Sense and nonsense of a geometric or arithmetic mean medium QC

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on behalf of the EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

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http://www.europeanbioanalysisforum.eu

The QC Problem/Challenge/Issue

Quality control (QC) sample (EMA definition)

A spiked sample used to monitor the performance of a bioanalytical method and to assess the integrity and validity of the results of the unknown samples analysed in an individual batch.

Sample Analysis - 3 QC levels:

- QC-LO (within 3xLLOQ; no debate)
- QC-ME (somewhere in some middle; mismatch industry practice & guidance/guideline)
- QC-HI (at least 75% of ULOQ; no debate)

Method Validation – 3 QC levels + LLOQ (+ ULOQ):

- Similar to above (iaw: QC-ME)

What is in the guidelines:

EMA 2011: within three times the LLOQ (low QC), around 30 - 50% of the calibration curve range (medium QC), and at least at 75% of the upper calibration curve range (high QC)

ANVISA 2012: amostra de controle de qualidade de média concentração (amostra de CQM): amostra de matriz adicionada do analito em concentração próxima à média entre os limites inferior e superior de quantificação *(Medium-concentration quality control sample (CQM sample): Matrix sample of the analyte in a concentration close to the mean between the Lower and upper quantification)*

FDA 2013 draft: one within three times the LLOQ (low QC), one in the midrange (middle QC), and one approaching the high end (high QC) of the range of the expected study concentrations

MHLW 2012 Chromatography: The low-level should be within 3 times the LLOQ, the mid-level is around the midpoint on the calibration curve, and the high-level should be at least 75% of the upper limit of the calibration curve

MHLW 2013 LBA: The low-level should be within 3 times the LLOQ, the mid-level is near the midpoint on the calibration curve, and the high-level should be at least one-third of the ULOQ of the calibration curve

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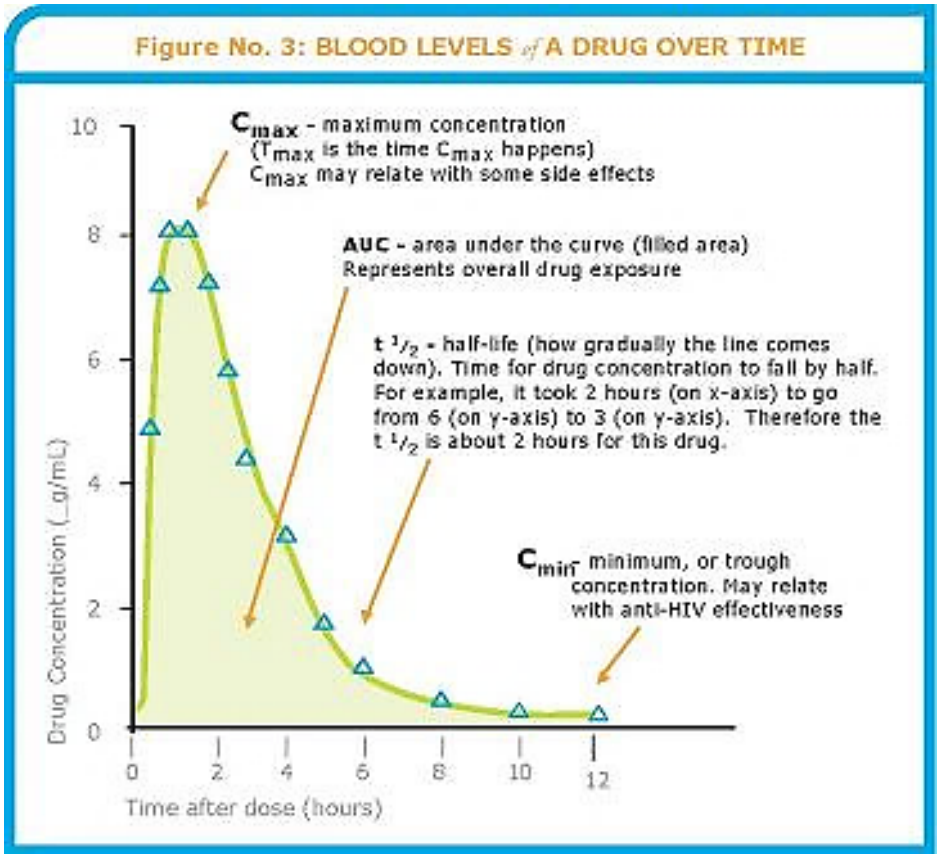
Pharmacokinetics: what is important

