Summary:

Traditionally, bioanalytical laboratories do not report actual concentrations for samples with results below the limit of quantification (BLQ) in pharmacokinetic studies. BLQ values are outside the method calibration range established during validation and no data are available to support the reliability of these values. However, ignoring BLQ data can contribute to bias and imprecision in model-based pharmacokinetic analyses. From this perspective, routine use of BLQ data would be advantageous.

We would like to initiate an interdisciplinary debate on this important topic by summarising the current concepts and use of BLQ data by regulators, pharmacometricians and bioanalysts. Through introducing the limit of detection and evaluating its variability BLQ data could be released and utilized appropriately for pharmacokinetic research.

Keywords:

- Lower limit of quantification (LLOQ)
- Below limit of quantification (BLQ) result
- Limit of detection (LoD)
- Pharmacokinetic (PK)
- Pharmacodynamics (PD)

Introduction

Studying the effects of drugs remains central to both medical research and clinical practice. Two key branches of pharmacological analysis are (i) pharmacokinetics (PK), including drug absorption, distribution, metabolism and elimination, and (ii) pharmacodynamics (PD), exploring

the effects of drugs on the living organism, including efficacy and toxicity. In PK studies the samples are collected in an effort to map the drug concentration over time in the patient. For samples collected many hours post-dose drug concentrations may be low, yet can still provide valuable information on pharmacokinetic parameters such as clearance [1,2]. Similarly, in the case of biomarker PD studies, concentrations that are too low to quantify with a particular bioanalytical method may still provide useful information.

Bioanalytical laboratories define the lowest concentration that can be quantified accurately by a method as the lower limit of quantification (LLOQ). For chromatographic methods, the precision and accuracy of the LLOQ calibrator are determined experimentally during the method validation process. In practice, the assigned concentration of the LLOQ calibrator may arise from many sources, including pre-existing experimental data or literature references suggesting a concentration range for a drug in a particular matrix, or predicted drug concentrations based on dosing information. In addition, chromatographic methods have a limited linear dynamic range (i.e. a range across which the instrument response is linear with respect to concentration). If the assay is designed to include a high upper limit of quantitation (ULOQ) to quantify accurately samples at peak drug concentration (without having to dilute too many samples), and the linear range of the assay/instrument is limited, this may result in a high LLOQ concentration.

For the LLOQ calibrator, the within-assay and between-assay coefficients of variation (CV, %) must be consistently (i.e. between-assay precision from at least three batch assays, with five replicates within each batch assay) *less than or equal to 20 %* [3–7]. For immunoassays, such as enzyme linked immunosorbent assays (ELISAs), larger CV values (25 % at LLOQ) are acceptable [3]. In study reports generated by bioanalytical laboratories, concentrations measured below the

LLOQ are typically reported textually as ‘below the limit of quantification’ (BLQ) or similar, rather than as a numeric value.

Since no precision and accuracy data are acquired during the method validation for concentrations below the LLOQ (BLQ), these data are considered invalid. The OECD Good Laboratory Practice (GLP) guidelines require that Study Directors ensure the quality and validity of the data handed out [8], which are simply unknown for data BLQ and therefore these data should not be released.

Design of the bioanalytical assay should be well aligned with the concentrations expected in the clinical samples. A suitable concentration range and the LLOQ for the assay should be selected. This may be based on pre-existing data about expected drug concentrations in real samples (e.g. from existing literature, animal models in case of first-in-human studies, adult models for paediatric studies, or at worst, data about similar drugs and dosing regimens). The aim is to ensure the maximum number of samples fall within the assay concentration range. In well-designed clinical studies, the amount of BLQ data should be minimal.

