PhUSE US Connect 2018

Paper DH05

Methods for Handling Concentration Values Below the Limit of Quantification in PK Studies

James R. Johnson, Summit Analytical, LLC., Cary, NC USA

ABSTRACT

Bioanalytical assays for drug concentrations are validated measures within a pre-specified range, with the lower end of that range defined as the "lower limit of quantification" (LLOQ). Concentrations that fall below the LLOQ are reported in the SDTM.PC domain as "Below the Limit of Quantification" (BLOQ). All concentration data, even information recorded as BLOQ, contains useful information for pharmacokinetic analysis, and concentration values reported as BLOQ are associated with a concentration value can be reported and potentially used in analysis: BLOQ measurements are just associated with more analytical bias than measurements outside a limit of detection (LOD). The methods for handling BLOQ data in pharmacokinetic analyses introduce some form of analytical bias, and the choice of which method to use for handling BLOQ information is predicated in part upon the type of pharmacokinetic analysis being completed. In this paper we present a pragmatic example of common methods for management and handling concentration data reported as BLOQ along with a pragmatic simple set of rules for managing BLOQ values in PK analyses. We also propose a solution for using all concentration data, including actual measurements identified as BLOQ in PK analysis, and identify further work to be completed to understand the impact of BLOQ values.

INTRODUCTION

Clinical pharmacokinetic (PK) studies are performed and submitted as part of an application package to examine the absorption, distribution, metabolism, and excretion (ADME) of a drug under investigation (investigational drug and approved drug) in human volunteers. Information from PK studies is used to provide context for profiles on the total drug exposure of the therapeutic agent, interaction with other drug products, interaction with disease states, interaction of patient characteristics (e.g. gender, age groups, genotypes of drug-metabolizing enzymes, and others), and relationship with pharmacodynamic endpoints. Information obtained from PK studies will also be included on the product label approved by regulatory agencies.

Design of PK studies for a therapeutic agent must define the conditions under which the PK study will be conducted and include selection of doses to be studies, control agents, number and type of subjects, fed or fasting conditions, the number of blood samples taken per subject and the optimal times when those samples are to be obtained. An optimal PK study design is one in which the design variables are chosen to maximize the information that can be obtained providing a robust assessment of the PK endpoints. PK parameters are all derived from the concentration information obtained from samples assayed by the bioanalytical laboratory. Therefore, understanding the limits of detection of the bioanalytical methods for the analytes and metabolites is an important consideration in PK study design and analysis. Tiwari (2010) provides a very good primer and summary of bioanalytical method validation.

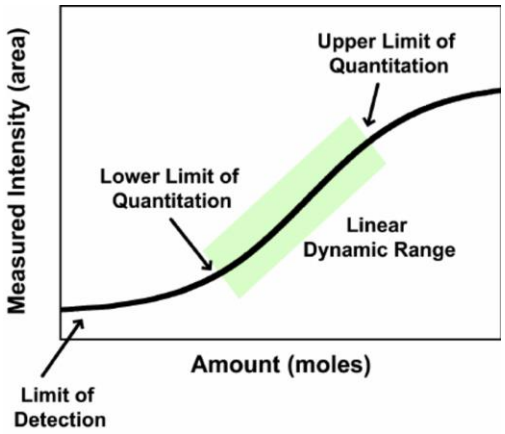
Regulatory agencies have provided guidance on validation of methods for measuring analyte and metabolite concentrations to establish an analytical limit defined as:

Lower limit of quantification: The LLOQ is the lowest amount of an analyte in a sample that can be quantitatively determined with suitable precision and accuracy(bias).

Upper limit of quantification: The upper limit of quantification (ULOQ) is the maximum analyte concentration of a sample that can be quantified with acceptable precision and accuracy (bias).

These boundaries are a method to provide assurance that concentration measurements made near the LLOQ or ULOQ concentration are unbiased measurements within the acceptance criteria for the analytical method.

Figure 1. Calibration Curve for defining the LLOQ, ULOQ



In the FDA Guidance on Bioanalytical Method Validation the agency defines key points in determining the LLOQ and ULOQ as:

Lower Limit of Quantification (LLOQ): The lowest standard on the calibration curve should be accepted as the LLOQ if the following conditions are met:

- *Analyte peak (response) should be identifiable, discrete, and reproducible, and the back-calculated concentration should have precision that does not exceed 20% of the CV and accuracy within 20% of the nominal concentration. The LLOQ should not be confused with the limit of detection (LOD) and/or the low QC sample.*

Upper Limit of Quantification (ULOQ): The highest standard will define the ULOQ of an analytical method.

- *Analyte peak (response) should be reproducible and the back-calculated concentration should have precision that does not exceed 15% of the CV and accuracy within 15% of the nominal concentration*

The 2013 Guidance further stipulates that for a validated method (Use, Data Analysis, and Reporting) should include the following:

Concentrations in unknown samples should not be extrapolated below the LLOQ or above the ULOQ of the standard curve. Instead, the standard curve should be extended and revalidated, or samples with higher concentration should be diluted and reanalyzed. Concentrations below the LLOQ should be reported as zeros.

