

Effective Dosage Regimens Selection Based-on PK/PD Targets within Simcyp Framework

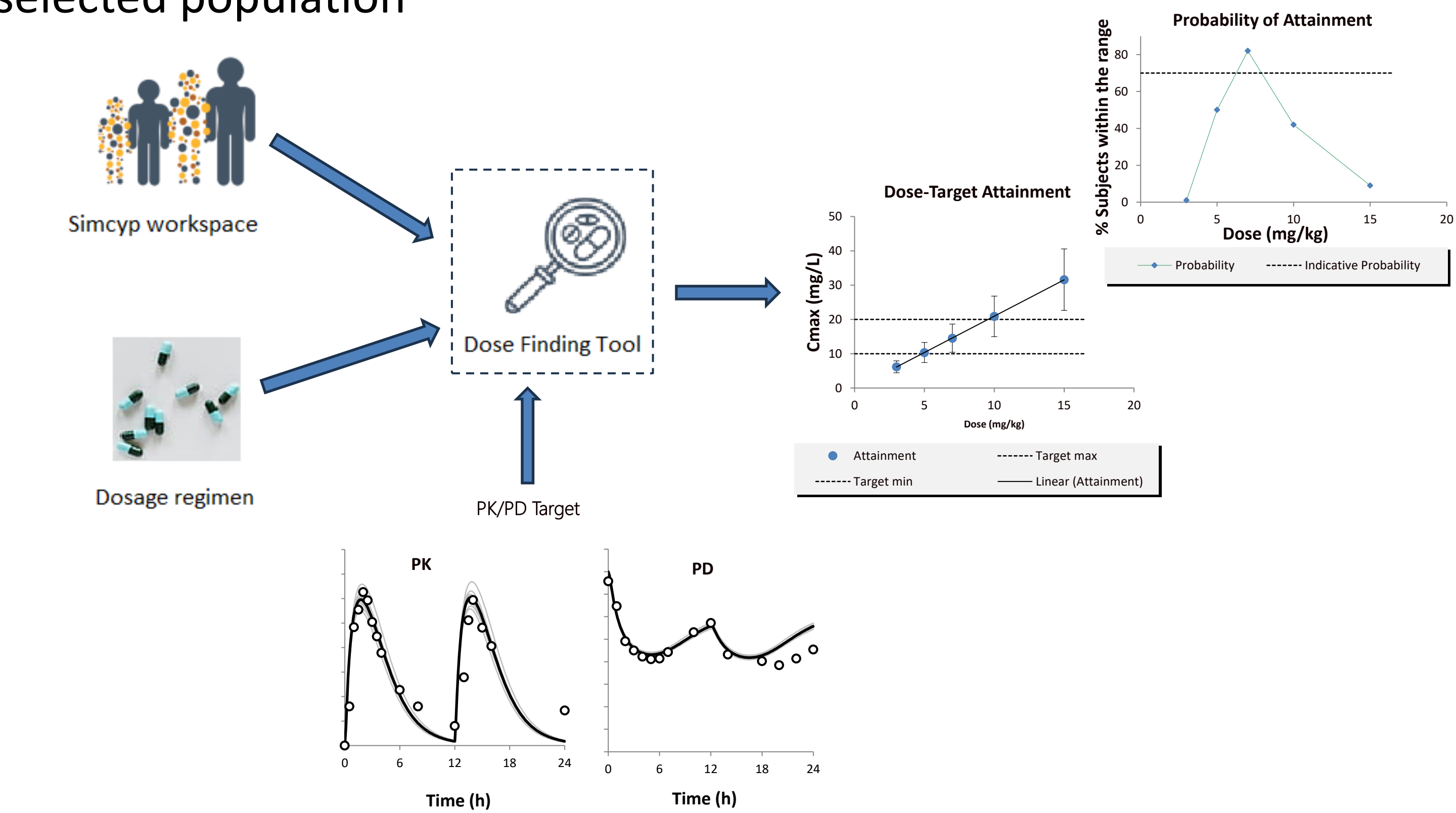
Vo Hong Thanh^{1*}, Eman El-Khateeb¹, Khaled Abduljalil¹ and Frederic Y. Bois¹