An example PK model is shown in Figure 1. The model is based on analysis of a drug using three different assays, each with a different LLOQ concentration, and different precision values at the LLOQ concentrations. The dashed line for each assay represents the LLOQ concentration, and the grey highlights show the experimentally determined between-day precision (CV, %) at the designated LLOQ concentration for each. All assays demonstrate acceptable CV at the LLOQ (i.e. $\leq$20 %). Assay A is appropriate for the task, and would provide quantitative results for all but the pre-dose time point. Assay C is clearly not suitable for this study, since the designated LLOQ is too high for the concentrations achieved. For assay C, the majority of data points are BLQ and therefore cannot be reported numerically. However, since the CV of the assay is low at the designated LLOQ concentration, a re-validation of the same assay using a lower calibration range

(inclusive of a lower LLOQ calibrator) might suffice to allow re-analysis of the study samples, and provide more usable numeric data.

******Figure 1 goes here.******

Of particular interest are the results produced using assay B. Technically, enough data points are available to formulate a PK model, but a number of data points are below the LLOQ and would therefore be reported as BLQ. These BLQ data points may be very useful in clarifying the clearance of the drug by improving the PK model [1]. These BLQ data can be used in the estimation if concentrations are reported numerically as shown in a previously published study where actual BLQ data were used [1]. Keizer et al. [1] used an indisulam data set with uncensored concentrations BLQ, excluding concentrations below LOD to compare different BLQ data handling approaches.

Current Status of Regulations and Bioanalytical Method Validation Guidelines

Missing BLQ values could be viewed as the consequence of an historical lack of communication between clinicians, pharmacometricians and bioanalytical chemists and missing information about the expected concentration range. During the assay development, the LLOQ is chosen for assay validation. Assay validation will ensure the precision limits for the method LLOQ. Whilst there are a number of validation guidelines available, we will be focusing herein on the guidelines deemed most relevant for bioanalytical laboratories at the time of writing [7]. In Europe this is currently the European Medicines Agency (EMA) guideline from 2011[3]. From the United States of America the Food and Drug Administration's (FDA) 'Guideline on bioanalytical method validation', updated in 2013 [4] is reviewed. From Brazil, the Brazilian Health Regulatory Agency (ANVISA) validation guideline dates from 2012 [5]. ANVISA and EMA, as well as others, are

mostly created in connection with, or on the basis of the FDA guideline, but extend the requirements in newer iterations [7]. China is preparing their own guideline (CFDA), a draft of which was issued in 2011. However, the finalised version has yet to be translated into English [9]. In Canada, the Health Canada Guidance for Industry Conduct and Analysis of Comparative Bioavailability Studies (2012) stipulates that EMA guidelines must be followed [10]. All three guidelines (FDA, EMA and ANVISA), as well as guidelines issued by Japan in [6], define the LLOQ as the lowest concentration of analyte which can be reliably quantified. Whilst the wording differs in each guideline document, the method for determining the LLOQ and the acceptance criteria do not. In all guidelines, LLOQ determination requires analysis of at least five samples at the LLOQ concentration, with (i) accuracy 80-120 % of the nominal concentration, (ii) precision lower than or equal to 20%, and (iii) a signal which is at least five times larger than that of a matrix blank response (noise) [6,7]. The limit of detection (LoD) is defined in the FDA draft guideline as the lowest concentration that can be reliably differentiated from blank samples [4]. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has started work on a bioanalytical method validation guideline in October 2016, with Step 4 (adoption of ICH harmonised guideline) planned for June 2019 [11]. Currently ICH has a general guideline "Validation of Analytical Procedures: Text and Methodology" Q2(R1) [11], which provides three options on how to determine LoD and LLOQ. However, only one of these options uses a mathematical formula for calculation (using standard deviation of the response and the slope of the calibration curve). The other two options use the signal-to-noise ratio value, and 'visual evaluation', respectively [11].

In the GLP regulatory environment, the release of BLQ data is not justified by the laboratory as the reliability of this data is not covered by the method validation experiments [8].