However, Wang (2015) in an FDA presentation provided some regulatory clarification in that (1) submission of data below the LLOQ can be done in a submission, (2) the Office of Generic Drugs at FDA does not give specific recommendations on the format of submitted BLOQ data and (3) the statement "Concentrations below the LLOQ should be reported as zeros" in the 2013 guidance will be revisited.

It is not uncommon that the measurement of concentrations of analytes and metabolites at individual sampling time points are low (LLOQ) or high (ULOQ) and that the concentration measurement assayed may be outside the precision and accuracy of the instrumentation for the validated analytical method. These values may be less precise estimates, with greater measurement error, of the true concentration observed in a sample. Yet, it is critically important to remember that concentration values observed below the LLOQ are not invalid measurements and a concentration value exists and can be reported and potentially used in analysis. Simply stated, the LLOQ (and ULOQ) is a statistical metric (or variability boundary) describing the assay performance at a laboratory with a defined and validated method. Consider that for any given analyte, the same assay performed at multiple laboratories with validated methods at the laboratory will often have different LLOQ and ULOQ boundaries depending upon many different analytical factors (e.g. instrumentation, sample processing, standards, etc.). All these laboratory and method specific factors are described in the laboratories' analytical method procedure and method validation documentation.

LLOQ should not be an arbitrary cut-off value for discarding (or not reporting) measurements which may be useful for pharmacokinetic analysis. How we manage, and handle concentration data reported as BLOQ can and does have a profound impact on pharmacokinetic parameter estimates. Beal (2001), in a landmark paper, considers seven different approaches (identified as M-M7) for handling BLOQ data. Senn, Holford and Hockey (2011) provide context for Beal's methods as described below in Table 1.

Table 1 Method for Imputation of BLOQ data from Beal (2001).

Beal Method	Description of Method
M1	Discard BLQ data and estimate using remaining values as if they came from a full distribution.
M2	Discard BLQ data and estimate by treating the remaining values as forming a 'truncated' sample. The likelihood of all remaining samples is calculated conditional on the value being greater than the LLOQ.
M3	Ignore any actual values of the BLQ data and estimate by treating the sample as a whole as one in which BLQ values are censored. The likelihood of the BLQ sample assumes that the value is less than the LLOQ.
M4	Estimate as in M3 but add an additional constraint that all BLQ values must be positive. The likelihood of all values is conditional on their being greater than zero with the additional constraint for BLQ values that they are less than the LLOQ.
M5	Impute BLQ data by LLOQ/2 and estimate as if all the values were real.
M6	When measurements are taken for a given individual over time, impute as for M5 for the first BLQ measurement and discard all subsequent BLQ data.
M7	Impute BLQ values by zero and estimate as if all the values were real.

Nick Holford writing on the pharmacokinetics discussion board (https://www.pharmpk.com/) noted that there are two avoidable sources of bias with BLOQ concentration values:

1. *Do not let your analytical chemists fail to give you the measurements they made that are below BLQ. There is no reason not to use these values. It is just silliness that chemists fail to give you the measurements because of an arbitrary cut off that has no real meaning for pharmacokinetic analysis. Omitting these values will always cause bias.*

2. *Substituting zero for the values that the chemist hides from you is even worse than only using values that not BLQ. Any value after a measurable value is certainly not zero. It may not be easily measured but it is not zero. Assuming it is zero is certain to be wrong.*

The measured concentration value is always the best estimate, regardless of whether it is above or below LOQ. Therefore, replacing it with any other value will always be worse than using the actual measured value. Remember, values below LOQ are not invalid (a common misconception) - they are simply likely to have more bias than an arbitrary, pre-defined threshold. But they are still the best estimates we have.

Unfortunately, it is widespread practice today in PK clinical trials to report concentrations that are below the LLOQ threshold as Below the Limit of Quantification (BLOQ or BLQ) with no other information (e.g. BLQ <0.025 ng/mL). This practice of reporting BLOQ values needs to be critically examined and reconsidered. Consider that a great deal of the values reported as BLOQ are very close to the LLOQ limit (e.g. BLOQ <0.0100 µg/mL: Actual concentration observed 0.0092 µg/mL). Senn, et al (2011) stated "*A common but not necessarily logical requirement in drug development is that a 'limit of quantitation' be set for chemical assays and that observations that fall below the limit should not be treated as real data but should be labelled as below the limit and set aside for special treatment.*" Maybe a change in this widespread practice should be considered as part of GLP and regulatory guidance such that when a value is BLOQ the values reported are both BLOQ and the measured concentration observed, along with the lower limit of quantification (e.g. BLQ <0.025 ng/mL (0.022 ng/mL)). This more precise level of reported concentrations will allow for sensitivity analysis with all concentration data as well as application of imputation of BLOQ information for analysis. By reporting both the BLOQ value and the actual observed concentration value the bioanalytical laboratory is still preserving the integrity of the precision and accuracy of the analytical method as well as giving the pharmacokineticist valuable information that can be used in PK analyses.

In this paper we focus on how to manage and handle concentrations that are reported as below the limit of quantification (BLOQ) and provide examples of common methods for management and handling concentration data reported as BLOQ along with a simple set of rules for managing BLOQ values in PK analyses. We also examine some of the biases in reporting PK parameter estimates evident with Beal's M1, M5, M6, and M7 imputation methods.

