



## **Workshop on ICH M10**

### **PC-02 - Choosing the right regression model**

**Lee Goodwin – on behalf of the EBF**

**14 November 2023 – Barcelona, Spain**

### 3.2.4. Calibration curve and range

....

- A simple regression model that adequately describes the concentration-response relationship should be used. The selection of the regression model should be directed by written procedures. The regression model, weighting scheme and transformation should be determined during the method validation. Blank and zero samples should not be included in the determination of the regression equation for the calibration curve. Each calibration standard may be analysed in replicate, in which case data from all acceptable replicates should be used in the regression analysis.

# Pre-meeting survey

	the question	Yes	No
Q1	Are you performing a validation data assessment to define your model for every assay?	2	28
Q2	If no, what are you defining as your "standard" model?		
Q3	If yes or deviating from your "standard" model, which fits are you assessing (linear, quadratic etc)		
Q4	If yes or deviating from your "standard" model, which weightings are you assessing (1/X, 1/X^2 etc)		
free text			

## Key message from the pre-meeting survey comments

- Almost all responding companies direct their standard regression model and weighting via a quality document
- Quality document directs linear  $1/x^2$  as standard model and weighting to be used if validation data fits this criteria
  - Deviation from this model and weighting driven if validation data does not fit acceptance criteria
- Alternative model tested, where required = quadratic
- Alternative weighting tested, where required = no weighting and  $1/x$

## Recommended "best or common" practice from responses

- Define standard regression model and weighting to be used via a quality document
  - If validation data meets criteria using this regression model and weighting, no further action needed
- For LCMS assays utilise linear model with  $1/x^2$  weighting as standard
- If validation criteria fails against standard model, choice of alternative model and/or weighting needs to be documented
  - Alternative model to be tested = quadratic
  - Alternative weighting tested =  $1/x$  (no weighting not recommended)



## Raw data from the pre-meeting survey comments

- In the next slides we provide the unredacted details from 56 survey files reaching us prior to the deadline.
- Surveys that have arrived after the deadline could not be included anymore, for logistic reasons. Please speak up if your comment wasn't already captured in the other 56 files

## Q1: Are you performing a validation data assessment to define your model for every assay?

- Y, as part of method development
- N, we go with linear  $1/x$  for MS/MS detection. With the modern equipment and a reasonable calibration range span it works
- N. Model is performed and confirmed on method development assays.

### Note: Individual comments

- A quadratic regression model could be also rarely applied (non-GLP studies only)
- few sponsors ask for an assessment (using least square method) and 100% of the time the best model is  $1/x^2$



## Q2: If no, what are you defining as your "standard" model?

- Linear, then quadratic+
- Linear  $1/x^2$  mentioned 14 times
- Easiest model according guideline
- $1/x$  for 2 decade calibration line.
- $1/x^2$  may be applied for 2.5 - 3 decade calibration line. Quadratic should be justified
- linear ,  $1/x$
- Linear weighted  $x^2$
- during method development, linear model is testing, first without regression, then  $1/x$  if needed, then  $1/x^2$  if needed
- more simply with lower bias for each standard
- Linear
- linear  $1/x$  for HPLC-MS/MS
- Development method define model

### Q3: If yes or deviating from your "standard" model, which fits are you assessing (linear, quadratic etc)

- linear Linear, then quadratic
- quadratic
- linear versus quadratic
- we only use linear
- depending on range and data set Linear and quadratic only
- Linear
- Quadratic

## Q4: If yes or deviating from your "standard" model, which weightings are you assessing ( $1/X$ , $1/X^2$ etc))

- only  $1/X$ ,
- $1/X^2$  mentioned 5 times
- $1/x$ , or  $1/x^2$
- .Reall time to do.
- in my view no weighing.  $1/x/ 1/x^2 1/y$  etc..a re the same complexity (i.e. none!)
- Just keep consistency
- depending on range and data set  $1/x$ ,  $1/x^2$
- Choose the simplest one if applicable
- $1/X$ ,  $1/X^2$
- $1 1/x$  and  $1/x^2$