Conc	Cmax	AUC0-t	AUC0-∞	t1/2	Cmin
1					
2					
5					
10					
20					
50					
100					
200					
500					
1000					

Adequately high level of accuracy and precision is important over the entire concentration range !



Just an example of a PK study

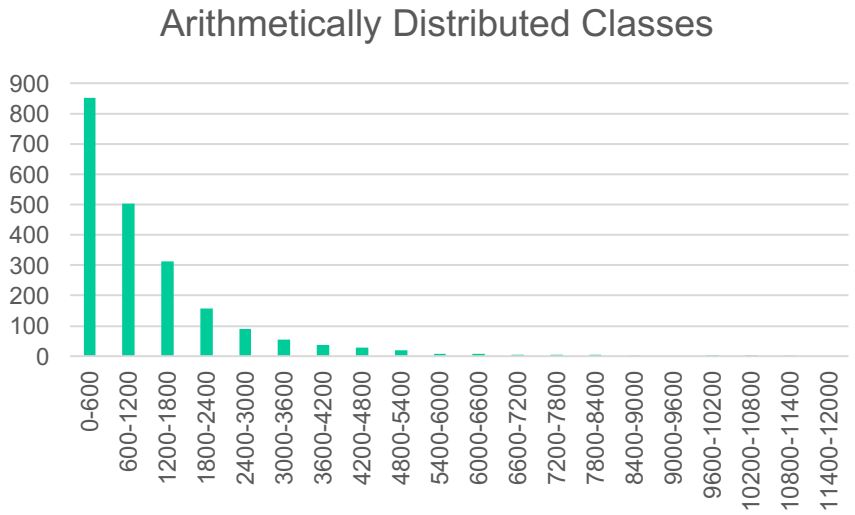
Arithm	Geom
0	Blank
	50
	100
	200
	500
	1000
2000	2000
4000	
	5000
6000	
8000	
10000	10000
12000	
14000	
16000	
18000	
20000	20000