SIMPLE AND PRAGMATIC RULES IN AN ANALYSIS PLAN FOR HANDLING BLOQ

Methods described by Beal (Table 1) offer a series of methods for handling concentration values identified as BLOQ. Linear interpolation methods M2, M3, and M4 were not presented in this paper and have been extensively discussed in Senn, et al (2011), Dorababu (2012), and Duval (2002). Beal's method M1, M5, M6, and M7 are all or none methods to be applied across the concentration profile when BLOQ values are reported in a concentration profile and each has a biased impact on the computation of pharmacokinetic parameters. We offer a simple and pragmatic solution that takes elements of Beal's methods into consideration when BLOQ values identified prior to Cmax and then BLOQ values reported after Cmax and during the elimination phase of the profile. This approach is in addition to using all available concentration data as noted by Holford. We recommend completing the planned pharmacokinetic analyses with all data reported, including concentration values that are also identified as BLOQ, and then with an imputation strategy like that outlined below. The two analyses can be viewed as sensitivity analyses, and both sets reported. We do not recommend Beal's method M7 (setting concentration values to zero) except as outlined below. Concentration data that have many concentration values reported as BLOQ in a concentration time profile may be associated with different PK parameter estimates than those observed with all data, and the impact can be profound, especially in bioequivalence studies where test and Reference products may have some differences in the ADME characteristics (e.g. an IR versus an ER drug product).

In a statistical or pharmacokinetic analysis plan a section should be included for the handling of concentration values reported as BLOQ that has language like the rule set as follows:

The bioanalytical assay for <analyte> an LLOQ assay sensitivity of <value, units>. Values assayed below this limit will be identified as BLOQ in the data reported by the bioanalytical laboratory. In addition, the bioanalytical laboratory will also report the extrapolated concentration value for concentrations identified as BLOQ. Concentrations that are not detected will be identified as "Not Detected" and recorded as BLOQ.

For the pharmacokinetic analysis, calculation of mean concentration profiles, and individual concentration vs time plots, values reported as BLOQ will be handled as follows:

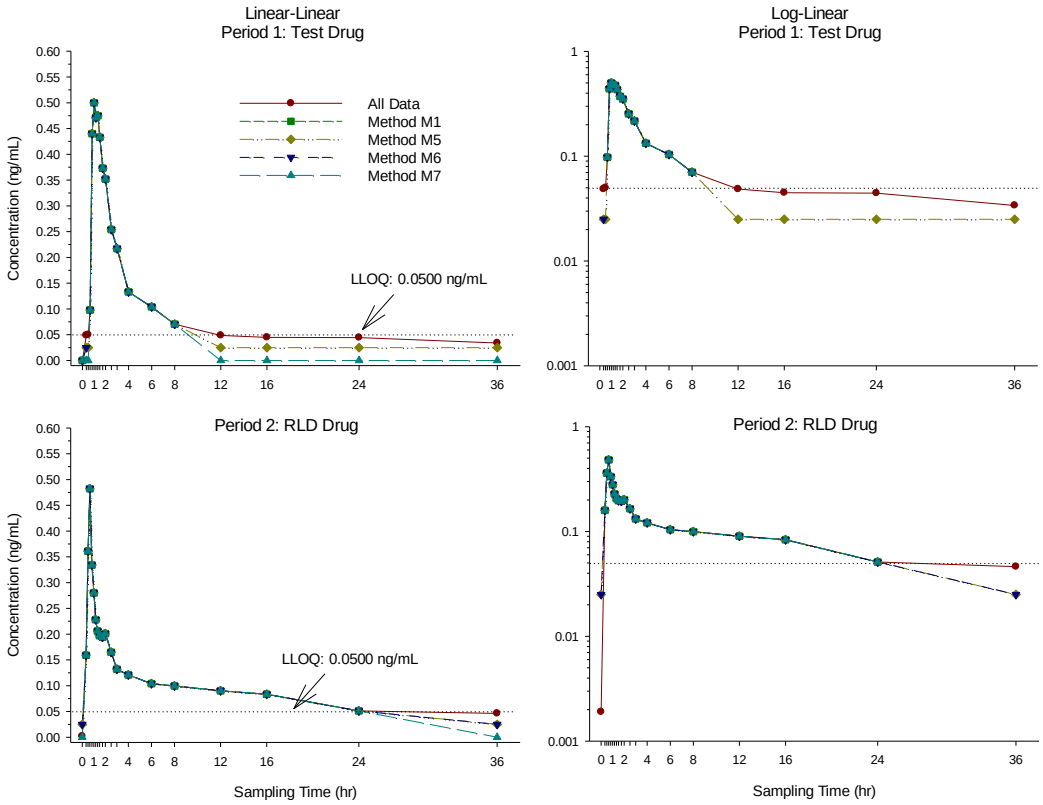
- *A concentration that is BLOQ is assigned a value of zero if it occurs in a profile after dosing at time zero and before the first measurable concentration.*
- *If a BLOQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLOQ is treated as missing data, and the time point is ignored in the computations.*
- *If a BLOQ value occurs at the end of the collection interval (after the last quantifiable concentration) it is treated as missing data.*
- *If two BLOQ values occur in succession after Cmax, the profile is deemed to have terminated at the first BLOQ value and any subsequent concentrations and time points are omitted from pharmacokinetic calculations.*

This conservative approach to managing and handling concentrations reported as BLOQ does not arbitrarily assign an imputed value such as identified in Beal's M5, M6, or M7. Instead this approach uses available data (observed data) on the elimination phase (after Cmax) and treats as missing those values as BLOQ. On the absorption side, prior to Cmax those values after dosing and before he first quantifiable concentration are set to zero and included in the profile, using elements of Beal's M1, and M6. It should be noted that this pragmatic and simple method for handling BLOQ is also a biased approach, like the other methods identified by Beal and Senn. However, when pharmacokinetic analyses are completed with all data and with BLOQ imputed as reported the ability to examine the impact of BLOQ reported data on the pharmacokinetics for a drug product can be completed and reported in the study report.

