PopPk analysis of an intravenous dose ranging study evaluating and antineoplastic agent in adult patients

Background

- The drug is an agent used to treat solid tumours
  - Both parent and metabolite are active
- A single dose is given every 3 weeks
- Data
  - Pharmacokinetic data were available from 41 patients providing 301 parent and 309 metabolite concentrations

Aim

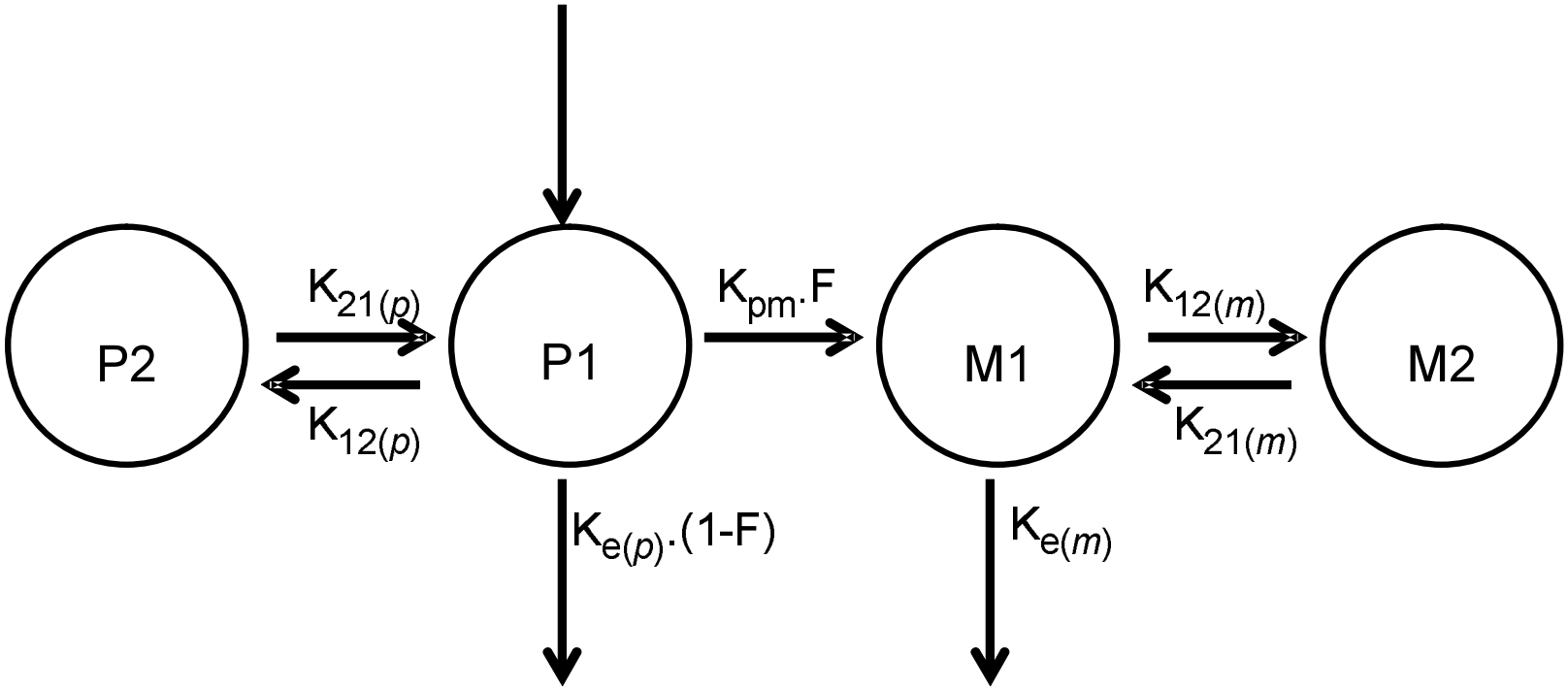
- To explore the time course of effect and concentration of parent and metabolite

Modelling (parent & metabolite separately)

- All model building was performed using NONMEM
- Parent
  - Model building was unsuccessful using FO (most runs terminated unsuccessfully)
  - FOCEI was used to provide the best base model: 2-cpt; CL, V1, V2, Q, ALAG1, with BLOCK(3) on CL, V1, V2)
- Metabolite
  - No runs converged with FO
  - FOCEI was used to provide the best base model: 2 cpt; CL, V2, V3, Ka, Q, with BLOCK(3) CL, V2, V3 + Ka

Modelling
(Parent + metabolite simultaneously)

- Best base model provided by 2 linked 2 compartment models using FOCEI
- Final model = minimization successful, $COV failed
- Parameters included:
  - CL(p), CL(pm), V1(p), V2(p), Q(p), CL(m), V1(m), V2(m), Q(m), ALAG1
  - BSV BLOCK(CL(p), CL(pm), V1(p), V2(p))
  - BSV BLOCK(CL(m), V1(m), V2(m))
  - Proportional + additive for both parent and metabolite
- Run-time = 45 hours (P4 2.8 GHz, 1Mb RAM)


P2
P1
M1
M2
$K_{21(p)}$
$K_{12(p)}$
$K_{pm}.F$
$K_{12(m)}$
$K_{21(m)}$
$K_{e(p)}.(1\text{-}F)$
$K_{e(m)}$