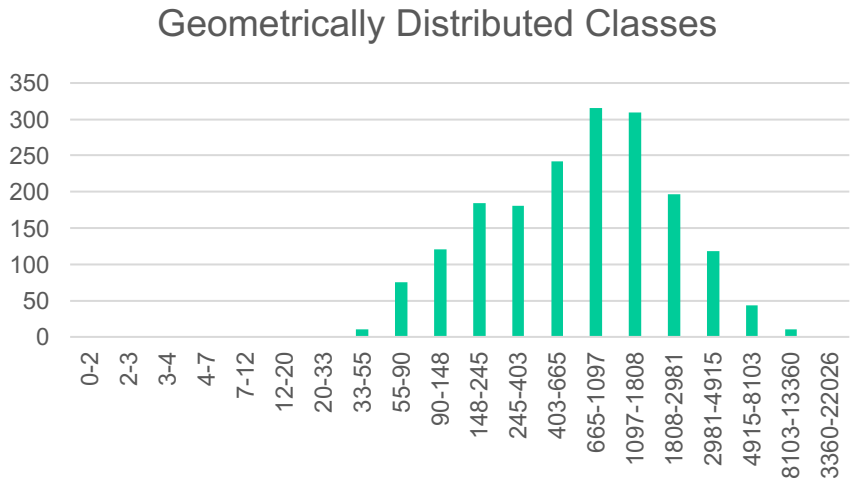
qd, bid & tid SD/MD study, N=36

2664 samples

Range 50-20000 pg/ml

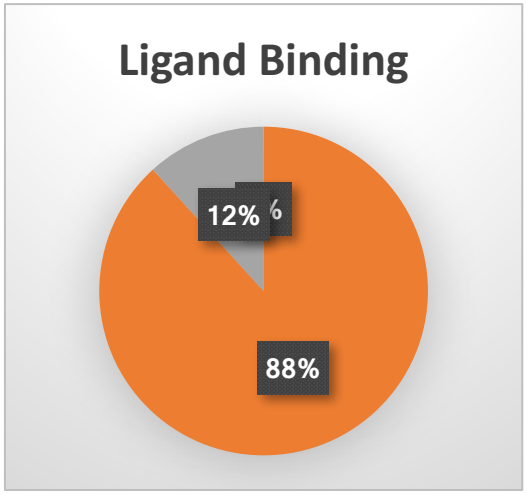
Where to place (how to distribute) the Cals?

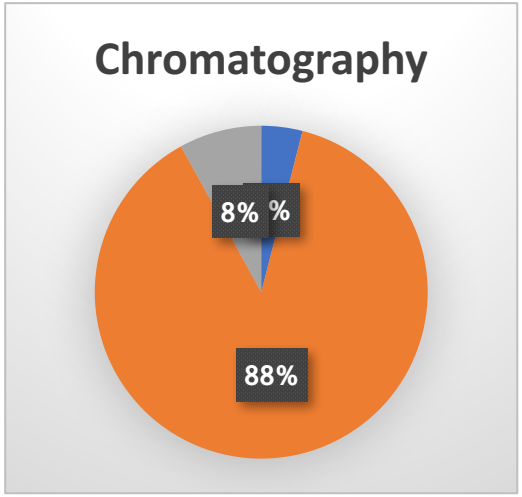




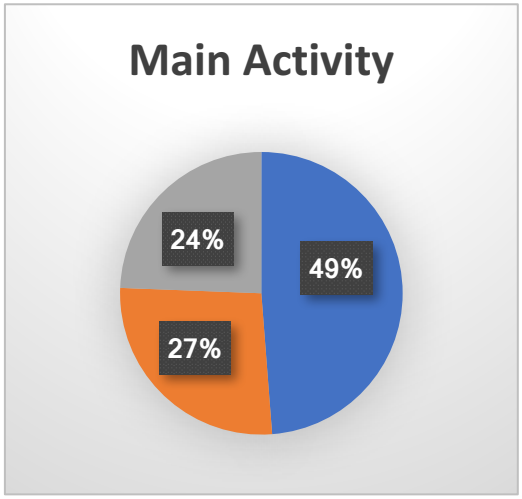
What we (the EBF community) do:

How do you distribute the concentrations of your calibration standards?





- Pedominantly use an arithmetical distribution
- Predominantly use a geometrical distribution
- Use both arithmetical and geometrical distributions



- Small molecules/ chromatography
- Large molecules/LBA
- Both chromatography and LBA