IMPUTATION METHODS FOR HANDLING BLOQ CONCENTRATIONS

In a 2-period cross over study to evaluate the PK of a drug that has been formulated as both an immediate release (IR) and extended release (ER) formulation consider the impact of the various methods for handling BLOQ samples on the concentration profile for a single subject (Figure 2, Table 2). In this example we present the reported and actual concentrations for an analyte with an LLOQ assay sensitivity of 0.0500 ng/mL. We have then applied the methods for imputation of values associated with concentrations reported as BLOQ for comparisons. It is critically important to note that methods M1, M6, and that identified in this paper will set to missing (terminate the profile) at the BLOQ values, whereas methods M5 and M7 will impute values to the end of the sampling profile.

Figure 2 Linear-linear and Log-Linear Concentration profiles.



We then examined the actual and predicted concentration profiles, with calculation of the terminal rate constant (Lambda_z) for each method. Figure 3 presents the observed and predicted profiles for the actual data, including the concentration values reported as BLOQ, Figure 4 presents Beal's method M1, Figure 5 presents Beal's method M5, Figure 6 presents Beal's method M6, Figure 7 presents Beal's method M7, and Figure 8 presented the blended method identified in our paper. The impact (and potential biases) can be seen in the calculation of Lambda_z with both the starting point and the number of data points used in the calculation of this important rate constant.

Table 2 Subject Concentration data with actual data and imputation methods applied for 2-period cross-over (Period 1: Test product, Period 2: Reference product).

				Imputation Methods for BLOQ				
Period	Time (hrs)	Reported Concentration (ng/mL)	Actual Concentration (ng/mL)	Beal Method M1	Beal Method M5	Beal Method M6	Beal Method M7	Paper
1	Predose (0)	BLQ <0.0500	Not Detected	0	0	0	0	0
	0.33	BLQ <0.0500	0.0486	.	0.0250	0.0250	0.0000	0
	0.50	BLQ <0.0500	0.0499	.	0.0250	.	0.0000	0.000
	0.66	0.0978	0.0978	0.0978	0.0978	0.0978	0.0978	0.0978
	0.83	0.4400	0.4400	0.4400	0.4400	0.4400	0.4400	0.4400
	1	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000	0.5000
	1.16	0.4710	0.4710	0.4710	0.4710	0.4710	0.4710	0.4710
	1.33	0.4750	0.4750	0.4750	0.4750	0.4750	0.4750	0.4750
	1.5	0.4330	0.4330	0.4330	0.4330	0.4330	0.4330	0.4330
	1.75	0.3730	0.3730	0.3730	0.3730	0.3730	0.3730	0.3730
	2	0.3520	0.3520	0.3520	0.3520	0.3520	0.3520	0.3520
	2.5	0.2540	0.2540	0.2540	0.2540	0.2540	0.2540	0.2540
	3	0.2170	0.2170	0.2170	0.2170	0.2170	0.2170	0.2170
	4	0.1330	0.1330	0.1330	0.1330	0.1330	0.1330	0.1330
	6	0.1040	0.1040	0.1040	0.1040	0.1040	0.1040	0.1040
	8	0.0704	0.0704	0.0704	0.0704	0.0704	0.0704	0.0704
	12	BLQ<0.0500	0.0486	.	0.0250	.	0.0000	.
	16	BLQ<0.0500	0.0449	.	0.0250	.	0.0000	.
	24	BLQ<0.0500	0.0445	.	0.0250	.	0.0000	.
	36	BLQ<0.0500	0.0339	.	0.0250	.	0.0000	.
2	Predose (0)	BLQ<0.0500	0.0019	.	0.0250	0.0250	0	0
	0.33	0.1590	0.1590	0.1590	0.1590	0.1590	0.1590	0.1590
	0.50	0.3610	0.3610	0.3610	0.3610	0.3610	0.3610	0.3610
	0.66	0.4820	0.4820	0.4820	0.4820	0.4820	0.4820	0.4820
	0.83	0.3340	0.3340	0.3340	0.3340	0.3340	0.3340	0.3340
	1	0.2800	0.2800	0.2800	0.2800	0.2800	0.2800	0.2800
	1.16	0.2280	0.2280	0.2280	0.2280	0.2280	0.2280	0.2280
	1.33	0.2060	0.2060	0.2060	0.2060	0.2060	0.2060	0.2060
	1.5	0.1970	0.1970	0.1970	0.1970	0.1970	0.1970	0.1970
	1.75	0.1940	0.1940	0.1940	0.1940	0.1940	0.1940	0.1940
	2	0.2010	0.2010	0.2010	0.2010	0.2010	0.2010	0.2010
	2.5	0.1650	0.1650	0.1650	0.1650	0.1650	0.1650	0.1650
	3	0.1320	0.1320	0.1320	0.1320	0.1320	0.1320	0.1320
	4	0.1210	0.1210	0.1210	0.1210	0.1210	0.1210	0.1210
	6	0.1040	0.1040	0.1040	0.1040	0.1040	0.1040	0.1040
	8	0.0996	0.0996	0.0996	0.0996	0.0996	0.0996	0.0996
	12	0.0901	0.0901	0.0901	0.0901	0.0901	0.0901	0.0901
	16	0.0834	0.0834	0.0834	0.0834	0.0834	0.0834	0.0834
	24	BLQ<0.0500	0.0499	.	0.0250	0.0250	0.0000	.
	36	BLQ<0.0500	0.0462	.	0.0250	.	0	.

