Physiologically Based Pharmacokinetic (PBPK) Modelling: Testing a Model

Ramesh Jayaraman, DoseQuantics Consulting Pvt Ltd

The strength of a PK model is evaluated by its ability to predict the behaviour of the drug at a dose or regimen that is different from the dose for which the model was developed. When the model successfully predicts PK across dose levels or regimens its robustness and reliability increase. This is illustrated with a PBPK model developed for the HDAC targeted anti-cancer agent Pracinostat

Case Study: PBPK model built to predict oral PK of Pracinostat at 10 mg (FTIH dose) in healthy humans and compared with cancer patients. Model predictions in HH were in agreement with observed data in patients.

Pracinostat data

Parameter	Value
Mol Weight (g/mol)	358.48
log P	2.39
Compound Type	Diprotic Base
pKa 1	7.45
pKa 2	4.13
B/P	1.0
f_u	0.082
f_u(Gut)	1.0
Enzyme	CYP1A2
CL_{int} (µL/min/pmol isoform)	0.894
$f_{u\ mic}$	0.34 (Turner)
Enzyme	CYP3A4
CL_{int} (µL/min/pmol isoform)	0.180
$f_{u\ mic}$	0.34

System

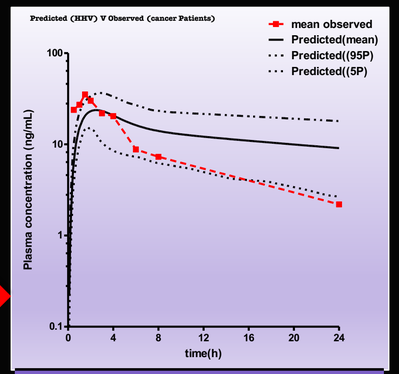
Healthy Human volunteer population (10 subjects /trial; total subjects =100).

PBPK Model

- Simcyp (9.5)
- Assumptions

1) major plasma binding protein : 1 acid glycoprotein (SB939 – weak base)
2) fraction unbound in enterocytes (f_g) =1
3) metabolism main clearance mechanism
- Absorption - ADAM model
- Formulation – IR
- Physiologically based distribution model (method 2, basic pKa of SB939 =7.0).
- Elimination- recombinant enzyme (CYP3A4, 1A2)

Single oral dose 10 mg (FTIH dose) administered to population



Parameter	Predicted Mean (5-95% Percentile) N=100 healthy subjects)	Observed (Mean, Range) N=3 patients
AUC (ng.h/ml)	316 (141-523)	229 (171-275)
T_{max}(h)	2.6 (1.6-3.5)	1.8 (0.5-4)
C_{max} (ng/ml)	25 (17-37)	39 (27-58)
CL/F(l/h)	37 (19-71)	39 (27-58)

PBPK model used to predict PK in HH at 60 mg (recommended dose, RD)

- **Single oral dose 60 mg**
- **10 subjects/trial**
- **Total 100 subjects**

Predictions compared with PK in cancer patients (n=6)

Predicted V observed PK of Pracinostat in humans : 60 mg

Parameter	Predicted (Mean, 5-95% Percentile) N=100 healthy subjects)	Observed (Mean, Range) N=6 patients
AUC (ng.h/ml)	1899 (848-3166)	1152 (711-1945)
T_{max}(h)	2.7 (1.5-3.4)	1.8 (1.0-3.0)
C_{max} (ng/ml)	148 (98-220)	178 (73-320)
CL/F(l/h)	37 (19-71)	59 (31-84)

- Predicted HH population PK parameter ranges at RD were in agreement with observed mean data from cancer patients
- Fold difference between mean predicted & observed values was < 2-fold for AUC, t_{max}, C_{max}, CL/F

- **PBPK model developed for healthy humans adequately described PK of Pracinostat in cancer patients at FTIH dose (10 mg) and RD (60 mg).**
- **Model should be refined using systems data from cancer patients.**

Reference: : Jayaraman et al. 2011. Drug Metab Dispos. 39(12):2219-3.