Modelling
Covariates

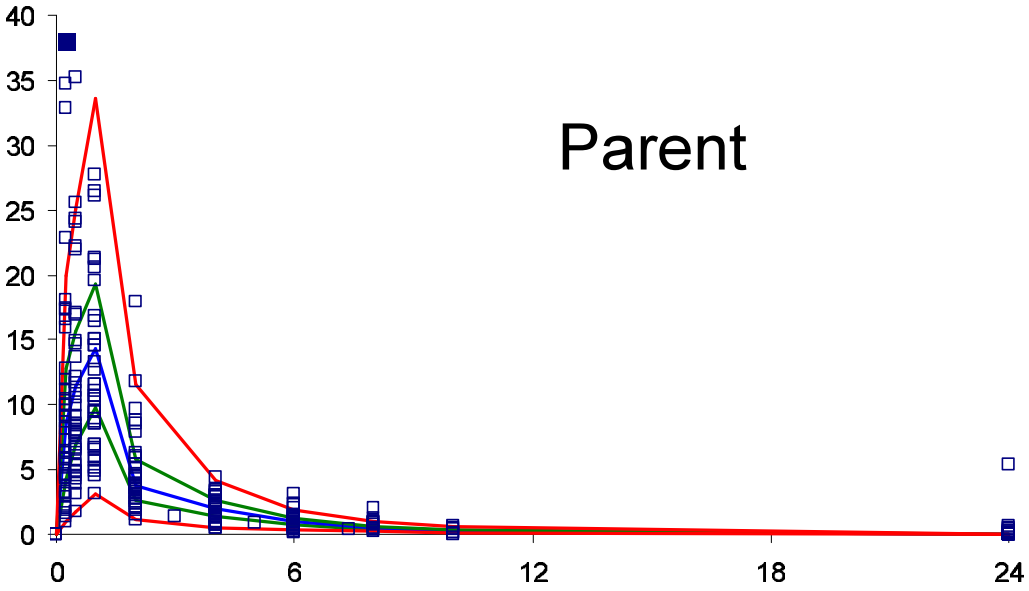
- The full model consisted of weight on CL(p) and V1(m)
  - Produced a 11.6 unit drop in objective function &
  - (-)42% and (-)73% reduction in the unexplained BSV on CL(p) and V1(m), respectively
- Run-time = 47 hours

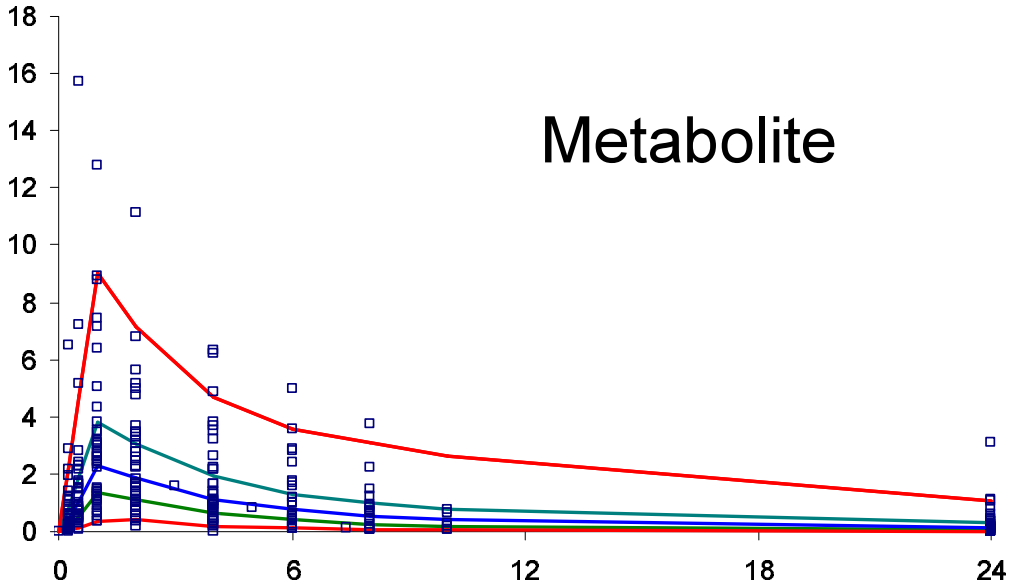
How should this model be evaluated?

- Total number of models evaluated = 139
- Run-time for all simultaneous popPK models ≈ 48 hours
- $COV was not successful on any of the combined parent-metabolite models
- All GOF plots looked good for base and full models

What was done…

- Assessment of model and parameter values – via visual inspection of a predictive check
- Confidence interval estimation – via limited likelihood profile


Parent
40
35
30
25
20
15
10
5
0
0
6
12
18
24


Metabolite
18
16
14
12
10
8
6
4
2
0
0
6
12
18
24

Limited likelihood profiling

- Sensitivity analysis – compute sensitivity index
  - ΔOBJF was computed for all parameter values when each parameter value was perturbed in turn by $\pm$ 20% (each run takes 3-5 minutes)
  - MAXEVAL=0, all other parameters fixed at MLE values
- Limited likelihood profiling
  - For only high values of the sensitivity index (> 5 unit change for 20% difference = x parameters)
  - Compute the ΔOBJF by fixing the parameter of interest (fixed effect at $\pm$ 25%, random effect at $\pm$ 50%) and refitting remaining parameters (run-time $\approx$ 24-36 hours)
  - Does the ΔOBJF change by more than 3.84 units?
    - YES = 95% CI is less than range tested (all parameters tested)
    - NO = 95% CI is greater than range tested