Performance validation for models translated between development software and commercial healthcare platforms

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Background

- Model-informed precision dosing (MIPD) can aid clinicians with dose selection for some drugs[1]
- Translation of population PK/PD models from development software to MIPD software can introduce performance discrepancies due to differences in ordinary differential equation (ODE) solvers, rounding precision, and coding errors
- It is crucial to quantify model equivalence between platforms to ensure accurate model implementation for clinical use

Aims

- To compare the performance of a published population PK model[2], in current use for paediatric vincristine dose optimisation, between the development software (NONMEM) and an under-development commercial MIPD platform
- To assess the clinical implications of any differences in model outputs between platforms

Methods

- Individual parameter estimates (clearance (CL) and area under the curve (AUC)) were compared between **NONMEM** v7.5 (original model control stream) and the **DosoLogic** platform (Vesynta Ltd; under-development and based on the open-source R nlmixr2 package[3])
- Data used for comparison (n=142) included patients from previous therapeutic drug monitoring requests (n=111; various cancers) and a phase III clinical trial (n=31; acute lymphoblastic leukaemia/lymphoma; ISRCTN64515327)
- Patients were issued vincristine as a bolus or short IV infusion with sampling up to 24h
- Assessment by graphical interpretation, significance (Wilcoxon Signed-Rank test), mean absolute error (MAE), root mean square error (RMSE), bias and % difference in estimates

Dataset Characteristics	Mean ± SD (range)
Dose (mg)	0.86 ± 0.64 (0.1—2.0)
Age (years)	4.8 ± 5.2 (0.04—17.3)
Weight (kg)	21.1 ± 20.7 (2.9—102)

Results

PK parameter	NONMEM (mean ± SD (range))	DosoLogic (mean ± SD (range))	p-value	MAE	RMSE	Bias
CL (L/h)	11.6 ± 9.7 (1.2—55.7)	11.8 ± 9.7 (1.2—55.7)	0.350	0.288	0.972	0.242
AUC (µg·h/L)	82 ± 39 (23—274)	80 ± 38 (21—273)	0.084	2.604	9.203	-2.503

Table 1. Summary and statistical analysis of CL and AUC estimates between platforms

- Overall, strong agreement of predicted clearance and exposure (AUC) between platforms for this model
  - CL and AUC not significantly different between NONMEM and DosoLogic platforms (p>0.05)
  - Slight over-estimation of CL and under-estimation of AUC on average
- DosoLogic AUC within ±1% of NONMEM estimates for 126/142 (88%) of patients
- Differences in estimates attributable to ETA (inter-individual variability model components) handling differences between platforms
  - PRED equal for all patients while IPRED differed for some

