Slide 1

# Censored Observations

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Slide 2

# The LOQ Problem

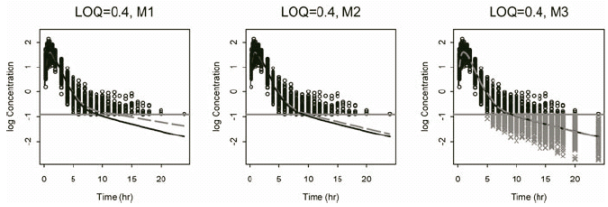


**Fig. 1** Illustration of effects of different methods of handling BQL data on estimation (Plots were made from the first replicate of simulations)

M1=Replace with zero; M2=YLO; M3= PHI()

Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2008;35(4):401-21.



Slide 3

# Unrealistic View of Measurements

M4 takes into account that a measurement cannot be negative [4] and an extra adjustment step to the likelihood is used with this method. The likelihood for an observation above the LOQ is the normal density function as in M3 but is conditioned on the fact that observations can only be positive (Eq. 7 in [4]). The likelihood for a BQL

The authors fail to understand the difference between the true value of concentration (which cannot be negative) and the measurement of a concentration which can be negative where there is additive residual error.

Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2008;35(4):401-21.

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# Beals' Method 2

```
$ESTIM METHOD=CONDITIONAL LAPLACIAN

$THETA
(0,1,) ; RUV_ADD Additive error mg/L
(0.0.1,); RUV_CV Proportional error
$SIGMA 1 FIX ; EPS1

$ERROR
ADD=THETA(1)
PROP=F*THETA(2)
SD=SQRT(ADD*ADD+PROP*PROP) ; Combined error model
LLOQ = 2 ; mg/L

YLO=LLOQ
Y = F + SD*EPS(1))
```

Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2008;35(4):401-21.



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# Method 2 (YLO) Example

```
$PK
CL=THETA(1)*EXP(ETA(1))
V=THETA(2)*EXP(ETA(2))
S1=V
$ERROR
; Limit of Quantification
(LOQ) is 1
; DV's below LOQ are given
; MDV=1 in dataset
; PR_Y (PRB) is probability
, that DV is > LOQ
YLO=1
PRB=PR_Y
Y = F+ERR(1)
$TABLE ID TIME PRB Y
```

```
#ID    TIME     DV      AMT   EVID     MDV
  .       .      .        .      .       .
  .       .      .        .      .       .
  .       .      .        .      .       .
  2       0      0      100      1       1
  2   0.333   2.47        0      0       0
  2       2   3.26        0      0       0
  2       6   2.32        0      0       0
  2  15.917   2.46        0      0       0
  2      24      0      100      1       1
  2      48      0      100      1       1
  2      72      0      100      1       1
  2  95.917   4.04        0      0       0
  2      96      0      100      1       1
  2   96.08   8.85        0      0       0
  2     120   3.16        0      0       0
# Last observation record (below) has DV<LLOQ
# (LLOQ = 1) and MDV = 1. This observation
# does not contribute to the -2LL estimate.
# However, probability that DV is > LLOQ can
# be tabled using PRB=PR_Y.
  2     168  0.163        0      0       1
```



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# Beals' Method 3

```
$ESTIM METHOD=CONDITIONAL LAPLACIAN

$ERROR
ADD=THETA(1)
PROP=F*THETA(2)
SD=SQRT(ADD*ADD+PROP*PROP) ; Combined error model
LLOQ = 2 ; mg/L
IF (DV.GE.LLOQ) THEN ; non BQL values
     F_FLAG=0
     Y = F + SD*EPS(1))
ELSE ; BQL values
     F_FLAG=1
     Y = PHI((LLOQ-F)/SD)
ENDIF
```

Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2008;35(4):401-21.

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# Beals' Method 4

```
$ESTIM METHOD=CONDITIONAL LAPLACIAN

$ERROR
ADD=THETA(1)
PROP=F*THETA(2)
SD=SQRT(ADD*ADD+PROP*PROP) ; Combined error model
LLOQ = 2 ; mg/L
IF (DV.GE.LLOQ) THEN ; non BQL values
     F_FLAG=0
     Y = F + SD*EPS(1))
ELSE ; BQL values
     F_FLAG=1
     CUMD  = PHI((LLOQ-F)/SD)
     CUMD0 = PHI(-F/SD)
     Y=(CUMD-CUMD0)/(1-CUMD0)
ENDIF
```

Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn. 2008;35(4):401-21.