¹ Certara Predictive Technologies, Simcyp Division, Sheffield, UK

* Email: thanh.vo@certara.com

Objectives

Assess the performance of a dose-finding tool implemented within the Simcyp Simulator V24^[1] to support the selection of dosage regimens, considering PK/PD targets variability and physiological differences of the selected population



Results

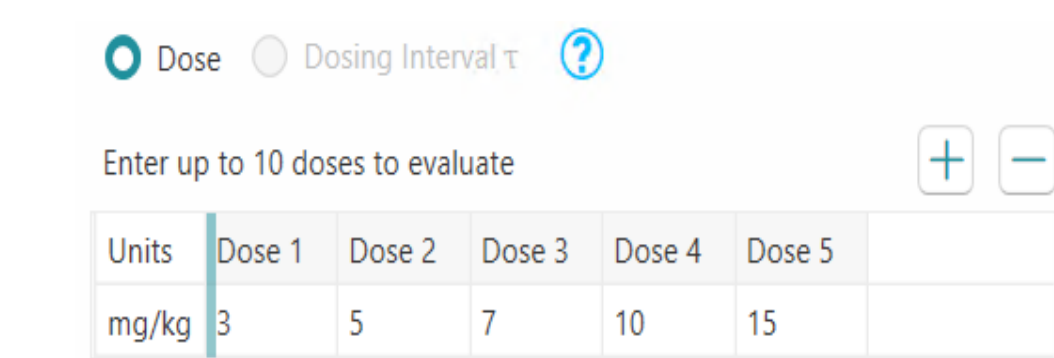
Case study 1: Theophylline

Research question: Which dose will give the best probability of attainment of C_{max} without causing toxicity for adults?

PBPK model

- First-order oral absorption
- Minimal PBPK
- Elimination: Enzyme kinetics & renal clearance

Dosages for evaluation



Target

- C_{max} within the therapeutic window of 10 – 20 mg/L

Case study 2: Ciprofloxacin

Research question: Which dosage regimen, *i.e.*, increasing dose amount or reducing dosing interval, will give the better probability of reducing log₁₀ CFU below 4?

