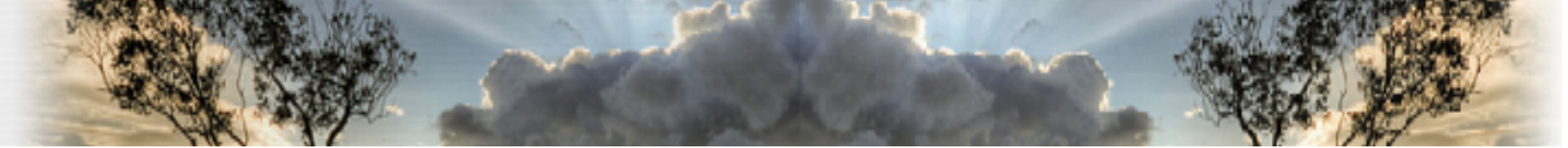

ICH M10 2019 and FDA BMV 2018

Boris Gorovits

Calibration curve and QCs

Section / Line	ICH M10	FDA BMV	comment
Line 317	The calibration curve should be prepared using freshly spiked calibration standards in at least one assessment. Subsequently, frozen calibration standards can be used within their defined period of stability	Freshly prepared QCs are recommended for precision and accuracy analyses during method development, as stability data are generally not available at this time	ICH M10 language adds clarity
3.2.5.1 Preparation of Quality Control samples Line 327	Calibration standards and the QCs may be prepared from the same stock solution, provided the accuracy and stability of the stock solution have been verified	The sponsor should use freshly prepared **c**alibrators and QCs in all A & P runs. Use of freshly prepared QCs in all A & P runs is preferred; however, if this is not possible, the sponsor should use freshly prepared QCs in one or more A & P runs	

Stability

Section / Line	ICH M10	FDA BMV	comment
LCMS 3.2.8 Long-Term matrix stability Line 451	For chemical drugs, it is considered acceptable to extrapolate the stability at one temperature (e.g., -20°C) to lower temperatures (e.g., -70°C). For biological drugs, it is acceptable to apply a bracketing approach, e.g., in the case that the stability has been demonstrated at -70°C and at -20°C, then it is not necessary to investigate the stability at temperatures in between those two points at which study samples will be stored.	**Long-term stability:** The sponsor should determine the long-term stability of the sample over a period of time equal to or exceeding the time between the date of first sample collection and the date of last sample analysis. The storage temperatures studied should be the same as those used to store study samples. Long-term stability QCs should be compared to freshly prepared calibration curves and QCs. Determination of stability at minus 20ºC would cover stability at colder temperatures	The idea of potential instability at very low temps is still there. Why? Good to see that no additional stability assessment is requested between (-20C) and (-70C)

Anchor Points

Section / Line	ICH M10	FDA BMV	Comment
LBA 4.2.3 Calibration curve and range Line 710	A calibration curve should be generated with at least 6 concentration levels of calibration standards, including LLOQ and ULOQ standards, plus a blank sample. The blank sample should not be included in the calculation of calibration curve parameters. Anchor point samples at concentrations below the LLOQ and above the ULOQ of the calibration curve may also be used to improve curve fitting.	**Calibration Curve** For LBAs, in addition to the calibration standards, anchor points outside the range of quantification can facilitate the fitting of the curve. Anchor points should not be used as part of the acceptance criteria for the run. **Table 1: Acceptance Criteria for BMV and in-Study Conduct** Anchor points should not be included in the curve fit.	BMV statement is confusing. ICH M10 language adds clarity

Additional QCs. Calibration range

Section / Line	ICH M10	FDA BMV	Comment
LCMS 3.3.3 Calibration Range Line 563	At the intended therapeutic dose(s), if an unanticipated clustering of study samples at one end of the calibration curve is encountered after the start of sample analysis, the analysis should be stopped and either the standard calibration range narrowed .. existing QC concentrations revised, or QCs at additional concentrations added to the original curve within the observed range .. The same applies if a large number of the analyte concentrations of the study samples are above the ULOQ. The calibration curve range should be changed, if possible, and QC(s) added or their concentrations modified. If it is not possible to change the calibration curve range or the number of samples with a concentration above the ULOQ is not large, samples should be diluted according to the validated dilution method.	**B: Bioanalytical Parameters of CCs and LBSs. Dilution Effect** If the method measures diluted samples, the integrity of the dilution should be monitored during validation by diluting QC samples above the ULOQ with like matrix to bring to within quantitation range, and the accuracy and precision of these diluted QCs should be demonstrated. **C. Validated Methods** If the study sample concentrations are clustered in a narrow range of the standard curve, additional QCs should be added to cover the sample range. If the additional QC concentrations are not bracketed by QCs validated before the study, the accuracy and precision of the additional QCs should be demonstrated before continuing with the analysis.	ICH M10 statement is not very clear – “number of samples that are above ULOQ is not large”? What is the reason to expand calibration curve range if dilution linearity was successfully demonstrated during validation? BMV language adds flexibility

