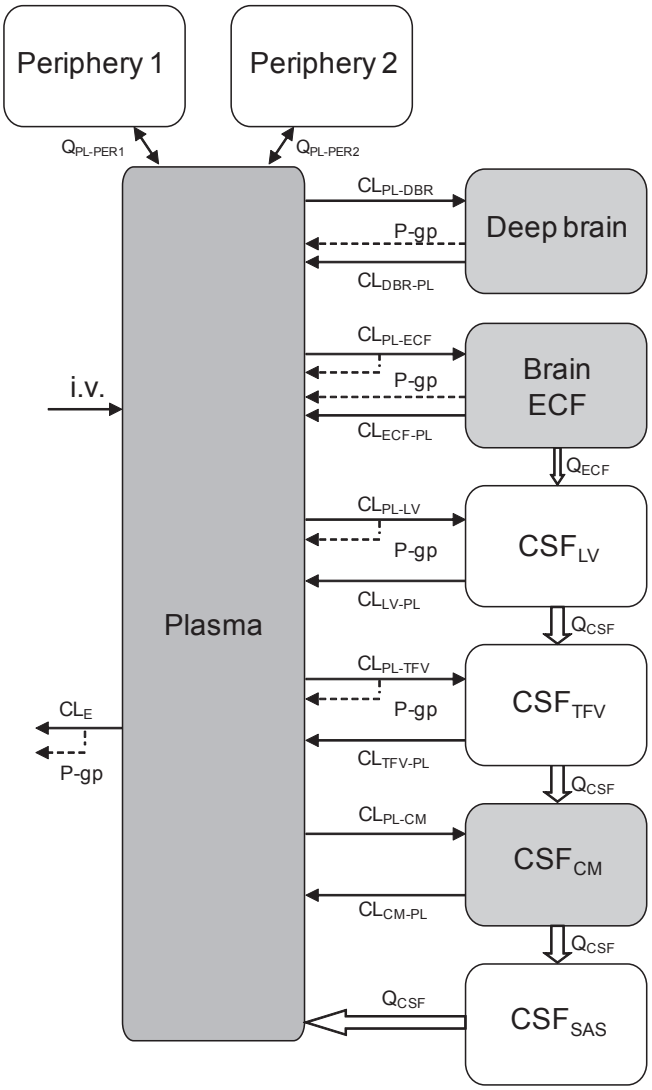


**Supplemental Figure 1. Diagram of the PBPK model used to describe quinidine brain distribution.** I.v. denotes the intravenous dose that enters the plasma compartment. $CL_E$ is the elimination clearance from plasma. $Q_{PL-PER1}$ and $Q_{PL-PER2}$ are the clearances from the plasma compartment to the two peripheral compartments. Drug distribution from plasma to the brain is described by bi-directional clearance between the plasma compartment and the deep brain compartment ($CL_{PL-DBR}$ and $CL_{DBR-PL}$), brain ECF compartment ($CL_{PL-ECF}$ and $CL_{ECF-PL}$), and different CSF compartments (lateral ventricle: $CL_{PL-LV}$ and $CL_{LV-PL}$; third and fourth ventricle: $CL_{PL-TFV}$ and $CL_{TFV-PL}$ and cisterna magna: $CL_{PL-CM}$ and $CL_{CM-PL}$). $Q_{ECF}$ denotes the flow rate of brain ECF to CSF and $Q_{CSF}$ is the flow rate of CSF between the different CSF compartments ($CSF_{SAS}$ refers to CSF in the subarachnoid space). Dashed arrows with the subscript P-gp represent P-glycoprotein mediated transport, which can either hinder drug influx or enhance drug efflux. The effect of P-gp on $CL_{PL-CM}$, $CL_{CM-PL}$, $CL_{TFV-PL}$, $CL_{LV-PL}$ and $CL_{PL-DBR}$ was not estimated, so these arrows were not included in the diagram. The grey physiological compartments indicate the data specifically obtained in the current study. All analyses were performed by using the subroutine ADVAN 6 and first-order conditional estimation with interaction.