PBPK model

- Oral absorption with ADAM
- Full PBPK model
- In-vivo clearance

PD effect

- Logistic growth model to model the formation and reduction of bacteria

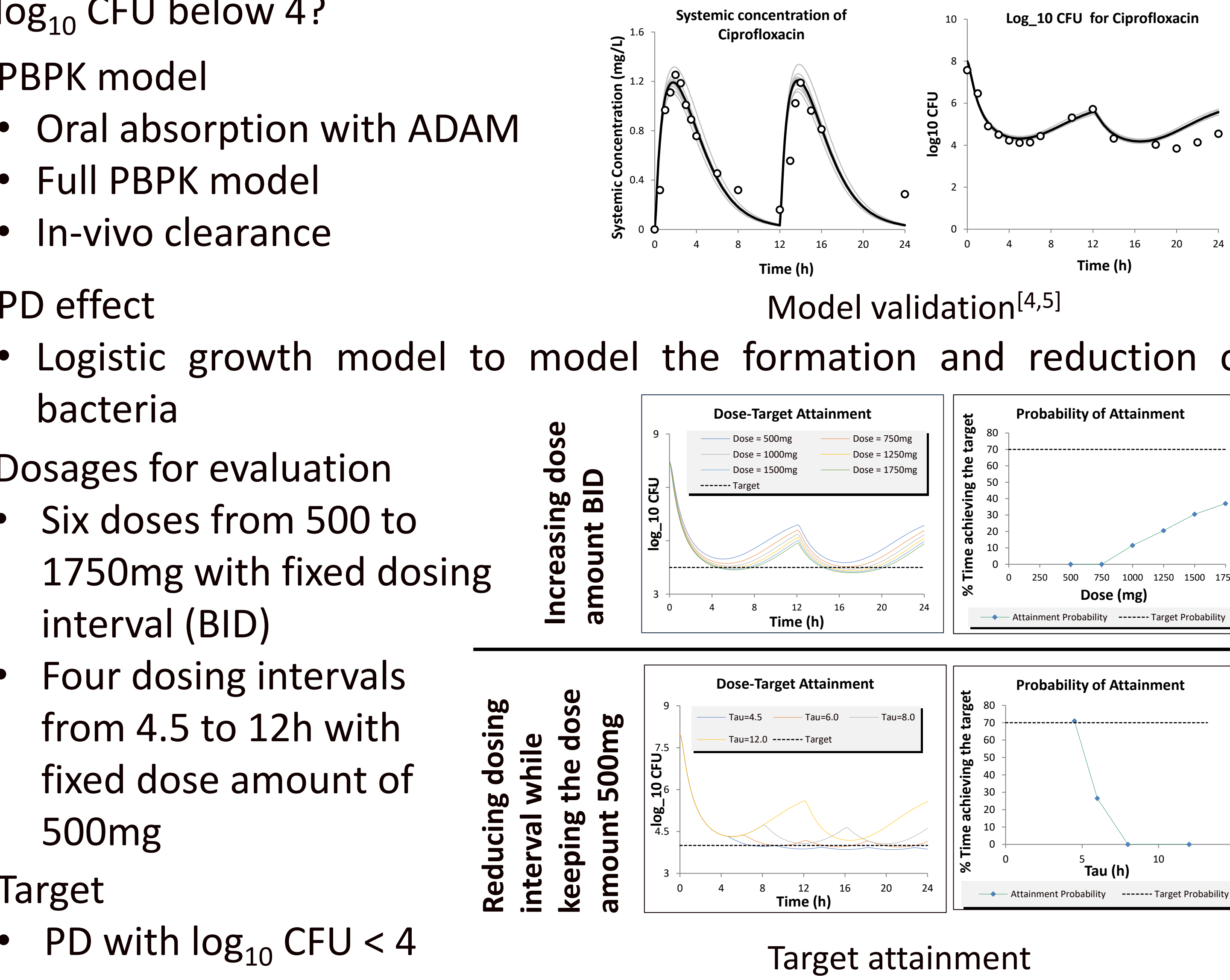
Dosages for evaluation

- Six doses from 500 to 1750mg with fixed dosing interval (BID)