N=37, 17 European portfolio & 20 Global portfolio

Just an example of a PK study

qd, bid & tid SD/MD study,
N=36, 2664 samples

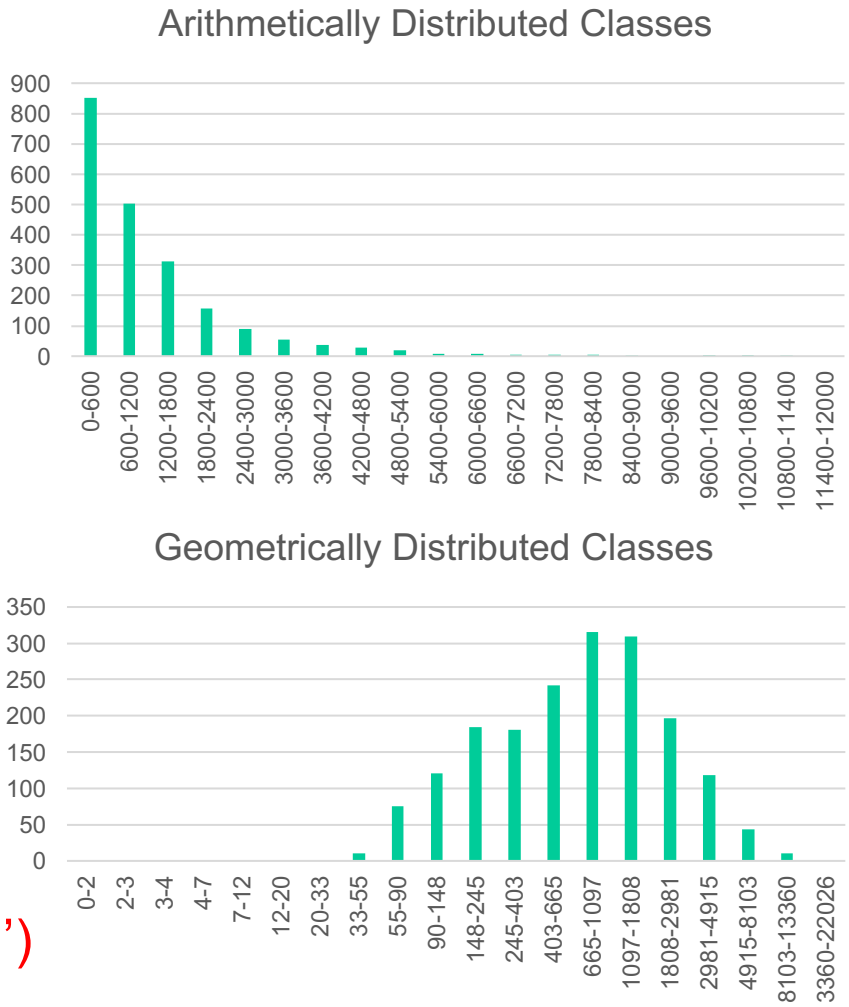
Range 50-20000 pg/ml

Where to put the QCs?

QC-LO: 100-150 pg/ml
QC-HI: 15000-16000 pg/ml

QC-ME:

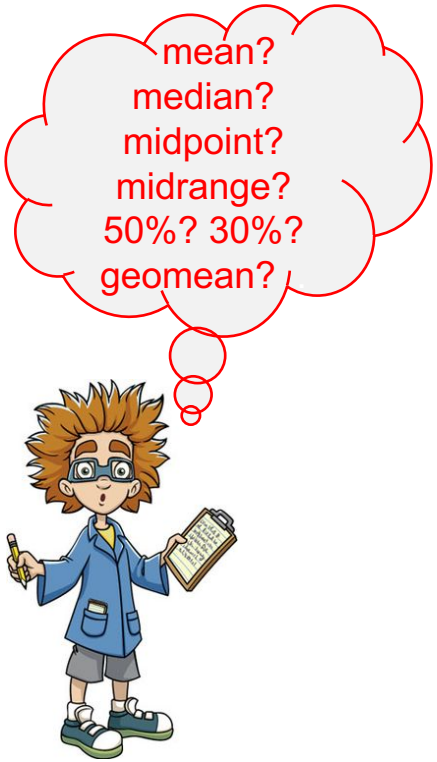
? 1000 pg/ml (geomean)
or 6000 pg/ml (30%)
or 10000 pg/ml (50% / mean')
or ….



