Title: Comparison of the Performance of Likelihood-Based Methods Implemented in NONMEM and MC-PEM/S-ADAPT to Account for Pharmacokinetic (PK) Data Below the Lower Limit of Quantification (LLOQ)

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Objective: The objective of this simulation study was to assess the ability of likelihood-based methods, implemented in NONMEM VI and MC-PEM/S-ADAPT 1.54 to account for data below the LLOQ, when applied to an intravenous (IV) drug with biexponential disposition in two separate assay sensitivity scenarios.

Methods: A total of 50 replicate datasets were created each containing 500 subjects. Concentrations were simulated after IV administration of 200 mg infused over 30 minutes q12hr for 5 days, at the times shown in Figure 1, using a linear 2-compartment (CMT) model [clearance (CL)=20 L/hr; central volume (Vc)=100 L; distribution clearance (CLd)=25 L/hr; peripheral volume (Vp)=250 L]. Inter-subject variability (ω^2) of CL, Vc, Q and Vp were assumed to be log-normal and were 30%, 45%, 50%, and 50% CV, respectively. Residual error (σ^2) was assumed to be proportional (10% CV).

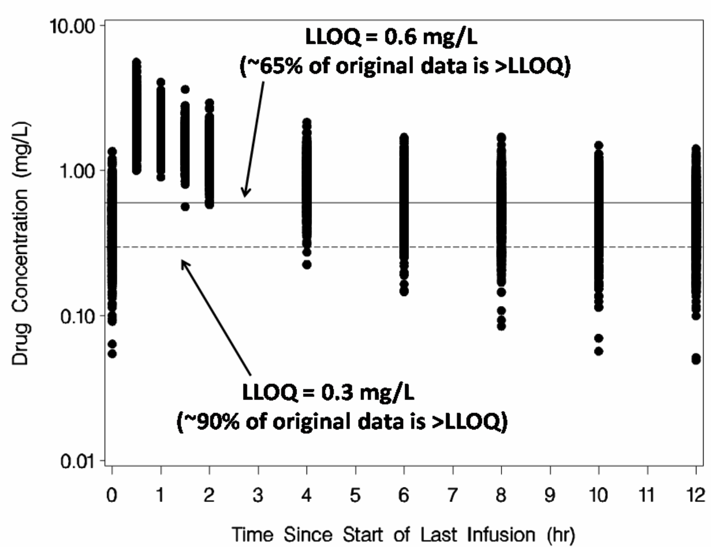

Fig 1. Steady-state conc.-time data for a single replicate, with reference lines for LLOQ two levels (0.3 and 0.6 mg/L)

Each dataset was analyzed in NONMEM VI, with the same 2-CMT model, using the following methods assuming a LLOQ of either 0.3 mg/L or 0.6 mg/L: (1) omitting data <LLOQ (M1 approach), (2) omitting data <LLOQ and using likelihood estimation (M2 approach using Y_LO functionality); (3) including all data and using likelihood estimation for data < LLOQ (M3 approach using F_FLAG functionality). The simulated data was similarly analyzed using MC-PEM/S-ADAPT 1.54 using either the M1 or M3 approach [in M3, data <LLOQ was retained (OMIT=L and DV=LLOQ)].

Perfomance of each method was evaluated by comparing the prediction error percents (PE%) of the population mean parameter estimates across the 50 replicate datasets (Table 1), calculated as the difference between the predicted and true value divided by the true value. Run times and minimization status based upon a single attempt were also assessed. The median PE% for the Bayesian parameters was calculated overall (N=500) and for subjects in the upper (N=125) and lower (N=125) quartiles of the true parameter distributions for each dataset; the median of these median PE% values across the 50 replicate datasets was reported (Table 2).

Results: Use of the M1 approach generally performed reasonably well (with the exception for ω^2 for CLd and Vp) at a 0.3 mg/L LLOQ for both software. However, at a 0.6 mg/L LLOQ, the M1 approach overpredicted CLd and Vp, and greatly underpredicted ω^2 for CL, CLd and Vp. The consequences of this bias were a moderate underprediction of the higher individual CL values, as well as severe overprediction of the lower individual CLd and Vp values, which together would provide a falsely high elimination half-life. Use of the M2 approach in NONMEM VI did little to prevent this bias, and resulted in prolonged run times and greater model instability. The M3 approach generally provided more accurate population mean parameter estimates than did the M1 approach, even at a LLOQ of 0.6 mg/L (with the exception of ω^2 for Vp), and helped reduce the magnitude of the bias observed in the lower and upper quartiles of the true parameter distributions. The perfomance of the M3 approach across software was generally comparable, but only about half of the NONMEM runs minimized successfully. This instability may entice the analyst to deviate from the correct model (i.e., reducing the number of parameters), to alter the default settings (i.e., significant digits in $EST) estimates to achieve successful minimization, which may adversely impact the accuracy of the parameter estimates.