- Four dosing intervals from 4.5 to 12h with fixed dose amount of 500mg

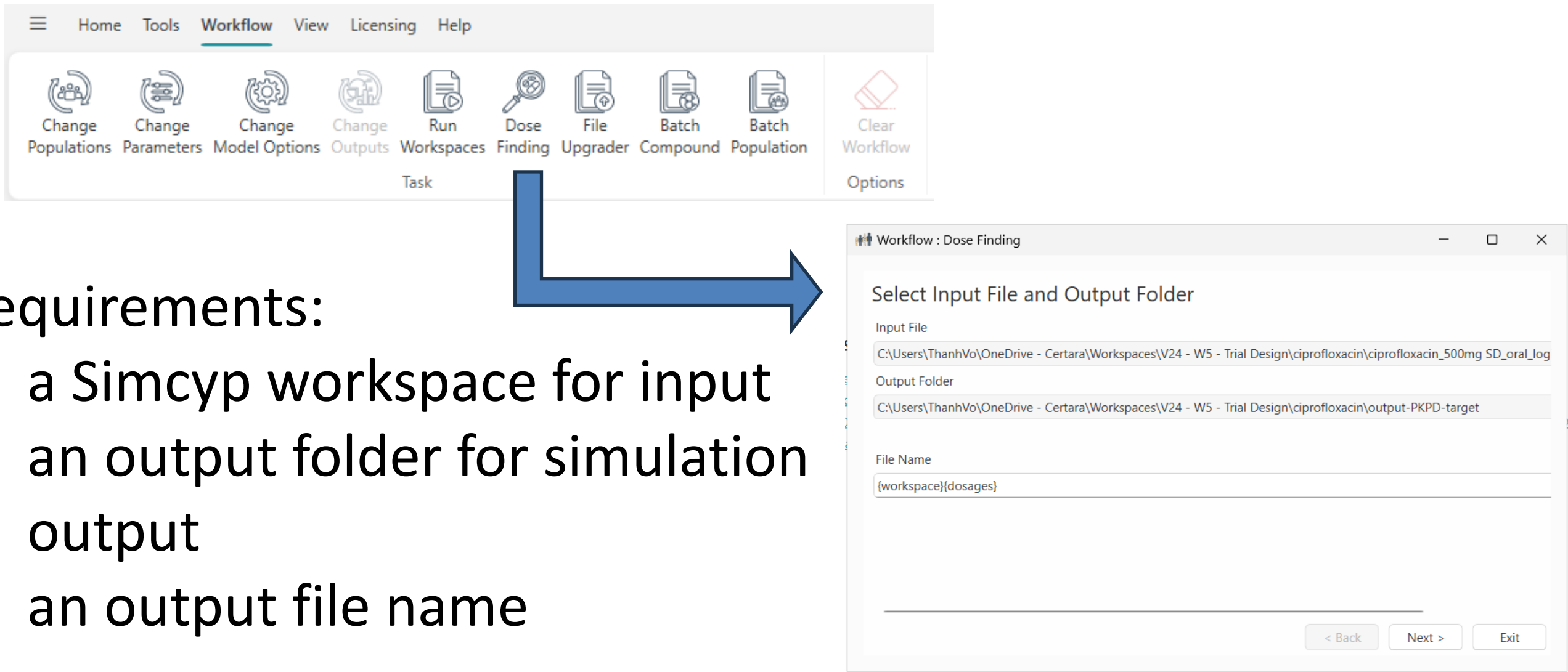
Target

- PD with log₁₀ CFU < 4



Workflow