Current Status of Bioanalytical Methods

Commonly used chromatographic methods (liquid chromatographic (LC) and gas chromatographic (GC) with different detectors and also liquid chromatography-tandem mass spectrometry (LC-MS/MS)) use linear calibration curves for the quantification of analytes in samples, with confinements for accuracy and precision throughout the whole range. Even if the permitted accuracy (% nominal concentration) at the LLOQ is 80-120 %, and the permitted precision is less than or equal to 20 %, the measured precision for the designated LLOQ concentration can differ significantly between methods. For some validated bioanalytical methods, precision at the designated LLOQ concentration can be well below 5 %, whilst for other methods the precision may be much closer to the 20 % limit of acceptance (Figure 2). In the current regulatory environment, BLQ data should not be released by the analytical laboratory for PK modelling because these data are deemed unreliable [8]. In practice, depending on the performance of the assay, some of these BLQ data may in fact be at concentrations which, if tested during validation, would be within the requisite 20 % precision limits. It is the lack of supporting data which is critical in the release of these data.

It can safely be assumed that the variance of the data increases sharply at concentrations below the LLOQ concentration. This can be demonstrated simply by plotting the assay precision against the nominal concentrations of calibrators (Figure 2). Following current method validation guidelines, no precision data are collected at concentrations below the designated LLOQ. Therefore, the exact concentration at which the precision exceeds the 20 % limit, and indeed how far below the designated LLOQ that concentration is, are both unknown quantities. With a method that displays a precision of 5 % at the LLOQ concentration, the precision at concentrations far below the LLOQ might very well be fit for purpose (assay C in Figure 2), but this information is simply not available

without additional validation using a lower calibration range (i.e. with a re-assigned LLOQ calibrator). For methods where the precision at the LLOQ is already approaching 20 %, one may expect the actual concentration at which the 20 % limit is exceeded to be just below the designated LLOQ (assay A in Figure 2), but again this cannot be guaranteed or proven without additional validation work. Potentially, if bioanalytical laboratories could evaluate the accuracy and precision of BLQ data using pre-defined guidelines, recognised by the regulators, and ensure that PK modelling takes this analytical variability into account, BLQ data could be released for use in PK analyses, which could therefore improve our pharmacological understanding.

*****Figure 2 goes here.*****

BLQ Data Treatment

If BLQ data are censored one has to resort to statistical treatment [12]. Before Beal suggested different options to include samples BLQ into the modelling in 2001 [12], this data was merely discarded for non-compartmental analysis. Frequently the drug concentration decreases to BLQ in the case of the late time points in PK studies[13–17] or when the administered dose is very small [18–22]. BLQ data may also result from inter-individual variability that can influence drug absorption, excretion or degradation [23–26]. Occasionally, the majority of samples analysed within a PK study series are not quantifiable, for example due to a different administration procedure (e.g. subcutaneous) [27], rapid degradation of the parent drug [28] or usage of 'an inadequate analytical method' [29]. Sometimes it is even desired to push the analyte's level BLQ with medication [21,30].

For methods to manage BLQ data points, when they present a relatively small fraction of the total data, different procedures have been proposed, such as exclusion, partial exclusion, or substitution

(e.g. with half the LLOQ, the LLOQ, or zero) [For references please see Table 1]. A comparisons of the most prominent options can be found here [1,12,31–35]. A brief overview of the different approaches used to treat BLQ data is provided in Table 1.

*****Table 1 goes here.*****

Table 1: Summary of methods used to treat censored BLQ data. Method numbering system according to Beal, 2001 [12] where appropriate.

BLQ data treatment option	Method number	Example study references
Discard all BLQ data and model with remaining data	M1	[1,12,31–76]
Discard BLQ data and estimate the likelihood of the remaining values to be greater than the LLOQ	M2	[12,31,77–79]
Keep BLQ observations in the model and estimate the likelihood of those values being below LLOQ	M3	[1,12,31,33,34,39,48,52,53,55–57,59,60,63,69,71–73,77–185]
Keep BLQ observations in the model and estimate the likelihood of those values being between 0 and LLOQ	M4	[12,35,116,180,186,187]
All BLQ data are substituted with LLOQ/2	M5	[12,24,30–33,35,55,62,133,153,188–224]
BLQ data are substituted with LLOQ/2, however subsequent, consecutive BLQ observations from the same subject are discarded	M6	[1,12,34,35,59,63,117,225–243]
All BLQ data are substituted with 0	M7	[12,31,33,207,244]
All BLQ data are substituted with LLOQ		[245,246]
Using data between LoD and LLOQ		[1,32,41,247–249]