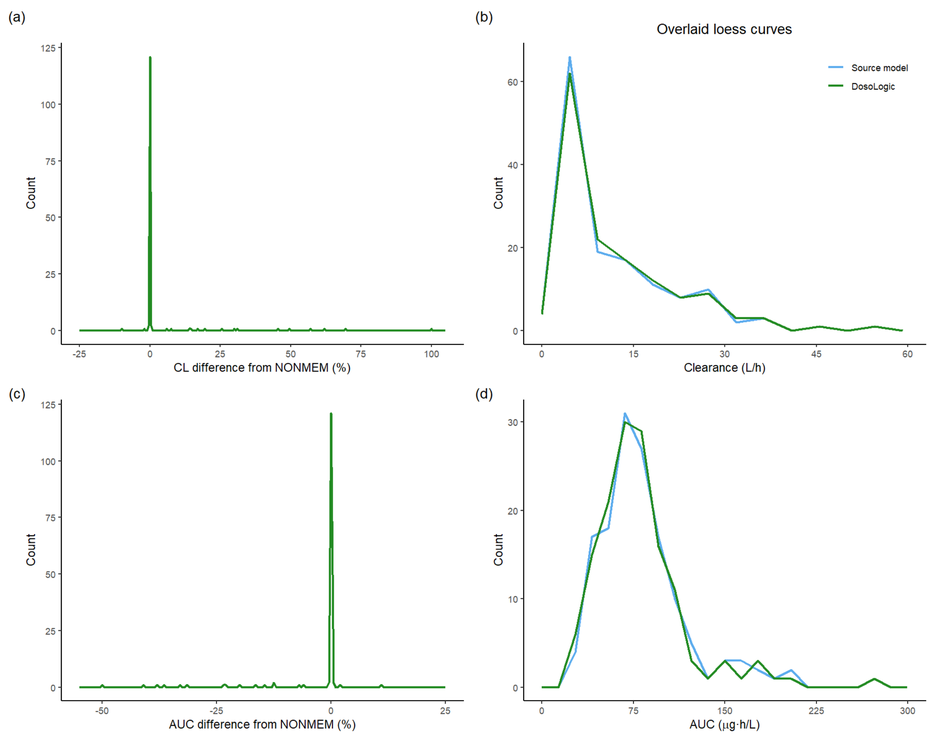

Figure 1. Distribution of CL and AUC estimates between platforms. Optimum bin widths for loess curves determined by Freedman-Diaconis rule[4]

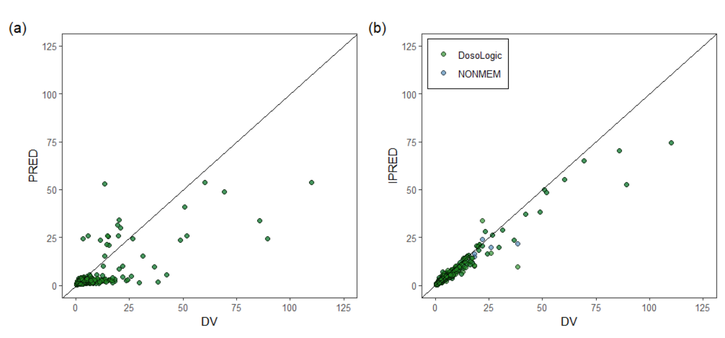

Figure 3. Overlaid GOF plots: Vincristine concentration (DV; ng/mL) vs population- (PRED) and individual-predicted (IPRED) concentrations from each platform

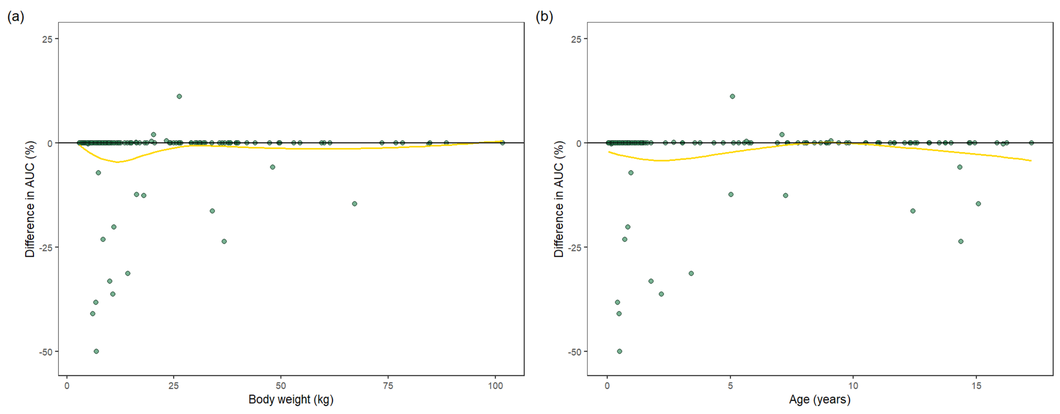

Figure 2. Percent difference in AUC estimates (DosoLogic vs NONMEM) plotted against (a) body weight; (b) age, with loess curves in yellow

Conclusions

- An in-use population PK model was successfully transcribed from NONMEM to the R nlmixr2-based DosoLogic platform, demonstrating its potential for use in MIPD
- Differences in estimates for some (12%) patients a likely a result of ODE solver differences, and may produce clinically relevant differences in PK prediction between platforms; this warrants further investigation

References

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