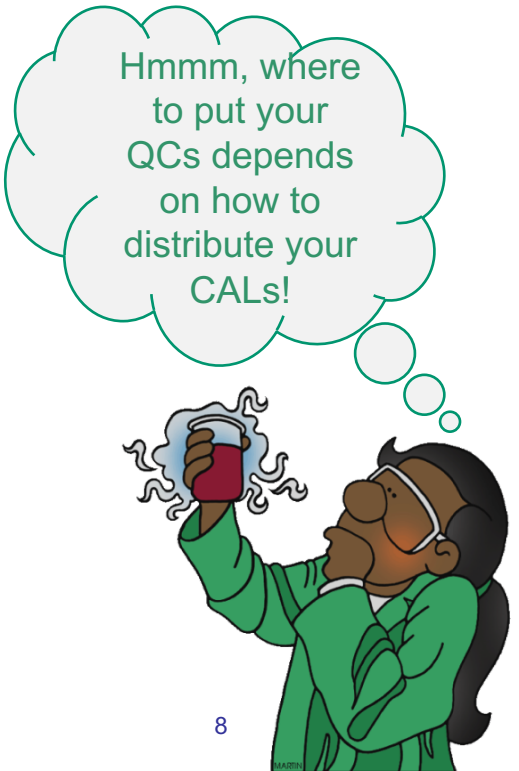
Mean, Midpoint, Midrange, 30-50%

Range 1-1000, 10 Cals

Calibration Standards	Mean	Midpoint	Midrange	30-50%
Arithmetically Distributed	500	500	500	300-500
Geometrically Distributed	501	20-50	20-50 or 500	300-500



Arithmetically Distrib Cals			Geometrically Distrib Cals		
Cal	QC-Arithm	QC-Geo	Cal	QC-Arithm	QC-Geo
0			Blank		
100			1		
200	QC-LO	QC-LO QC-ME	2	QC-LO	QC-LO
300			5		
400			10		
500	QC-ME		20		QC-ME
600			50		
700			100		
800	QC-HI	QC-HI	200		
900			500	QC-ME QC-HI	QC-HI
1000			1000		

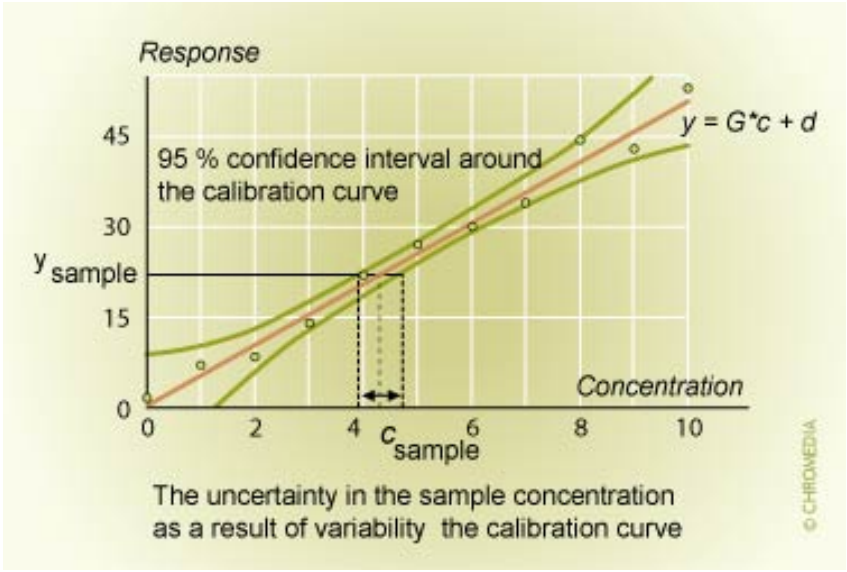


The error distribution

Fitting of calibrator response data to concentration is usually done using the ‘Least Squares’ approximation. The best fit in the least-squares sense minimizes the sum of squared residuals (the difference between an observed value, and the fitted value provided by a model).

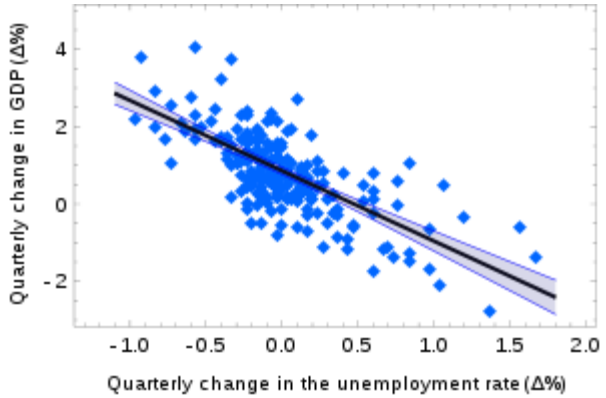
A prerequisite is that the variance in response (y) is similar for each of the concentrations (x). Log transformation e.g. or weighting is thus often necessary for large x ranges.