Figure 3 Concentration profile: Actual Concentration Data (Periods 1 and 2), Values reported as BLOQ included in analysis.

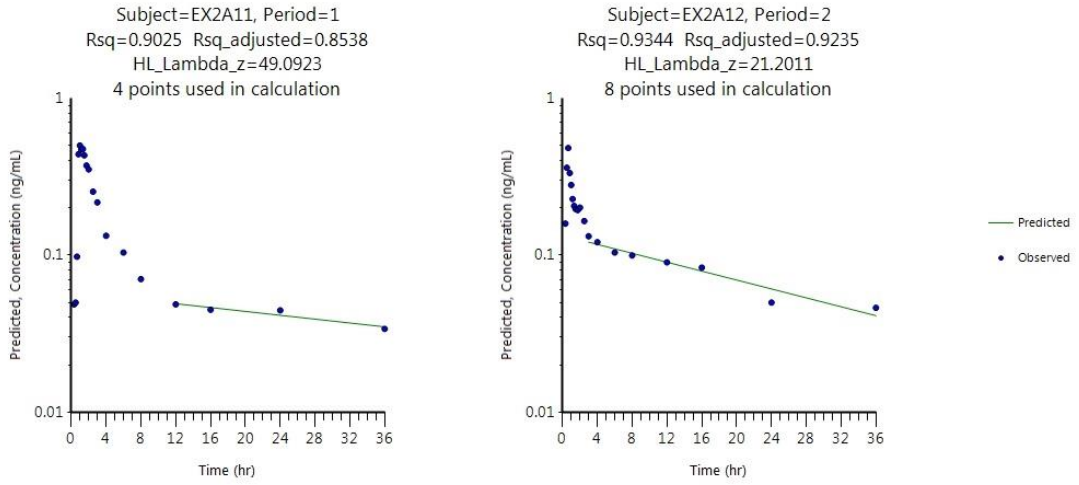


Figure 4 Concentration profile: Beal Method M1 BLOQ Imputation (Periods 1 and 2).

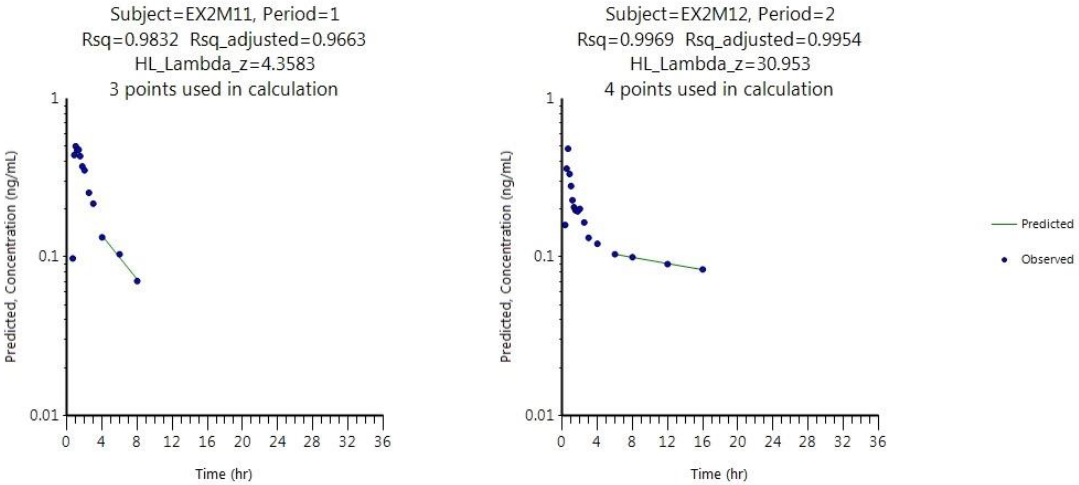


Figure 5 Concentration profile: Beal Method M5 BLOQ Imputation (Periods 1 and 2).

