

Data quality impacts on modeling results



Vincent Buchheit, MSc¹ and Nicolas Frey, PharmD¹

(1) F. Hoffmann–La Roche Ltd., Pharma Research and Early Development (pRED), Clinical Pharmacology (CP), 4070 Basel, Switzerland

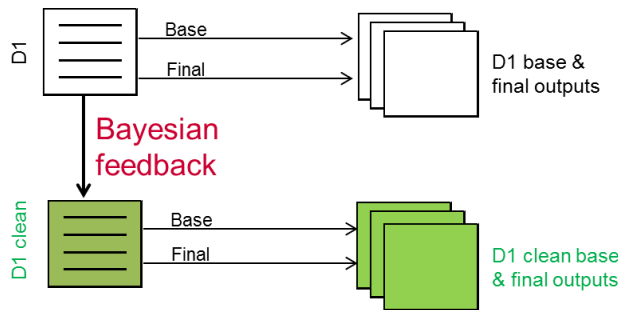
1 – Background

The pharmacokinetic (PK) data from one phase III study and three phases II studies, from an oncology compound, have been pool together in order to study the sources and correlates of variability in drug concentrations among individuals.

The most important data issues, such as covariate outliers, rate of infusion too high have been fixed.

From this pooled dataset, (D1) we generated a second dataset (D1 Clean) where additional PK data issues, mainly identified using a previous developed PK model with a Bayesian feedback analysis, haven been corrected.

The final model, developed from the clean dataset (D1 Clean), has then been run with the non-fully clean dataset (D1) and modeling outputs were compared to investigate the data quality impacts.



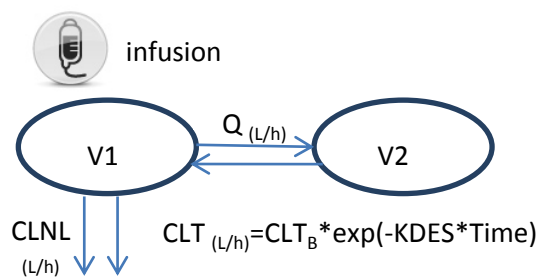
2 – Data and Model

D1 consist of 594 patients, with a total of 11930 PK samples.

D1 clean consist of 590 patients, with a total of 11784 PK samples. The differences between the 2 datasets are summarized below.

Excluded	Concentrations too high	31	0.26%
	Concentration too low	45	0.38%
	Incoherent concentration	70	0.59%
Change	Inversion Ctrough-Cmax	2*27	0.46%
	Dose amount change	7	0.06%
TOTAL		207	1.74%

The PK model is a two-compartment PK model with a time-dependent clearance.



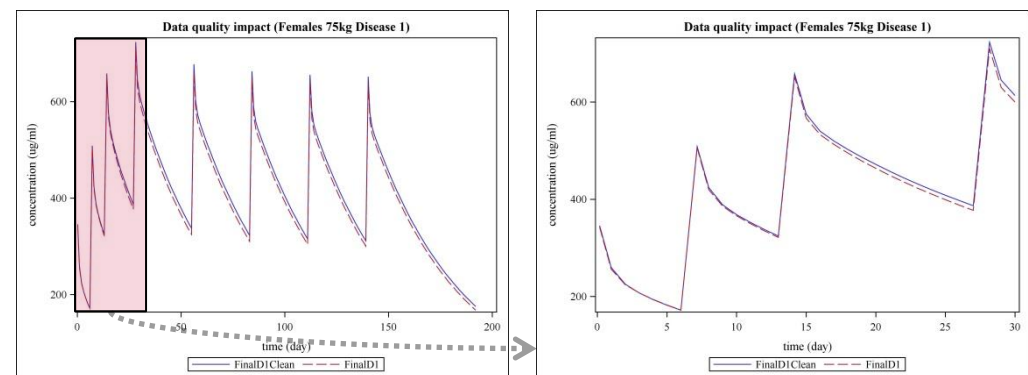
3 – Population results

The **main difference is observed on DIS₂₃₄** (disease 2, 3 and 4 compare to disease 1) to **KDES** (decrease coefficient of time-dependent clearance).

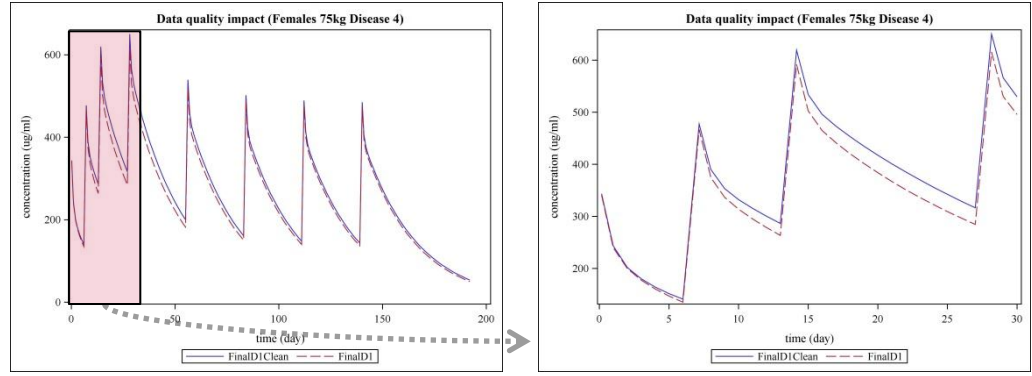
# PK samples	11930		11784			
# Patients	594		590			
running time	362 minutes		414 minutes			
	Value	RSE	Value	RSE	%Parameter change	%RSE change
1*KDES	0.523272	12.20%	0.450385	12.40%	16.18%	1.61%
2*CLNL	2.644143	9.42%	2.752053	8.78%	3.92%	7.29%
3*CLL	0.992376	4.02%	0.972726	3.52%	2.02%	14.20%
4*V1	31.89174	1.52%	31.57441	1.48%	1.01%	2.70%
5*V2	11.13783	5.39%	11.21382	5.14%	0.68%	4.86%
6*Q	15.83697	10.20%	14.9147	12.20%	6.18%	16.39%
7 WT to CLT CLNF	0.546	20.30%	0.596	16.50%	8.39%	23.03%
8 WT to V1	0.413	12.40%	0.398	12%	3.77%	2.48%
9 SEX to CLT	1.593607	11.10%	1.511345	10.40%	5.44%	6.73%
10 SEX to CLL	1.206834	4.38%	1.225072	4%	1.49%	14.36%
11 SEX to V1	1.179393	2.06%	1.181754	1.97%	0.20%	4.57%
12 DIS ₂₃₄ to KDES	1.541876	13.70%	1.967965	13.60%	21.65%	0.74%
13 DIS ₂₃ to CLL CLT	0.760332	4.27%	0.81955	3.77%	7.23%	13.26%
14 DIS ₄ to CLL CLT	1.69215	17.20%	1.722885	16.90%	1.78%	1.78%
15 BSIZ to KDES	2.095936	13.70%	2.514314	13%	16.64%	3.79%
	FinalD1		FinalD1Clean			

