

Title: Impact of Censoring Data Below an Arbitrary Quantification Limit on Structural Model Misspecification

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Objectives: The current simulation study investigated the impact of the percentage of data censored as BQL on the PK structural model decision; evaluated the effect of different coefficient of variation (CV) values to define the LLOQ; and tested the maximum conditional likelihood estimation method in NONMEM VI (YLO).

Methods: Using a one-compartment intravenous model, data were simulated with 10 to 50% BQL censoring, while maintaining a 20% CV at LLOQ. In another set of experiments, the LLOQ was chosen to attain CVs of 10, 20, 50 and 100%. Parameters were estimated with both one- and two-compartment models using NONMEM VI (GloboMax LLC, Hanover, MD). A type I error was defined as a significantly lower objective function value for the two-compartment model compared to the one-compartment model using the standard likelihood ratio test at $\alpha=0.05$ and $\alpha=0.01$.

Results: The type I error rate substantially increased to as high as 96% as the median of percent censored data increased at both the 5% and 1% alpha levels. Restricting the CV to 10% caused a higher type I error rate compared to the 20% CV, while the error rate was reduced to the nominal value as the CV increased to 100%. The YLO option prevented the type I error rate from being elevated.

Conclusions: This simulation study has shown that the practice of assigning a LLOQ during analytical methods development, although well intentioned, can lead to incorrect decisions regarding the structure of the pharmacokinetic model. The standard operating procedures in analytical laboratories should be adjusted to provide a quantitative value for all samples assayed in the drug development setting where sophisticated modeling may occur. However, the current level of precision may need to be maintained when laboratory results are to be used for direct patient care in a clinical setting. Finally, the YLO option should be considered when more than 10% of data are censored as BQL.

References:

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