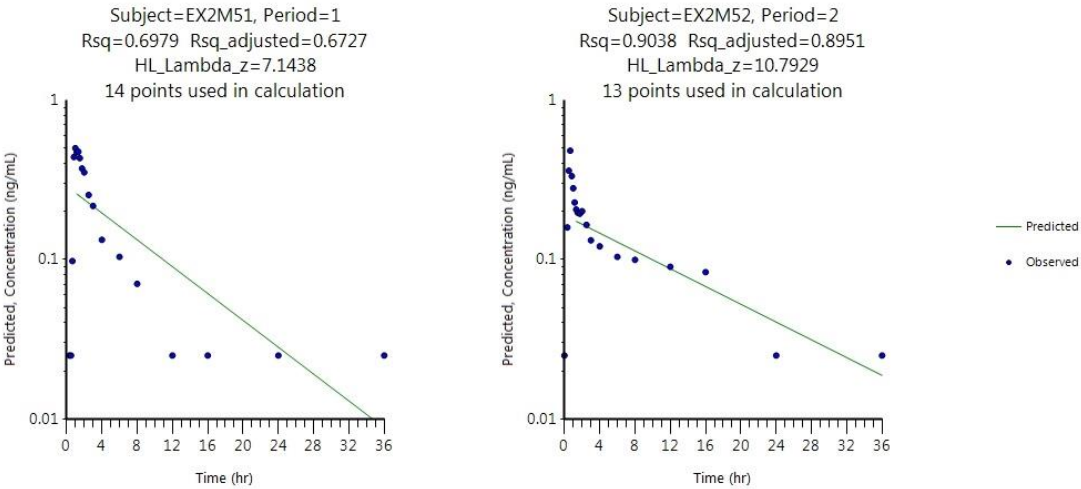


Figure 6 Concentration profile: Beal Method M6 BLOQ Imputation (Periods 1 and 2).

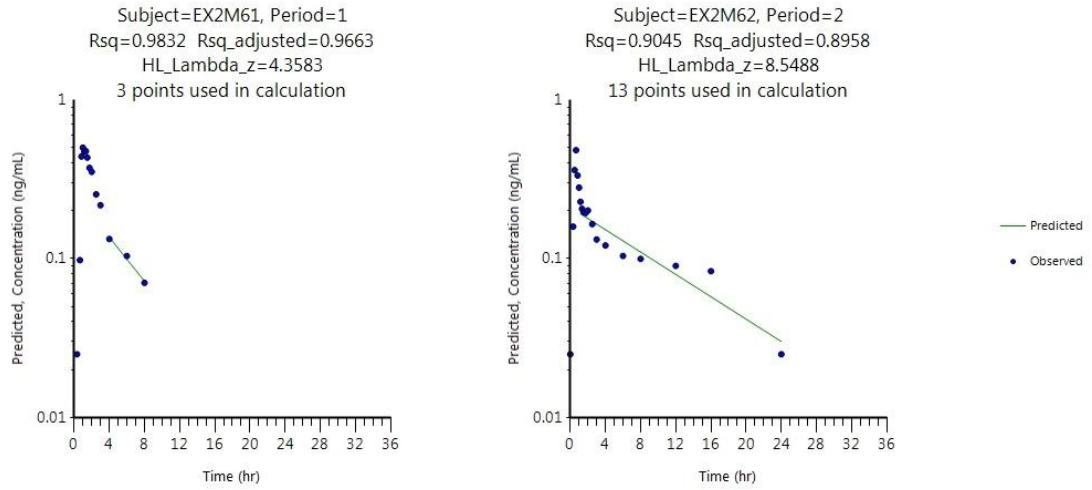


Figure 7 Concentration profile: Beal Method M7 BLOQ Imputation (Periods 1 and 2).

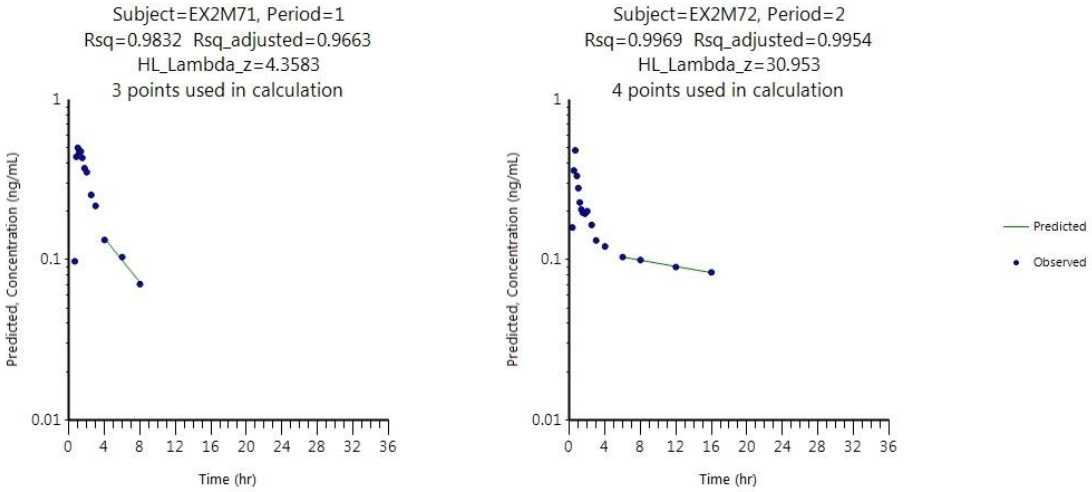
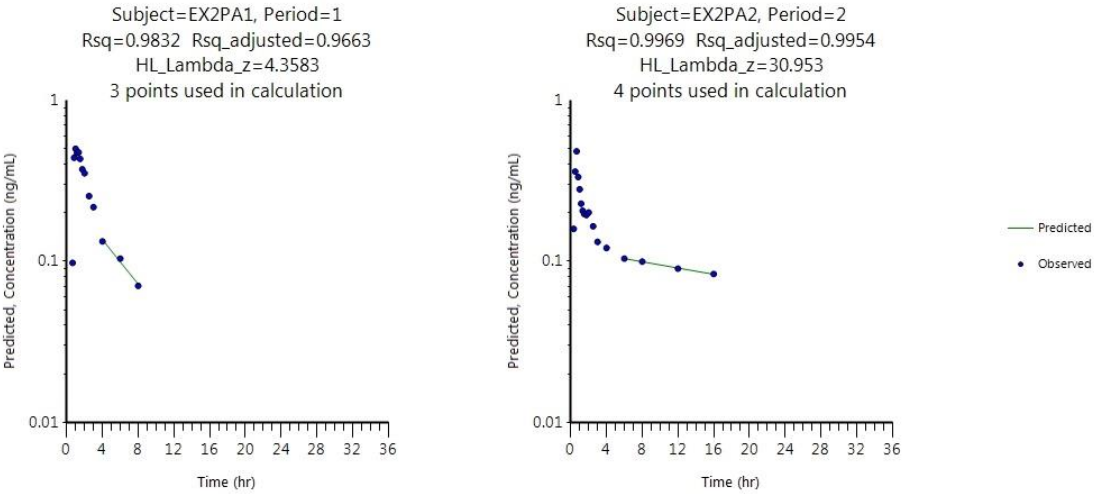


