ICH-M10: JBF Workshop Report - Consideration from JBF

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on behalf of the Japan Bioanalysis Forum (JBF)

SCAS Sumika Chemical Analysis Service

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ICH-M10: JBF Workshop

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No.of participants: 62 (from 31 companies)

Section	JBF Comment	Suggested Changes
Page: 4 Line: 103 1.3 Scope	It is unclear what the term “pivotal nonclinical PK studies” implies. Based on the fact that nonclinical PK studies are outside the scope of JP and EMA BA guidelines and that there are diverse aspects for the “pivotal” study among in vivo/in vitro studies conducted in phases of drug development, the term “pivotal PK” should be changed or omitted.	*Replace with:* The guideline is applicable to the validation of bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples (e.g., blood, plasma, serum, other body fluids or tissues) obtained in nonclinical TK studies and in all phases of clinical trials in regulatory submissions. Validation items should be appropriately selected/conducted for the purpose of the measurement, e.g., Selectivity or Matrix Effect in hyperlipidemia plasma is not applicable in nonclinical studies.
Page: 9 Line: 223 3.2.1 Selectivity	Investigation of the selectivity of haemolysed matrices is acceptable because haemolysis could occur at the step of blood collection. It is a limited case that the study samples are the lipaemic matrices; however, selectivity will be estimated if there are any doubts.	*Replace with:* In clinical studies, selectivity should be estimated, if necessary, in case the study samples are expected to be lipaemic matrices. For the investigation of selectivity in lipaemic matrices at least one source of matrix is used. To be scientifically meaningful, the matrix used for these tests should be representative as much as possible of the expected study samples. A naturally lipaemic individual with abnormally high levels of triglycerides should be obtained from donors. Although it is recommended to use lipaemic matrix from donors, if this is difficult to obtain, it is acceptable to spike matrix with triglycerides even though it may not be representative of study samples.
Page: 10 Line: 273 3.2.3 Matrix Effect	Because the matrix effect is evaluated by individual differences, it was not necessary to estimate the accuracy and precision in triplicate assessment from one source.	*Replace with:* The matrix effect should be evaluated by analysing at least one replicate at every individual/lot of low and high QCs, each prepared using matrix from at least 6 different sources/lots and by mean accuracy and precision from observed concentration at each concentration. The accuracy should be within ±15% of the nominal concentration and the precision (percent coefficient of variation (%CV)) should not be greater than 15% in all individual matrix sources/lots.
Page: 10 Line: 278 3.2.3 Matrix Effect	Evaluation of the matrix effect in relevant patient populations or special populations should be recommended only when it is expected that these samples could be obtained during clinical development. The timing of the matrix effect evaluation using such samples should not be limited to the preanalytical validation, and it can be conducted as a partial validation.	*Replace with:* The evaluation of matrix effect ~~should also be evaluated~~ in relevant patient populations or special populations (e.g., hepatically impaired or renally impaired) is recommended when these samples are expected to obtain during clinical development. An additional evaluation of the matrix effect is recommended using haemolysed or lipaemic matrix samples during method validation (or partial validation) on a case-by-case basis, especially when these conditions are expected to occur within the study.
Page: 14 Line: 403 3.2.8 Stability	It is practically difficult to implement as described. In addition, we believe that in this case it is enough to evaluate only the selectivity. It is considered that a drug that exists only in a small amount in the biological matrix may not affect the stability of other drugs. In the experience of companies participating in the JBF conference, there has been no case where the drug stability was affected by coexisting drugs. If it is absolutely necessary to evaluate the stability of the sample, we would like to request that the tests to be evaluated be limited.	[1st Suggestion] *Delete this sentence* [2nd Suggestion] *Replace with:* When there is a concern about the impact on the stability of coexisting analytes, for example, the analyte in the actual sample significantly changes the matrix properties such as pH or causes a chemical reaction with other analytes, it is recommended that the stability test of each analyte be performed using a matrix containing all the analytes. [3rd Suggestion] *Replace with:* In the case of a fixed combination drug or a specific drug regimen in which multiple analytes are present in the actual sample, it is recommended that the stability test of each analyte be performed using a matrix containing all the analytes.
