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Incorporation of extrapolated concentration data below the limit of quantification in population PK analyses

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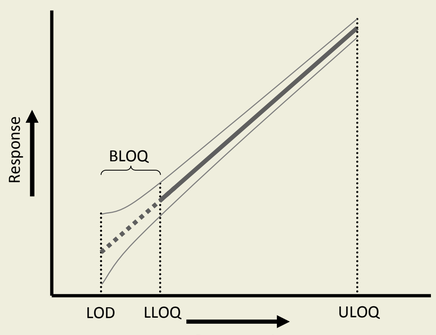
Introduction

Problem: BLOQ data often encountered in PopPK modeling. Several methods have been proposed to deal with such data:

- discarding BLOQ data ("DISCARD")
- replace with LLOQ/2 ("LLOQ/2")
- likelihood-based methods.[1-3] ("M3")

Hypothesis: using actual concentration data, **extrapolated** below the LLOQ ("BLOQ" method) has superior performance over established methods, and decreases bias and imprecision of parameter estimates.



M&S Study:

1. Construct credible residual error model
2. Simulate datasets for several PK models
3. Re-estimate using BLOQ methods
4. Evaluate performance

1. Residual error (RE model)

Method:

- RE model was constructed and fitted to results from QA reports from our own laboratory / analyses published in literature. *(solid line)*
- Another model was defined which described a 'worst-case' analytical method that just complied with FDA standards. *(dashed line)*
- RE model combined with a proportional error model (20%) to account for model misspecification:

$$y = (\hat{y} \cdot (1 + a \cdot \varepsilon_1) + b \cdot \varepsilon_2) \cdot (1 + 0.2 \cdot \varepsilon_3)$$

Results:

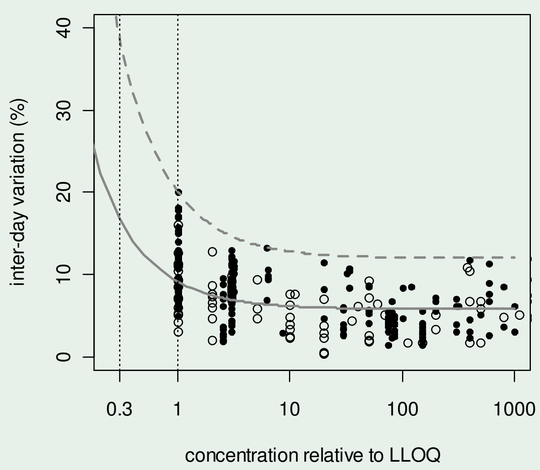


Figure 1. Inter-day variation (CV%) plotted versus concentration relative to LLOQ. Black dots represent data from validations performed in our own labs, open circles represent data from published validation reports.

2. Simulations

Automation, simulation and plotting was performed using R and Perl. Re-estimation analyses were performed in NONMEM VI/VII

Simulations:

- *n* = 25 patients, *n* = 100 simulations
- Various levels of BLQ censoring (10%, 20% and 40%)
- PK models: oral, iv; 1,2,3-compartmental

3. Model re-estimations

Re-estimate using all four methods, use same PK model used as in simulations.

Additional evaluations:

- 'worst-case' residual error model
- NONMEM7 instead of NONMEM6
- SAEM estimation method
- the use of another approach '$M3_{LOD}$' in which the M3 method was only used for points <LOD.

Key findings

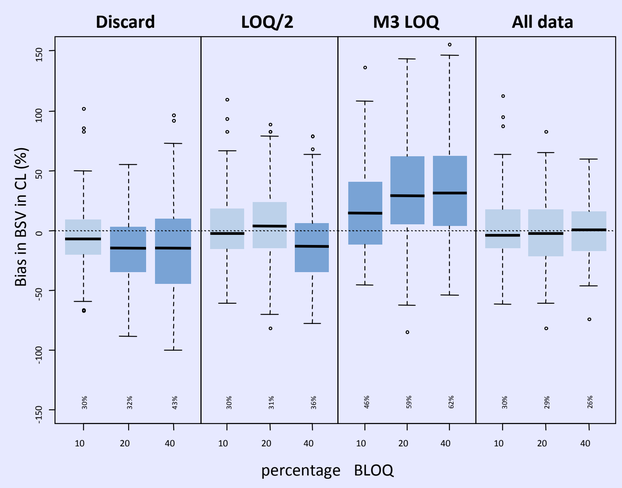
- When fraction BLOQ is low (<10%) all methods showed similar performance
- incorporation of BLQ concentration data showed superior performance in terms of bias and precision over established BLOQ methods.

The use of BLQ data as a continuous data source is a valid approach in PopPK modelling.

References

1. Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn. 2001 Okt;28(5):481-504.
2. Ahn J, Karlsson M, Dunne A, Ludden T. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. Journal of Pharmacokinetics and Pharmacodynamics. 2008 Aug 7;
3. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. AAPS J. 2009 Jun;11(2):371-380.

4. Evaluation of performance



*Figures 2a-e. Performance of LLOQ methods for **oral one-comp. linear model**, RMSE is shown in the bottom of each plot. Significance of systematic bias ($p < 0.05$) is shown by colouring of the box: dark-blue indicates bias.*

Results:

- Generally, `Discard' method showed largest bias.
- At 10% BLOQ, all methods showed similar performance
- For all models, `all data' methods showed lowest RMSE, especially apparent at higher % BLOQ.
- Only with 'worst-case' res. error model, and at 40% BLOQ, did M3 show lower RMSE than 'All data'
- `M3' method showed low % of successful minimizations / covariance steps (table 1)
- `M3' method seemed very sensitive to initial estimates
- '$M3_{LOD}$' did not perform better than `all data' method

Table 1. NONMEM minization performance for various methods

	LOQ	*Minimization successful* (%)*				*Covariance step successful (%)*			
PK model	**censoring**	**Discard**	**LOQ/2**	**M3**	**All data**	**Discard**	**LOQ/2**	**M3**	**All data**
I.v., 1 cmp.	10 %	100	98	53	100	100	98	34	100
	20 %	100	99	43	100	100	99	15	100
	40 %	96	100	25	100	94	100	7	100
I.v., 2 cmp.	10 %	68	87	13	86	28	40	4	38
	20 %	65	84	18	88	24	50	2	48
	40 %	64	79	26	82	11	50	5	53
Oral, 1 cmp	10 %	93	96	46	93	91	94	20	91
	20 %	96	97	34	98	95	93	14	97
	40 %	99	98	21	100	98	98	1	98
Oral, 1 cmp NM7	10 %	100	100	62	100	100	100	32	100
	20 %	100	96	54	100	100	95	16	100
	40 %	99	97	54	98	98	93	18	98