Use of Multiple Replicates

Section / Line	ICH M10	FDA BMV	Comment
LBA 4.2 Validation Line 659	When using LBA, study samples can be analysed using an assay format of 1 or more well(s) per sample. The assay format should be specified in the protocol, study plan or SOP. If method development and assay validation are performed using 1 or more well(s) per sample, then study sample analysis should also be performed using 1 or more well(s) per sample, respectively. If multiple wells per sample are used, the reportable sample concentration value should be determined either by calculating the mean of the responses from the replicate wells or by averaging the concentrations calculated from each response. Data evaluation should be performed on reportable concentration values.	No mention of potential use of a single well	ICH M10 offers a clear step forward

LBA: Critical Reagents

Section / Line	ICH M10	FDA BMV	Comment
LBA 4.1.2 Critical Reagents Line 636	Reliable procurement of critical reagents, whether manufactured in-house or purchased commercially, should be considered early in method development. The data sheet for the critical reagent should include at a minimum identity, source, batch/lot number, purity (if applicable), concentration (if applicable) and stability/storage conditions Retest dates and validation parameters should be documented in order to support the extension or replacement of the critical reagent. Stability testing of the reagents should be based upon the performance in the bioanalytical assay and be based upon general guidance for reagent storage conditions and can be extended beyond the expiry date from the supplier. The performance parameters should be documented in order to support the extension or replacement of the critical reagent.	**B. Bioanalytical Parameters of CCs and LBAs** 1. Reference Standards and Critical Reagents The sponsor should appropriately characterize and document (e.g. determine the identity, purity, and stability) all reference standards and critical reagents, such as antibodies, labeled analytes, and matrices and store them under defined conditions The sponsor should appropriately characterize and document (i.e., determine the identity, purity and stability) the critical reagents, including – but not limited to – any reference standards, antibodies, labeled analytes, and matrices.	ICH M10 is more definitive on Critical Reagent characterization and stability

Brief Mentions – 1

Section / Line	ICH M10	FDA BMV	Comment
7.4 Minimum Required Dilution	<only?> Partial validation is requested when MRD is change.		ICH M10 - most likely a full validation needed?
7.6 New or Alternative Technologies	Data from previous platform should be cross validated to the new platform	… data should be bridged .. best is to assess the output of both methods with a set of incurred samples .	ICH M10 doesn't propose use of incurred samples
Selectivity. LCMS: 3.2.1 Line 233 LBA: 4.2.2 Line 697	Selectivity should be evaluated in lipaemic samples and haemolysed samples	.. the impact of hemolyzed samples, lipemic samples, or samples from special populations can be included in the selectivity assessment	ICH M10 has less flexibility vs. BMV
Frozen Calibrator LBA: 4.2.3 Line 725	If freshly spiked calibration standards are not used, the frozen calibration standards can be used within their defined period of stability	If a bulk frozen calibration curve was used for the original analysis, then it is acceptable to use a frozen curve for the ISR evaluation	ICH M10 offers slightly more definition

Brief Mentions – 2

Section / Line	ICH M10	FDA BMV	Comment
QCs for the P&A test LBA: 4.2.4 Accuracy and Precision Line 735	LLOQ, low QC (3xLLOQ), around the geometric mean of the calibration curve range (medium QC), and at least at 75% of the ULOQ (high QC) and at the ULOQ	**LCMS:** LLOQ, low QC (3xLLOQ), mid (M: defined as mid-range), high QC (defined as high-range) **LBA:** LLOQ, L, M, H, and ULOQ	Mid QC definition in the ICH M10
7.2 Parallelism Line 1129	Although lack of parallelism is a rare occurrence for PK assays, parallelism of LBA should be evaluated on a case-by-case basis	**In Study analysis:** Parallelism should be conducted if not done during validation.	ICH M10 offers more flexibility