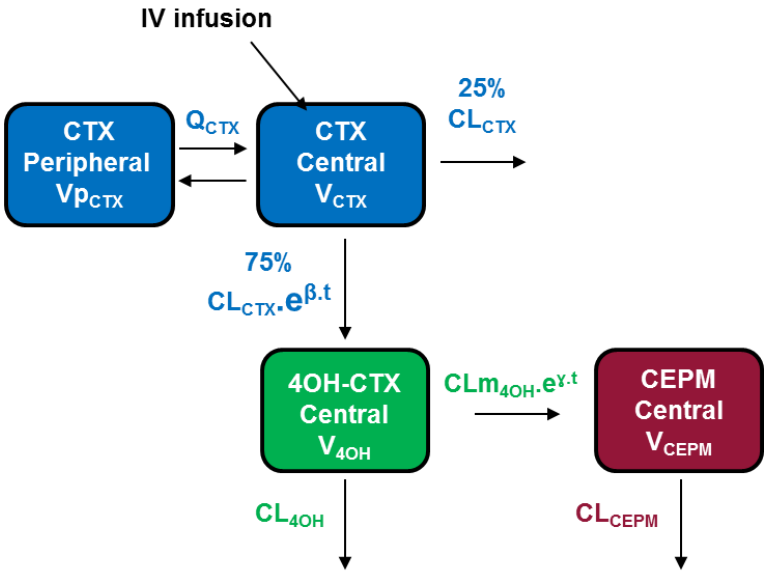
Figure S1. Pharmacokinetic model structure for cyclophosphamide, 4OH-CTX, and CEPM.



Cyclophosphamide data were fitted with a two-compartment model (blue structure), parameterized with central volume V_{CTX}, and clearance CL_{CTX}, peripheral volume Vp_{CTX}, and clearance Q_{CTX}. CL_{CTX} was divided in two processes. 75% of cyclophosphamide clearance accounted for the formation of 4OH-CTX (3-7), denoted as the cyclophosphamide metabolic clearance CLm_{CTX}. A time-dependent coefficient β was associated with CLm_{CTX}, such that CLm_{CTX} increased with time in an exponential manner. The remaining 25% of cyclophosphamide elimination accounted for other metabolic processes and urinary excretion.

4OH-CTX data were fitted with a one-compartment model (green structure), parameterized with apparent volume V_{4OH} and two clearances CLm_{4OH} and CL_{4OH}. CLm_{4OH} represents the metabolic clearance leading to the formation of CEPM. Similar to CLm_{CTX}, a time-dependent coefficient γ was associated with CLm_{4OH}, such that CLm_{4OH} increased with time in an exponential manner. CL_{4OH} accounted for other elimination processes.

CEPM data were fitted with a one-compartment model (red structure), parameterized with apparent volume V_{CEPM} and linear clearance CL_{CEPM}.