A comparison of several approaches for treating BLQ data points was conducted by Xu et al. [76]. They found that if the dataset contains a low percentage (≤10%) of BLQ data, then discarding these data is a valid option and does not increase the bias of the study [76]. Substituting BLQ

values with 0 was found to be worse than substituting with half the value of LLOQ, since substitution with 0 introduced bias to the assessment [12].

The likelihood-based methods – discarding BLQ data, but maximizing the likelihood of the remaining data being above LLOQ [12,34] – were found to work even better. Simulation of datasets is an option offered by the NONMEM® program [250–253]. Overall caution is advised, when using BLQ data due to the large variability of these data [2].

It has been recommended by pharmacometricians that bioanalytical laboratories should release the BLQ data if the values are above the LoD [1] or the 'lower limit of an assay's ability to distinguish a concentration from zero' [254]. Moreover, recently it has been demonstrated that uncensored BLQ data may be useful, even for the studies where <10 % of data are BLQ [1]. By comparing the M3 and M6 approaches (Table 1) for treating censored data and actual BLQ data, inclusion of uncensored BLQ data gave less bias and more precise parameter estimates [1].

A critically important piece of information that is currently missing from a standard bioanalytical method validation is the LoD. Whilst it is defined by the regulatory and guidance documents [4,255–260] it is not yet required to establish it experimentally in bioanalysis [4,7]. Furthermore, this parameter is not easily determined experimentally. There are a number of possible ways to determine the LoD, and these result in concentrations which may differ up to ten-fold [261,262].

Bridging the Divide

If possible, those assays used to analyse study samples which result in critical amounts of BLQ data should be re-designed and re-validated as a rule. Thereafter, the samples should be re-analysed

in order to provide adequately reliable PK data (Figure 3). Resources to be considered and discussed between the analyst and the pharmacometricians are: (i) the sample amount left, (ii) the stability of the analyte in question, (iii) the funds necessary to re-validate the assay.

If assay re-design is not possible, BLQ data precision should be evaluated. The following issues emerge when calculating values for BLQ data. Firstly, as a rule, BLQ data are outside the calibration range. Thus, aside from the precision considerations already discussed, calculating concentrations outside the calibration range from the calibration curve involves extrapolation assuming linearity. In reality, this might not hold true and the signal might behave in a non-linear fashion.

For the purpose of PK modelling, it would be useful to evaluate the precision for BLQ data during method validation, although current guidelines do not require these experiments to be carried out. The LLOQ is the lowest concentration at which the precision is measured. Below this concentration, variability likely becomes unacceptable for the specific sample. In the case of PK modelling, however, especially if there are a number of data points, the precision requirements can be less stringent. Thus, data that are BLQ from the point of view of determining analyte concentration in a specific sample, might still be usable and reliably informative in model development [1].

*****Figure 3 goes here.*****

Releasing results for extrapolated concentrations outside the validated calibration range of an assay is not justifiable from the point of view of the analytical chemist. One possible approach to overcome this, would be to include an additional experiment either during, or following, method validation to establish precision and accuracy at a concentration BLQ, and then report any BLQ

data with the estimated CV (Figure 3). Using this approach, BLQ data are clearly labelled as 'outside the validated range of the assay' and the decision whether and how to incorporate these data into a PK model can be taken by the data analyst (PK modeller/pharmacometrician).

This suggestion involves amending current bioanalytical method validation protocols, to include (i) calculating the assay LoD and then (ii) experimentally measuring the accuracy and precision of the assay at the LoD concentration. For the former, the authors would strongly discourage the use of signal-to-noise calculation algorithms [261,262]. Results obtained using such approaches are software-dependent, and can be significantly influenced by data processing, e.g. chromatographic smoothing [263].