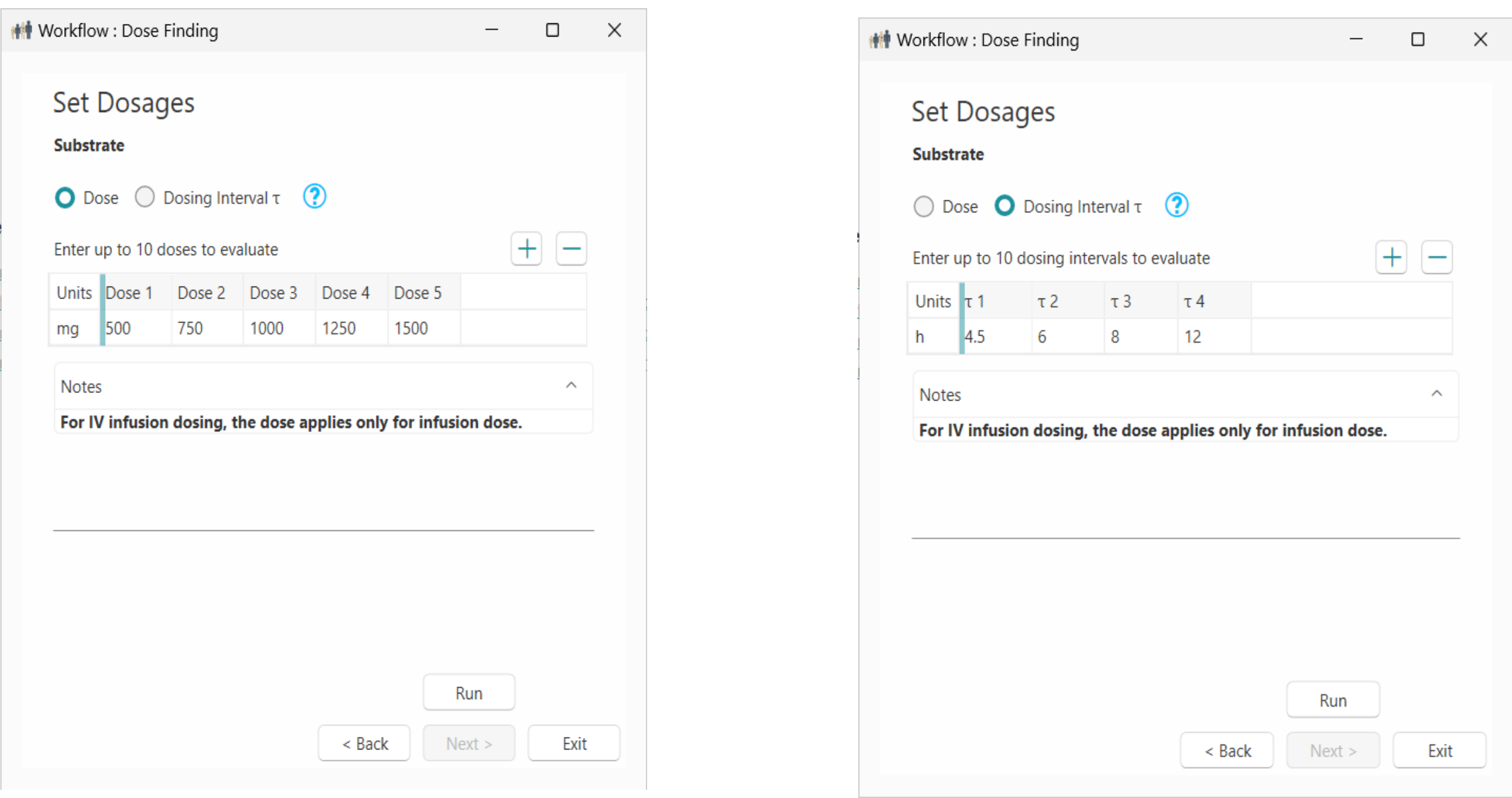
1. Select Input/Output



Requirements:

- a Simcyp workspace for input
- an output folder for simulation output
- an output file name

