Investigating the identifiability of one-stage IVIVC population models for extended-release dosage forms

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Background

- In-vitro/in-vivo correlation (IVIVC) models can aid in the development of modified-release dosage forms such as extended-release (ER) products [1].
- One-stage IVIVC population models allow to account for non-linear disposition kinetics as well as for inter-individual variability (IIV) in drug dissolution and absorption [2].
- These models are often developed based on Phase I cross-over pharmacokinetic (PK) studies in healthy subjects, where the sample size is relatively low (10-20 subjects).

Objectives

- To investigate the identifiability of one-stage IVIVC population models developed from small Phase I PK studies.

Methods

- A published model for methylphenidate hydrochloride (MPH) ER capsules was used as a case-study [1], in which the in-vitro dissolution was described by a double-Weibull function (Figure 3). Two linear time scaling models were evaluated: no time scaling (Slope=1) and with time scaling (Slope=0.5).
- The Phase I study was designed as a cross-over study where each healthy subject received 3 ER formulations (slow, medium and fast release), with the individual disposition parameters assumed to be known.
- The analysis was performed sequentially:
  1. Optimal design was used to derive adequate PK sampling schedules, assuming sample sizes of 12 and 24 subjects
  2. Stochastic simulations and re-estimations (SSE) were performed to assess bias and root-mean-square error (RMSE) of the IVIVC model parameters (N=100)
  3. FDA internal predictability criteria for Level A IVIVC [3] were evaluated.
- Two competing models were investigated (Figure 3):
  - 1-IIV model: one exponential IIV term on the overall absorption rate
  - 5-IIV model: 5 IIV terms on each of the Weibull parameters (exponential for all parameters but FF, which used a logit transformation).
- Design optimization was done using the R package popED [4], PsN [5] was used to carry out the SSE step.

Results

Table 1. *RSEs predicted by optimal design for the model with 1 IIV term (1-IIV model).*

Time scaling	Sample size	Slope	F_{rel}	IIV K_{abs}
No	12	0.9	6.7	26.9
No	24	0.6	4.7	19.0
Yes	12	0.6	6.8	27.4
Yes	24	0.4	4.8	19.4

Table 2. *RSEs predicted by optimal design for the model with 5 IIV terms (5-IIV model).*

Time scaling	Sample size	Slope	F_{rel}	IIV				
				SS1	TD1	SS2	TD2	FF
No	12	4.3	3.5	45.3	24.1	38.3	21.7	32.1
No	24	3.1	2.5	32.1	17.1	27.1	15.4	22.7
Yes	12	4.2	3.7	23.7	21.5	25.3	21.0	29.5
Yes	24	3.0	2.6	16.7	15.2	17.9	14.9	20.9

- Optimal design suggested that the expected precision in structural IVIVC parameters was adequate for all scenarios and models (Table 1 and 2).
- Table 1 shows that the predicted relative standard error (RSE) for the IIV parameter was < 30% for the 1-IIV model for all scenarios, while in the 5-IIV Model some IIV parameters were associated with an RSE > 30% (Table 2).

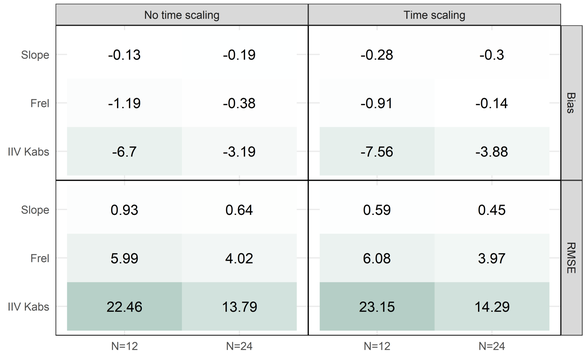

Figure 1. *Bias and RMSE obtained with SSE for the 1-IIV model.*

Figure 2. *Bias and RMSE obtained with SSE for the 5-IIV model.*

- SSE confirmed the adequate precision and indicated satisfactory accuracy in structural IVIVC parameters for both models (Figure 1 and 2).
- Accuracy and precision of IIV parameters were lower in the 5-IIV model vs. the 1-IIV model.
- Table 3 illustrates that the percentage of replicates satisfying the internal predictability criteria for a Level A IVIVC was lower with the 5-IIV model than with the 1-IIV model when time scaling was included.
- Therefore only the model presenting a single IIV term can be estimated accurately when assessing the IVIVC.

Table 3. *Percentage of study replicates satisfying the FDA internal predictability criteria for level A IVIVC.*

Sample size	No time scaling		Time scaling	
	1 IIV	5 IIV	1 IIV	5 IIV
12	96	96	83	58
24	100	100	95	77

Conclusions

- One-stage IVIVC population models with 1 IIV term appeared to be identifiable from Phase 1 PK studies, while 5 IIV terms were often not supported.
- In light of the small size of clinical studies employed in the development of IVIVC models, IIV parameters should be employed with parsimony as overparameterization could result in a loss of power to detect a Level A IVIVC.
- A prospective investigation of the model identifiability given the study design can help mitigating the risk of IVIVC failure.

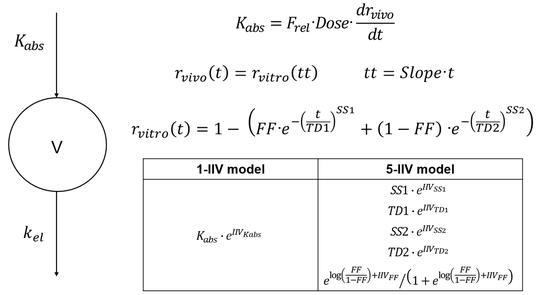

Figure 3. *Overview of the one-stage MPH model used in the analysis. F_{rel}: bioavailability of the ER formulations relative to the formulation used to derive individual disposition parameters (V and K_{el}).*

References

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