The parameters of the model, e.g. a and b in y = a + bx, are estimates and have a random error and therefor have a confidence interval (CI).



$$s_{\hat{\alpha}} = s_{\hat{\beta}} \sqrt{\frac{1}{n}\sum_{i=1}^{n} x_i^2} = \sqrt{\frac{1}{n(n-2)}\left(\sum_{j=1}^{n} \hat{\varepsilon}_j^{\,2}\right) \frac{\sum_{i=1}^{n} x_i^2}{\sum_{i=1}^{n}(x_i - \bar{x})^2}}$$

$$s_{\hat{\beta}} = \sqrt{\frac{\frac{1}{n-2}\sum_{i=1}^{n} \hat{\varepsilon}_i^{\,2}}{\sum_{i=1}^{n}(x_i - \bar{x})^2}}$$



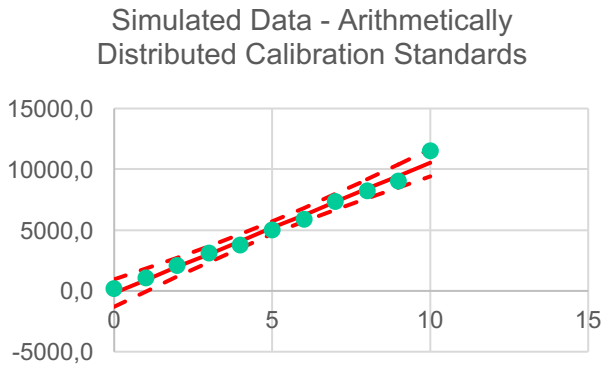
Where to place your QCs

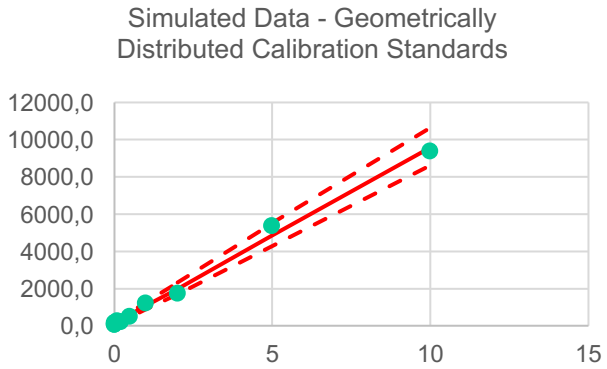
Confidence interval depends on the distribution of the calibrators. For both arithmetically spersed as well as weighted or log-transformed geometrically spaced CALs the CI is the widest at the extremes.

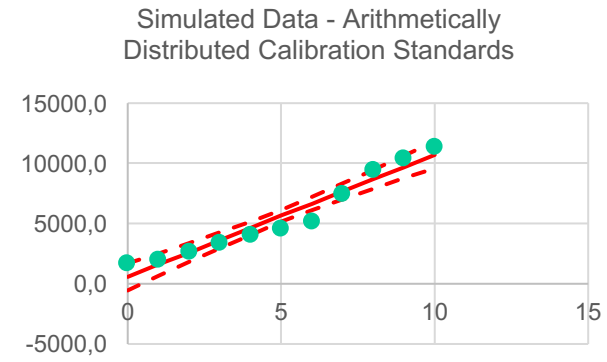
It makes perfect sense to have a QC-LO at the lower end and a QC-HI at the higher end of the curve.

… the CI is the narrowest at the (transformed or weighted) center of gravity the curve (x-mean,y-mean)….

There is little added value in having a QC-ME in the curve. However smart placing can help detecting lack of fit.