2. Set doses/dosing intervals of interest and run simulations



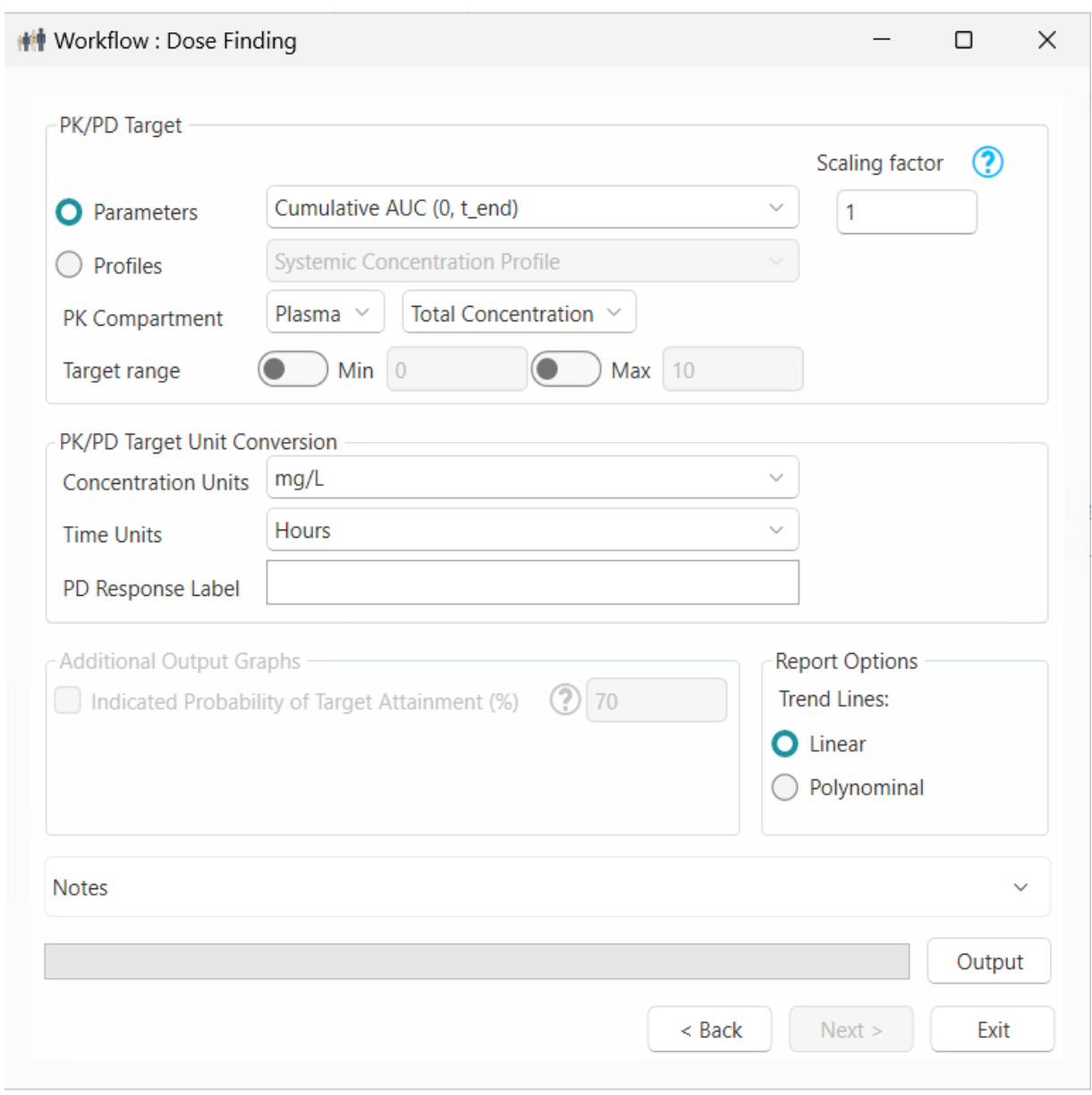
Dose amount

Dosing interval

3. Select PK/PD targets

PK/PD targets^[2] include:

- PK/PD parameters, e.g., C_{max}, C_{aver}, T_{max}, AUC, PD Rmin
- PK/PD indices: derivative parameters that quantitatively connect the PK/PD parameters and a clinical parameter, e.g., AUC/MIC
- PK/PD profiles: dynamics of exposure or exposure-response



