

Supplementary Table S1. Potential use of the PBPK/PD QSP approach in drug development.

Potential use of the presented PBPK/PD QSP approach in different phases of the drug development process. The conditions to apply the approach and the potential usage are additionally presented.

Phase	Conditions	Usage
Lead optimization/ Preclinical	- Target identification + Network modeling - In vitro binding data (e.g. IC50) - Physicochemistry, PPB, ADME screens	Efficacy
	- Adverse outcome pathway - 2 nd target, IC50 of 2 nd target - In vitro toxicity data	On-target toxicity Off-target toxicity
Preclinical	- Animal in vivo PK data - In vivo PD data	Optimize dosing
First in human	- In vitro binding data (e.g. IC50)	Efficacy
Clinical	- Human in vivo PK data - Clinical outcome data	Optimize dosing
	- CYP inducer/inhibitor - ADME/PK perpetrator drug	Clinical DDI study