Figure 8 Concentration profile: Blended BLOQ Imputation methods (Periods 1 and 2).



IMPACT OF IMPUTATION METHODS ON PK PARAMETER ESTIMATES

The impact of concentration values reported as BLOQ can be viewed in the context of missing data where we would often use multiple imputation methods to analyze data. The problem with multiple imputation methods for PK parameter estimation with concentration data reported as BLOQ is that the data are not really missing: these data are outside the precision of the assay sensitivity an thus less reliable (greater assay variability). Applying the imputation methods noted in Table 1 does not make the values more reliable estimates of the true concentration. These methods introduce another set of biases that affect the computation of PK parameters that are dependent on the terminal rate constant (lambda_z).

In our single subject example, we present the PK parameter estimates using WinNonlin 7 (NCA Model 202) for each of the methods described. Note that the impact of imputation of BLOQ samples in reflected in the number of points used to calculate Lambda_z, the estimate of Lambda_z (terminal rate constant), the terminal half-life (T½), and the AUC parameters. It is worth noting that when values reported as BLOQ are set to missing and omitted from analysis the estimated PK parameters shift. One can then consider the impact of how many BLOQ values in a profile are evident and that the shift in parameter estimates will increase with an increase in the number and percentage of concentration values reported as BLOQ.

Table 3 Pharmacokinetic parameter estimates from NCA Analysis with imputation methods applied.

Imputation Method	Per	No Points Lambda_z	Lambda_z	$T_{1/2}$	T_{max}	C_{max}	T_{last}	C_{last}	$AUC_{0\text{-}last}$	$AUC_{0\text{-}inf}$	$AUC_{0\text{-}inf}$ Percent Extrapol
All Data	1	4	0.0141	49.09	1	0.5000	36	0.0339	2.6891	5.0901	47.17
M1	1	3	0.1590	4.36	1	0.5000	8	0.0704	1.4402	1.8828	23.51
M5	1	14	0.0970	7.14	1	0.5000	36	0.0250	2.2169	2.4746	10.41
M6	1	3	0.1590	4.36	1	0.5000	8	0.0704	1.4323	1.8750	23.61
M7	1	3	0.1590	4.36	1	0.5000	8	0.0704	1.4157	1.8584	23.82
Paper	1	3	0.1590	4.36	1	0.5000	8	0.0704	1.4157	1.8584	23.82
All Data	2	8	0.0327	21.20	0.66	0.4820	36	0.0462	3.0268	4.4399	31.83
M1	2	4	0.0224	30.95	0.66	0.4820	16	0.0834	1.9167	5.6410	66.02
M5	2	13	0.0642	10.79	0.66	0.4820	36	0.0250	2.6544	3.0437	12.79
M6	2	13	0.0811	8.55	0.66	0.4820	24	0.0250	2.3544	2.6628	11.58
M7	2	4	0.0224	30.95	0.66	0.4820	16	0.0834	1.9167	5.6410	66.02
Paper	2	4	0.0224	30.95	0.66	0.4820	16	0.0834	1.9167	5.6410	66.02

CONCLUSION AND RECOMMENDATION

Thanks to advances in statistical estimation procedures (see Peck et al 1984) it is reasonable for the pharmacokinetic analyst to use all measured concentrations to estimate pharmacokinetic parameters. Note that pharmacokinetic statistics such as Cmax and Tmax are not very sensitive to the biases caused by discarding or imputing measurements below the LLOQ. AUC is often insensitive unless a large fraction of the AUC must be estimated by extrapolation. This fraction will increase with an increase in the number of samples reported as BLOQ. One must clearly note the number of samples reported as BLOQ in each subject profile and consider the impact of these imprecise data.