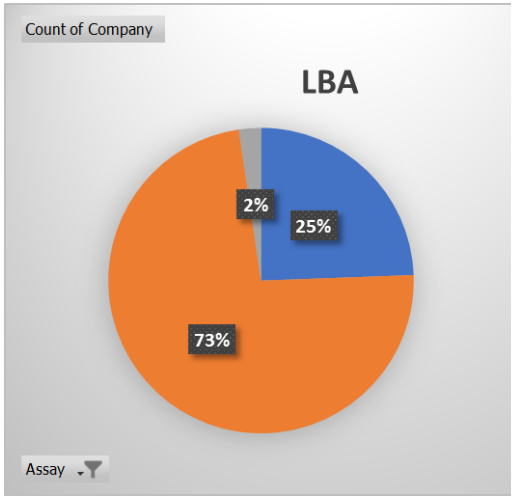


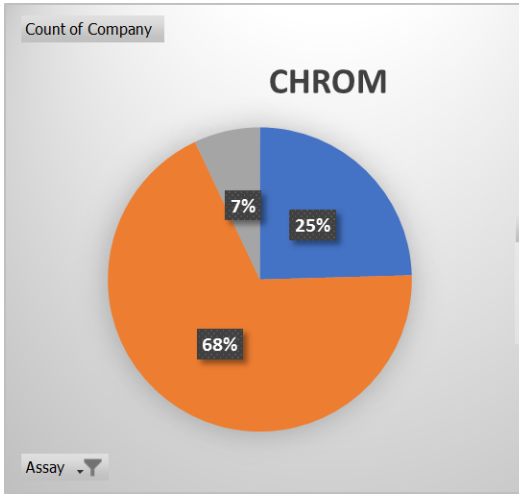




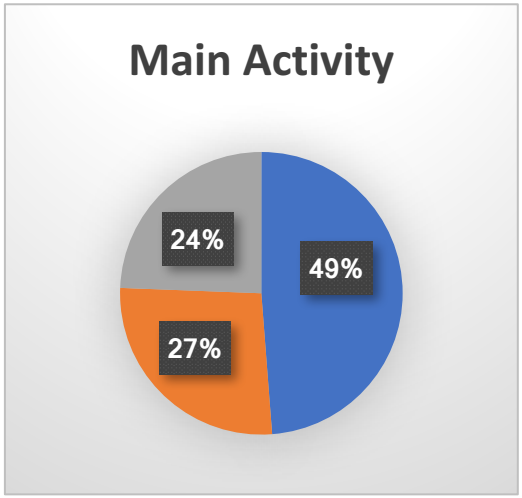
What we (the EBF community) do:

Where do you place the QC-ME relative to the calibration standards?





MQC 50%
MQC Geo
Other



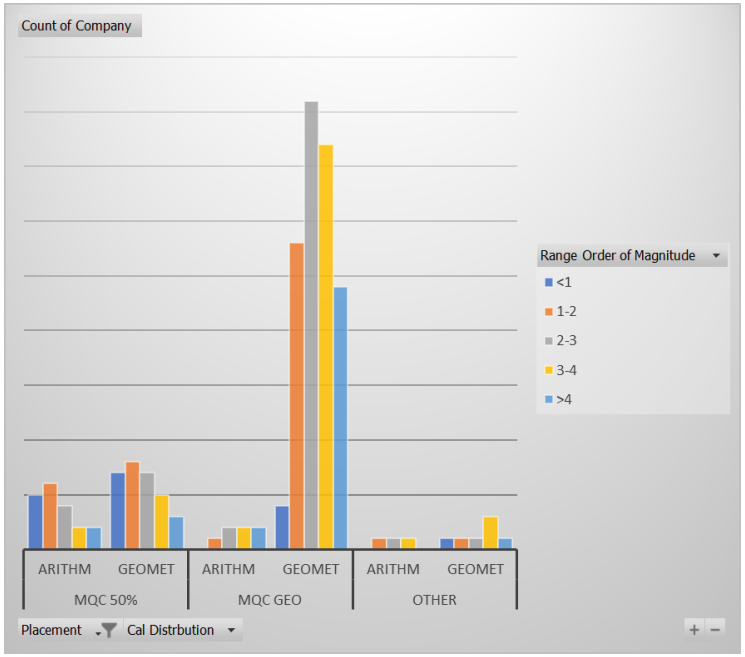
Small molecules/ chromatography
Large molecules/LBA
Both chromatography and LBA