More than 20% change in parameter estimates

To compare the two sets of POP PK parameters, population predictions of the PK profiles following the Phase III design were simulated for a women weighting 75 kg and having the disease 1 or 4. Predictions are different as illustrated with the graphics below. The main differences are observed during the first 30 days on the disease 4.

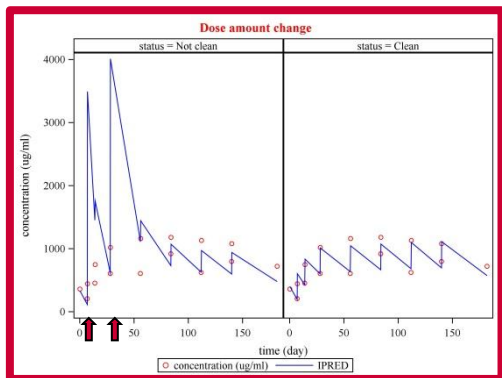
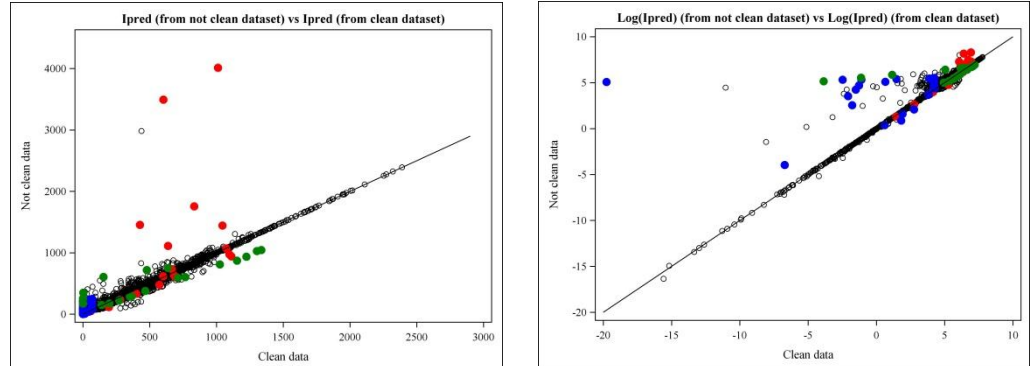


3 – Population results (continued)



4 – Individual results

As illustrated with the graphics below, comparing the IPRED from the two NONMEM runs, the predictions for some of the patients are different.

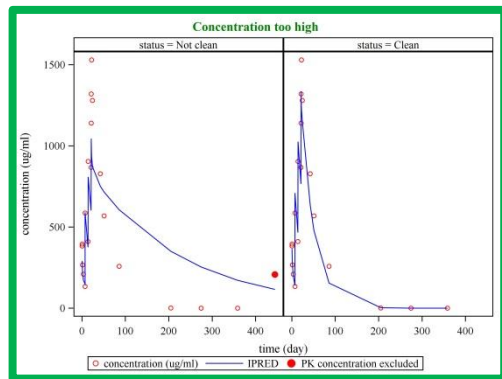


Modification:
Dose amount change from 10'000 to 1'000. The dose amount administered to patient could not be higher than 1'000.

Major Impacts:
CLNL from 0.47 to 0.36
KDES from 0.04 to 0.17

Modification:
PK concentration excluded, dv=608, time=334
PK sample incoherent

Major Impacts:
CLNL from 3.36 to 2.13
CLT from 0.02 to 0.09
KDES from 0.038 to 0.002



Modification:
PK concentration excluded, dv=207, time=444
PK sample too high

Major Impacts:
CLNL from 0.15 to 0.49
CLT from 0.02 to 0.08
KDES from 0.08 to 0.26

7 – Discussion

- The **quality of the modeling input to clinical team** depends on the **quality of the data¹**, therefore it is important to maximise the quality of the modeling input dataset².
- Data quality overall was good** for phase II/III studies. Only **4 patients have been removed** and about **2% of PK concentrations changed** between D1 and D1Clean
- As expected, we observed very **minor impacts on population PK parameters**
- However the **data quality** has mainly influenced **predictions at the patient level** which can **impact the exposure-efficacy and exposure-safety** analyses if not properly addressed.

8 – References

- Aarons, L. et al., Role of modelling and simulation in Phase I drug development.
- Buchheit, V. et al., Efficient quality review for modeling input dataset, PAGE 20 (2011) Abstr 2041 [www.page-meeting.org/?abstract=2041]