}$ values. Blue: The theoretical distribution of η based upon the assumption of N(0,ω^2), where ω^2 is the estimated value. The horizontal solid line is the mean of the posthoc distribution, which is overlying the mean of the theoretical distribution.**