Statistically, the LoD of a method depends on the sensitivity (as defined by the slope of the calibration graph), and variability at concentrations approaching the LoD and 0. To calculate the LoD using data already acquired during the requisite method validation, the following equation provides a simple, and useful estimate:

$$LoD = 3.3 * \frac{SD(LLoQ)}{S} \quad \text{(i)}$$

Where *SD(LLOQ)* is the standard deviation of the analyte response (or the response ratio to an internal standard) of replicate measurements of analyte in the sample matrix prepared at the LLOQ concentration, and *S* is the slope of a line drawn between the origin and the mean response of the replicates at the nominal LLOQ concentration (Figure 4). By using this SD(LLOQ) value, variance is assumed to be equal for BLQ concentrations, which leads to conservative (higher) LoD concentrations. Moreover, using this equation assumes linearity between LoD and LLOQ, and that the curve passes through the origin (i.e. blank samples give an intensity response that is not

significantly different from 0). This equation is based on commonly used approaches of estimating LoD. Detailed discussion about these LoD estimation approaches can be found in the following reference [261,262].

*****Figure 4 goes here.******

Alternative LoD estimation approaches are available [261,262] which make fewer assumptions than the approach described above, and therefore provide more statistically accurate estimates of the SD and slope at LoD concentrations. However, these approaches require additional measurements to be undertaken (e.g. preparation and replicate analysis of further quality control samples at additional concentrations), which are not included in the existing method validation guidelines.

The magnitude of the influence of the assumptions (made when using the approach suggested above) depends on the analytical method (its linearity and scedasticity) and the distance between LLOQ from LoD. Whether this approach is suitable or whether the assumptions made are unacceptably large should, in our opinion, form a topic of further debate.

The approach proposed is only useful for experimentally determining the precision at a concentration BLQ, called here calculated LoD. A blank matrix should be fortified at this LoD concentration and the between-day variability should be estimated using 5 samples in 3 batches each. Using this approach may even result in a CV below the 20% limit for LLOQ. Yet, the estimated concentration at that level may potentially be very different from the nominal concentration in the fortified sample. The potential difference is principally a result of the extrapolation of the calibration curve (Figure 4). Therefore, the reported assay LoD should be the nominal/calculated concentration and the precision must be calculated using that calculated LoD.

The approach proposed above is not suitable for standard addition methods for endogenous compounds analysis.

Any concentration below the calculated LoD concentration should be reported as ‘below LoD of xx’ or ‘not detected’ which means that this analytical method cannot differentiate the concentration of this sample from a blank sample. For results between the measured LoD concentration and the LLOQ concentration, results could be reported as a numeric concentration with the caveats that (i) the concentration is below the validated LLOQ and (ii) the precision of these values was measured experimentally as XX % (CV).

Future perspective

There will always be studies that observe data BLQ. The goal is to minimise the impact of occurrence of BLQ data, thus maximising the utility of the whole dataset. For achieving this, pharmacometric modellers and bioanalytical scientists need to work together when designing study protocols. This will help to ensure that concentration ranges in PK/PD studies are, wherever possible, correctly anticipated in advance, and that assay sensitivity is calibrated accordingly.

If enough sample is left and the stability of the compound is acceptable, a new method validation with lower LLOQ is a viable option. Even a small fraction of BLQ data can be helpful in the estimation of PK and PD parameters, yet, when the imprecision of BLQ outweighs the benefits of using the data, new data needs to be generated to assure correct interpretation from the study concerned.

Where assay sensitivity is identified as being potentially problematic, in that a large proportion of points are under a standard study design are expected to be BLQ, it is incumbent on the

pharmacometrician to design an alternative sampling schedule that minimises the proportion of BLQ data.