Page: 16 Line: 457 3.2.8 Stability	Based on the description of “In addition, the following test should be performed if applicable,” we interpreted that assessment of “whole blood stability” is not mandatory. Moreover, based on the description of “subjects,” we interpreted that it is limited to validations performed for clinical trials. Please clarify these two points.	*Replace with:* Moreover, the following test is recommended to be performed when there is a concern about whole blood stability due to the structure of the analyte. 6) Whole blood stability For clinical trials, sufficient attention should be paid to the stability of the analyte in the sampled matrix (blood) directly after collection from subjects and prior to preparation for storage to ensure that the concentrations obtained by the analytical method reflect the concentrations of the analyte in the subject’s blood at the time of sample collection.
Page: 18 Line: 535 3.3.2 Acceptance Criteria for an Analytical Run	Sample dilution is not limited to reanalysis. If dilution integrity has been assessed in the validation study, it is not necessary to analyze the dilution QC in sample analysis. Even if dilution QC is analyzed in the sample analysis, it is not necessary to verify precision.	*Replace with:* In the case that study samples are analyzed with dilution, dilution integrity needs to be verified in validation study before sample analysis or in the sample analysis. In the validation study before sample analysis, dilution integrity should be verified for dilution factors to be used in the sample analysis. If dilution integrity is not verified before sample analysis, dilution QCs should be included and their integrity should be verified in the sample analysis. The concentration of the dilution QCs should exceed that of the study samples being diluted (or of the ULOQ) and they should be diluted using the same dilution factor.
Page: 18 Line: 546 3.3.2 Acceptance Criteria for an Analytical Run	Since quality control is performed within each analytical run, between-run analysis is considered as unnecessary. No criterion is necessary even if an analysis is to be performed. It is considered as *excessive* to reject the data despite the quality control within the analytical run meeting the criteria.	*Delete this section*
Page: 18 Line: 553 3.3.3 Calibration Range	It is desired to set the calibration range as wide as possible to correspond to various clinical studies for a long-term drug development. "a narrow range of analyte concentrations of the study samples" should be evaluated in whole clinical studies, not in an analytical batch or in a single study. So, a phase I dose-escalation study is not considered to be included in this objective because it is described as “at the intended therapeutic dose(s)." Moreover, in the discussion at the JBF M10 workshop, there were several opinions that the quantitative performance within the calibration range have already been evaluated by a validation study.	*Replace with:* If a narrow range of primary analyte concentrations of the study samples is known or anticipated before the start of study sample analysis, it is recommended to either narrow the calibration curve range, adapt the concentrations of the QCs, or add new QCs at different concentration levels as appropriate to adequately reflect the concentrations of the study samples. In a clinical study using ~~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 (i.e., partial validation), existing QC concentrations revised, or QCs at additional concentrations added to the original curve within the observed range before continuing with study sample analysis. *～～same as the original document～～* At least 2 QC levels should fall within the range of concentrations measured in study samples. If the calibration curve range is changed, the bioanalytical method should be revalidated. However, these actions should not be considered in a single analysis study but should be evaluated throughout clinical studies.
Page: 33 Line: 1013 6.2 Cross Validation	Study sample analysis may have a higher ability to detect any difference between the assays or laboratories, but it may be difficult to analyze using them due to limitations (lack of consent or insufficient sample volume, etc.). We recommend that cross-validation should be assessed by measuring the study samples or QCs.	*Replace with:* Cross validation should be assessed by measuring the same set of QCs (low, medium, and high) in triplicate ~~and~~ or study samples that span the study sample concentration range (if available n≥30) both assays or in both laboratories.
Page: 37 Line: 1119 7.1.5 Accuracy and Precision	In case of high concentration of the endogenous substance in the blank sample is determined, additional concentration (nominal concentration) in the spiked samples may be included in the error range. Therefore, it is recommended that accuracy be calculated using one of two formulas as described in the proposed text.	*Replace with:* It is recommended that accuracy be calculated using one of the following two formulas: Accuracy (%) =100 × (Measured concentration of spiked sample−endogenous concentration) / Nominal concentration or Accuracy (%) =100 × (Measured concentration of spiked sample / (Nominal concentration + concentration in the blank sample)

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