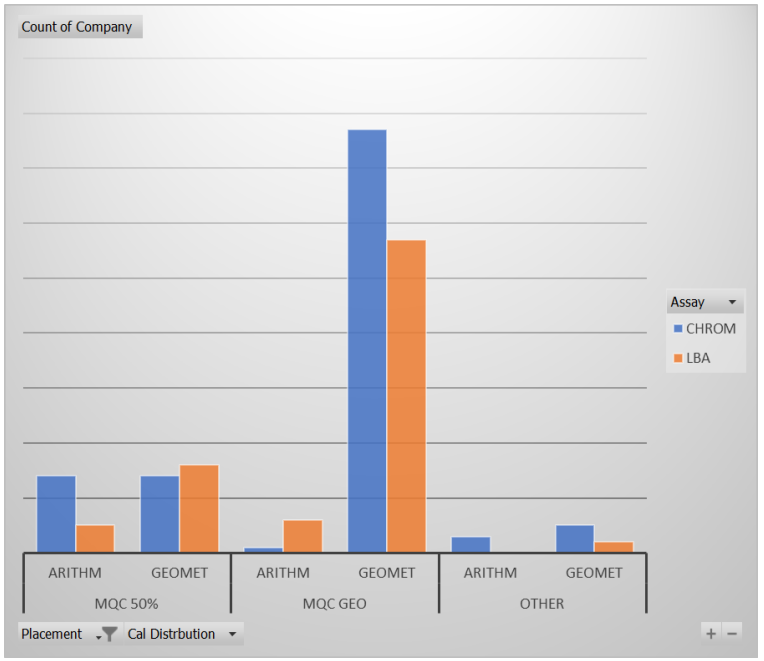
N=37, 17 European portfolio & 20 Global portfolio

Zooming in: what we do

Predominantly a QC-ME at around the geomean of the range of geometrically distributed calibration standards spanning about 3 orders of magnitude.

A QC-ME at around 50% is occasionally used for shorter ranges and/or arithmetically distributed calibration standards.





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Stating & Concluding that:

- The purpose of fitted calibration curves is to relate response to concentration
- The distribution and range of calibration standards can best be similar to the range and distribution of expected sample concentrations
- The purpose of QCs is to control/manage the quality of analysis batches
- Low and High level QCs express the quality of the assay whereas a Mid level QC could express the suitability of the calibration model provided it is placed wisely along the range

Implies that for the most commonly used geometrically distribute calibration standards:

- A mid level QC at 50% of the highest calibrator gives no extra information on assay performance and will usually always pass and is therefor a waste of effort and materials
- A mid level QC at 50% of the highest calibrator may incidentally give a false positive outcome (4:6:15 / 4:6:20)
- Ambiguity in number and placement of QCs (some labs use 5 levels in production batches) leads to increased costs, timelines and unethical increased use of blank matrices while it is unrelated to the safety and efficacy of medicines

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Recommendation

- Geometrically distributed calibration standards: place QC-ME at about the geomean of the lowest and highest standard
- Arithmetically distributed calibration standards: place QC-ME at about the mean of the lowest and highest standard
- Distribute your calibration standards in a geometrically fashion for large(r) concentration spans and arithmetically for short(er) ranges

Arithmetically Distrib Cals			Geometrically Distrib Cals		
Cal	QC-Arithm	QC-Geo	Cal	QC-Arithm	QC-Geo
0			Blank		
10			1		
20	QC-LO	QC-LO QC-ME	2	QC-LO	QC-LO
30			5		
40			10		
50	QC-ME		20		QC-ME
60			50		
70			100		
80	QC-HI	QC-HI	200		
90			500	QC-ME QC-HI	QC-HI
100			1000		

Acknowledgement

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