BLQ data cannot be released and used for PK analysis without evaluation of the precision. In case the suggested approach of determination of variance at the LoD is used, data analysts have to make the final decision about the suitability of these data for PK analytical purposes and should incorporate the between-day variance into their PK model specification.

Incorporation of a consistent LoD definition, independent of the signal to noise ratio, into the bioanalytical method validation guidelines is encouraged and welcomed. In contrast to the arbitrarily assigned 20% CV accuracy and precision for the LLOQ, the LoD could become the solid mark for analytical performance. A set definition of variance limits for the LoD however, might not be a good way forward, as it applies very tight restrictions for successful method validations.

With a clear, but not too restrictive, approach for determining the LoD in place, releasing BLQ data can become a standard procedure in PK studies.

Certainly, the BLQ topic needs further exploration using data simulations and actual real data from different assays to establish the most suitable approach for incorporating BLQ data variability in PK analyses.

The following recommendations can therefore be made:

For bioanalytical laboratories:

- If proportion of BLQ data is large, and if possible, re-design and re-validate the assay, lowering LLOQ

- If assay reanalysis of the study samples is not possible, estimate assay LoD using the proposed approach
- After evaluation of the between-day precision of the LoD, release the BLQ data with experimentally acquired CV

For regulators:

- Incorporate the LoD into validation guidelines
- Accept and trust laboratory data if the set tests are conducted by allowing the data release and shift the decision-making about the usability of these data to data analysts

For pharmacometricians and clinicians:

- Provide enough information about the study design and expected analyte concentrations to support method accuracy, precision and reliability of the results that will be obtained.
- Use mathematical models to incorporate the variability and measurement uncertainty throughout PK modelling – reflecting larger variance at lower concentrations. This does not have to entail estimation per sample, as estimates can be calculated from the actual validation data, and/or quality control samples.
- PK/PD study sampling time points derived using optimal design or simulation-estimation should take into account the expected LOQ values.

Executive summary

Below Limit of Quantitation data

- BLQ data is an issue for many PK/PD analyses, particularly when studies are poorly-designed
- Historically the handling and release of BLQ data have been hampered by a lack of communication between bioanalytical chemists, clinicians and pharmacometricians
- BLQ data is unvalidated and unreliable for making individual decisions on individual samples

Regulations and Bioanalytical Method Validation Guidelines

- Method validation regulations should investigate the possibility of incorporating LoD and BLQ variability estimation into the procedure.

Bioanalytical Assays

- Assays are designed based on the information provided. Assay precision at LLOQ level can be well below 5% or close to 20%.
- Bioanalytical assays are not required to measure LoD and are not currently validated BLQ.
- If extra validation experiments are not done, no information about the precision of BLQ data is available.

BLQ Data Treatment

- When comparing multiple ways of treating censored BLQ data, using the actual BLQ values is known to be the most accurate.
- PK and PD analysis should account for the variance of the analytical method across the calibration range and also below this range.

Bridging the Divide

- The LLOQ is the lowest concentration at which accuracy and precision are measured. Below this concentration, variability likely becomes unacceptable for the specific sample. In the case of PK modelling, however, especially if there are a number of data points, the precision requirements can be less stringent.
- LoD estimation and evaluation of its precision is proposed and encouraged in order to use this information to facilitate appropriate handling of the BLQ data.
- It would then be possible for BLQ to be released with evaluated precision.
- The decision regarding whether and how to incorporate the BLQ data into a PK(/PD) model, and the justification for such decisions, should ultimately be the responsibility of the PK/PD analyst and not the analytical chemist.

Figure captions:

Figure 1. Pharmacokinetic model measured with 3 different analytical methods, each having a different LLoQ and different CV.

Figure 2. Variability of data measured at different concentrations using 3 different analytical methods. Distinct assays display different CV-increases below LLoQ.

Figure 3. Proposed workflow to evaluate the options for a study with BLQ data.

Figure 4. Estimation of LoD from assay validation data and the impact of linear extrapolation of BLQ data from two batch calibration curves.

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