Senn et al 2012 note that ignoring BLQ values or replacing them with 0 will inevitably cause biased estimates of PK parameters. Using the actual measured value with an appropriate statistical model to account for the residual error will always be better. The method proposed in our paper that sets BLOQ values prior to Cmax to zero and to missing at the end of the concentration curve is a pragmatic and simple method for imputation of these values and can be used in concert with reporting all data for sensitivity. Completing the PK parameter estimates with all concentration data and with imputed BLOQ values should be done in each PK analysis.

The impact of BLOQ values on a subject's concentration profile is both a function of the analyte assay sensitivity and precision, and the number of reported BLOQ samples over the sampling interval. A reasonable conclusion is that more BLOQ values will lead to greater biased PK parameter estimates.

Additional simulation work needs to be completed with the all data. M1, M5, M6, M7 and the blended method proposed in this paper to evaluate the impact of the number of BLOQ samples in a profile, estimates of PK parameter means and variances, and the type of PK model (one-compartment, two-compartment, non-compartmental, etc.). Given the importance of establishing bioequivalence between test and reference products the impact of BLOQ imputation methods on bioequivalence ratios for the AUC parameters needs to be investigated with further simulation work. Replacing BLOQ values with zero (0) is inherently biased and highly influenced by the number of sample time points in the profile and the number of BLOQ samples reported so this additional simulation work would provide insight into the impacts of these imputation decisions for analysis and reporting the concentration profiles and PK parameter estimates.

REFERENCES

1. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). Guidance for Industry: Bioanalytical method Validation. September 2013. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm368107.pdf
2. Tiwari G, Tiwari R. Bioanalytical method validation: An Updated review. Pharm Methods. 2010 Oct-Dec;1(1):25-38. doi 10.4103/2229-4708.72226 (http://phmethods.net/article/91).
3. Beal SJ. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinetics and Pharmacodynamics 2001; 28:481-504.
4. Senn S, Holford N, Hockey H. The ghosts of departed quantities: approaches to dealing with observations below the limit if quantification. Statistics in Medicine. 2012;31:4280-4295.
5. Peck CC, Beal SL, Sheiner LB, Nichols AI. Extended least squares nonlinear regression: A possible solution to the "choice of weights" problem in analysis of individual pharmacokinetic parameters. J Pharmacokinet Biopharm. 1984;12(5):545-57.
6. Dorababu M (2012) Pharmacokinetic Modeling of Data with Below Quantification Limit. J Bioequiv Availab 4: ii-iii. doi:10.4172/jbb.10000e12.
7. Duval V, Karlsson MO. Impact of Omission or Replacement of Data below the Limit of Quantification on parameter Estimates in a Two-Compartment Model. Pharmaceutical Research 2002;19(12):1835-1840.
8. Sheiner LB. Population pharmacokinetics/dynamics. Annu. Rev. Pharmacol. Toxicol. 32:185–209 (1992).
9. Keizer RJ, Jansen RS, Rosing H, Thijssen B, Beijnen JH, Schellens JHM, Huitema ADR. Incorporation of concentration data below the limit of quantification in population pharmacokinetic analyses. Pharma. Res. Per. 2015;3(2). doi: 10.1002/prp2.131
10. Xu SX, Dunne A, Kimko H, Nandy P, Vermeulen A. Impact of low percentage of data below the quantification limit on parameter estimates of pharmacokinetic models. J Pharmacokinet Pharmacodyn 2011;38:423-432. doi 10.1007/s10928-011-9201-9.
11. Fang L, Chen P, Ke C, Lee E. Estimating area under the curve and relative exposure in a pharmacokinetic study with data below quantification limit. J Biopharmaceutical Statistics. 2010;21(1);66-76. doi 10.1080/10543400903572241. http://dx.doi.org/10.1080/10543400903572241
12. Hutson AD, Fishbein L, O'Brien P, Stacpoole PW. Accounting for plasma levels below detection limits in a one-compartment zero-order absorption pharmacokinetics model. J Applied Statistics. 2002;29:1181-1190.
13. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. The AAPS journal 2009; 11:371–380.
14. Byon W, Fletcher CV, Brundage RC. Impact of censoring data below an arbitrary quantification limit on structural model misspecification. J Pharmacokinet Pharmacodyn. 2008;35:101-116. doi 10.1007/s10928-007-9078-9.
15. Wang Y. For the Release of Bioanalytical Data below the LLOQ. A presentation entitled Evolution of Pharmacokinetics at FDA in the Last Decade. 2015. https://zerista.s3.amazonaws.com/item_files/0f21/attachments/58920/original/170.pdf
16. Booth B, Arnold ME, DeSilva B, Amaravadi L, et al. White Paper. Workshop Report: Crystal City V-Quantitative Bioanalytical Method Validation and Implementation: The 2013 Revised FDA Guidance. AAPS Journal 2015;17(2):277-288. doi 10.1208/s12248-014-9696-2

ACKNOWLEDGMENTS

I would like to thank my colleagues at Summit Analytical who have provided valuable insight and the freedom to pursue exploration of important topics to the analysis and reporting of pharmacokinetic data.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author(s) at:

James R. Johnson, PhD ("Jim")
Summit Analytical, LLC
Email: jrjphd@gmail.com