Table 1. Summary of median PE% for the population parameter estimates, median run time, and % minimized

Parameter	LLOQ = 0.3 mg/L					LLOQ = 0.6 mg/L				
	S-M1[a]	N-M1	N-M2	S-M3	N-M3	S-M1	N-M1	N-M2	S-M3	N-M3
CL	-1.36%	0.74%	-1.35%	0.89%	-0.11%	-13.0%	-6.80%	-15.2%	1.05%	0.62%
Vc	0.39%	1.60%	0.16%	-0.20%	-0.06%	4.86%	4.97%	3.95%	-0.37%	0.21%
CLd	5.71%	5.32%	3.25%	-0.42%	-0.39%	55.2%	40.5%	42.9%	-0.06%	-1.82%
Vp	15.2%	4.67%	12.0%	-6.85%	2.11%	62.9%	31.7%	66.5%	-11.6%	0.62%
ω^2 of CL	-17.1%	-10.7%	-9.06%	-3.97%	-1.33%	-45.7%	-28.7%	-30.4%	-2.33%	1.89%
ω^2 of Vc	-1.34%	-1.23%	-2.96%	-1.74%	-1.72%	6.77%	4.94%	7.16%	-1.81%	-3.70%
ω^2 of CLd	-13.1%	-11.6%	-19.0%	3.86%	-8.80%	-26.6%	-19.4%	-25.2%	3.74%	-12.2%
ω^2 of Vp	-19.5%	-27.2%	10.2%	-33.7%	-3.80%	-34.6%	-32.0%	108%	-27.7%	-36.6%
σ^2	-0.11%	-0.09%	0.00%	0.03%	0.50%	-0.07%	-0.34%	-0.15%	-0.01%	0.00%
Minimized		98%	26%		38%		100%	18%		56%
Run Time	31 min	2 min	9 min	34 min	9 min	26 min	2 min	6 min	43 min	8 min

[a] S = MC-PEM/S-ADAPT V 1.54 (50 iterations); N = NONMEM VI (FOCE with interaction)

Table 2. Summary of median PE% for the lower and upper quartiles of the individual parameter distributions

Parameter	LLOQ = 0.3 mg/L					LLOQ = 0.6 mg/L				
	S-M1	N-M1	N-M2	S-M3	N-M3	S-M1	N-M1	N-M2	S-M3	N-M3
$CL_{0-25\%}$	3.03%	2.33%	2.17%	3.13%	2.37%	-0.97%	0.53%	-0.55%	2.96%	2.30%
$CL_{75-100\%}$	-3.36%	-1.91%	-1.61%	0.04%	0.01%	-23.8%	-15.6%	-22.7%	-2.86%	-2.46%
$Vc_{0-25\%}$	3.23%	2.84%	3.01%	2.70%	2.88%	5.98%	4.29%	5.01%	2.74%	3.32%
$Vc_{75-100\%}$	-2.59%	-3.11%	-3.05%	-3.02%	-3.21%	1.51%	0.59%	1.57%	-3.20%	-2.86%
$CLd_{0-25\%}$	29.4%	29.1%	28.4%	17.0%	18.5%	149%	112%	122%	42.6%	45.8%
$CLd_{75-100\%}$	-12.7%	-11.0%	-13.0%	-11.3%	-13.4%	6.48%	-1.60%	0.58%	-19.3%	-21.5%
$Vp_{0-25\%}$	107%	77.6%	86.0%	55.5%	67.1%	202%	131%	217%	58.1%	75.2%
$Vp_{75-100\%}$	-30.9%	-38.3%	-34.7%	-44.2%	-39.2%	-3.39%	-24.8%	5.56%	-48.7%	-43.1%

Conclusions: This study demonstrates that implementing the M3 approach in NONMEM VI and MC-PEM/S-ADAPT 1.54 to account for data below the LLOQ can improve parameter estimation in population PK analyses when informative sampling strategies are utilized. However, use of the M3 approach in NONMEM VI may be limited due to both longer run times and stability concerns depending on the complexity of the model. MC-PEM/S-ADAPT is not susceptible to many of these same model instabilities and represents a very useful tool to implement this likelihood-based approach for censored data in both PK and PK/PD analyses.