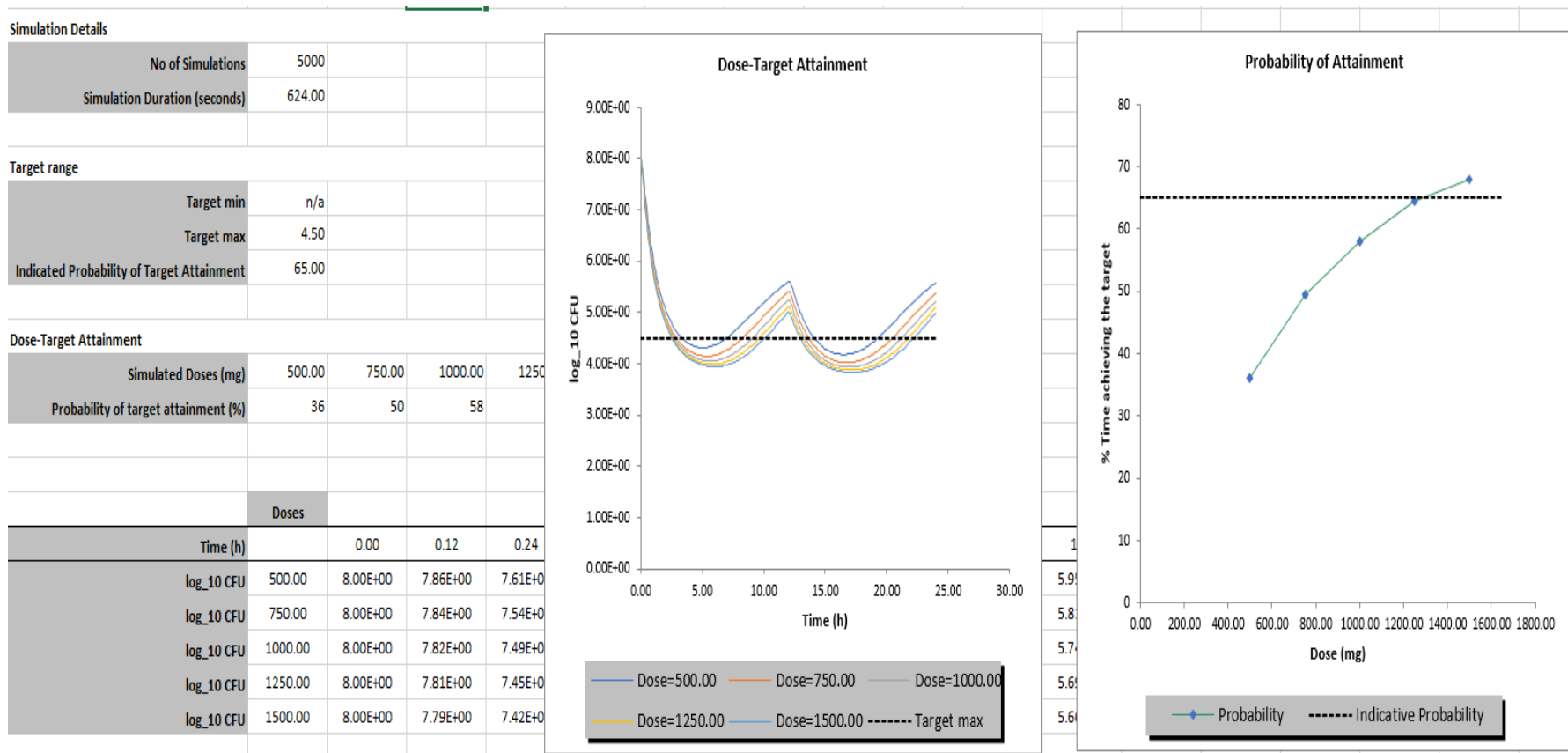
4. Evaluate probability of attainment and output

Evaluation of the probability of attainment for a target:

- For a PK/PD parameter or index: it is the percentage of subjects having the selected target in the target range
- For a PK/PD profile: it is the fraction of simulation time that the mean selected profile in the target range

Excel output

- Detailed information of simulations and calculations
- Plots for dose-target attainment and probability of attainment



References

- [1] Jamei *et al.* (2009). *Expert opinion on drug metabolism & toxicology* 5 (2):211–223.
- [2] Mouton *et al.* (2005). *Journal of Antimicrobial Chemotherapy*. 55:601–607.
- [3] Gillum *et al.* (1996). *Antimicrobial Agents and Chemotherapy* 40(8), pp. 1866–9.
- [4] Batty *et al.* (1995). *Br J Clin Pharmacol*, 39(3), pp. 305–11.
- [5] Meagher *et al.* (2004). *Antimicrobial Agents and Chemotherapy* 48(6), pp. 2061–2068.