Consideration from JBF
for requirements specific to chromatographic assays

Masanari Mabuchi
Mitsubishi Tanabe Pharma,
On behalf of Japan Bioanalysis Forum(JBF)

Background

- JBF steering committee members opinion base on the English version.

BIOANALYTICAL METHOD VALIDATION
M10
Draft *version* Endorsed on 26 February 2019
Currently under public consultation

- Japanese authority will publish the Japanese translated version.

3.2.1 Selectivity (1)

L230

- Responses detected and attributable to interfering components should not be more than 20% of the analyte response at the LLOQ and not more than 5% of the IS response in the LLOQ sample for each matrix.

IS response used for selectivity need not be limited to LLOQ samples.

- Change to: "… should not more than 20% of analyte response at the LLOQ and not more than 5% of IS response ~~in the LLOQ sample~~ for each matrix."

3.2.1 Selectivity (2)

L233

- For the investigation of selectivity in lipaemic matrices at least one source of matrix should be used..

Lipaemic matrices may affect quantitative values even if there is no problem in selectivity.

- It is appropriate to evaluate by matrix effect for the effect of lipaemic samples.
- Selectivity using lipaemic matrices is preferred for optional implementation.

3.2.2 Specificity

L250

- …, or concomitant medications that are expected to be used in the treatment of patients with the intended indication).

The number of concomitant medications is enormous, and it is not realistic to evaluate with all their metabolites.

- Only combination drugs and frequently used drugs should be evaluated.

3.2.5.2 Evaluation of Accuracy and Precision

L346

- If the within-run accuracy or precision criteria are not met in all runs, an overall estimate of within-run accuracy and precision for each QC level should be calculated.

Change to: If any within-run accuracy or precision are not met criteria, ...

- What is the difference between “overall estimate of within-run” and “between-run”?

3.2.8 Stability (1) >ULOQ

L399

- If the concentrations of the study samples are consistently higher than the ULOQ of the calibration range, the concentration of the high stability QC should be adjusted to reflect these higher concentrations.

The scientific rationale is understandable, but in practice, there is concern of significant delay in case the analytical report is not finalized until the stability of higher QC is guaranteed.

3.2.8 Stability (2) co-exiting drug L403

- If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix should be conducted with the matrix containing all of the analytes.

JBF Tasks pile up whenever concomitant medications are added and added

- It is not the target for stability assessment if the co-existing substance is not the analyte.
- It is considered that stability can be evaluated in the same way whether the analyte is present alone or co-existing in the matrix.

3.2.8 Stability (3) IS solution

L414

- if no isotope exchange occurs for the stable isotope-labelled IS under the same storage conditions as the analyte for which the stability is demonstrated, then no additional stability determinations for the IS are necessary.

It is difficult to show no isotopic exchange, but it is necessary that it does not affect the sample analysis.

- It can be applied if the stable isotope(e.g. ^{13}C or ^{15}N) labeled in the chemical skeletal structure.

3.2.8 Stability (4) in blood

L463

- If the matrix used is plasma or serum, the stability of the analyte in blood should be evaluated during method development (e.g., using an exploratory method in blood) or during method validation. The results should be provided in the Validation Report.

JBF Acceptable both exploratory method using blood and validated method using plasma/serum.

- The result could be provided in the validation report only by referencing data of method development.

3.2.9 Reinjection Reproducibility

L468

- if samples could be reinjected (e.g., in the case of instrument interruptions or other reasons such as equipment failure), reinjection reproducibility should be evaluated and included in the Validation Report or provided in the Bioanalytical Report of the study where it was conducted.

JBF What is the difference from stability in an autosampler?

- Is it the same procedure to evaluate in some cases?

3.3.2 Acceptance Criteria for an Analytical Run (1)

L535

- Analytical runs containing samples that are diluted and reanalysed should include dilution QCs to verify the accuracy and precision of the dilution method during study sample analysis.

Dilution QC in study sample analysis is not necessary if the dilution integrity has been evaluated in the validation study.

3.3.2 Acceptance Criteria for an Analytical Run (2)

L546

- The overall (between-run) accuracy and precision of the QCs of all accepted runs should be calculated at each concentration level and reported in the analytical report (Refer to Section 8 Documentation and Table 1).

If all runs meet the criteria, it is NOT necessary to re-evaluate, is it?

- Are there any bad case?

3.3.3 Calibration Range

L552

- If a narrow range of 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.

There is no need to reset the range if linearity, QC accuracy, and dilution integrity have been evaluated over the concentration range.

- Additional appropriate QCs setting is acceptable.

6.2 Cross Validation (1)

L1005

- Data are obtained from different fully validated methods across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.

- What is f “Different method”?
- What does the same bioanalytical method mean?

6.2 Cross Validation (2)

L1013

- Cross validation should be assessed by measuring the same set of QCs (low, medium and high) in triplicate and study samples that span the study sample concentration range (if available n≥30) with both assays or in both laboratories.

- It is appropriate to evaluate only QC samples when study samples cannot be obtained.
- Add "Pooling of the study samples are not encouraged but allowed if insufficient volume is available to perform the assays in both laboratories."

6.2 Cross Validation (3)

L1016

- Bias can be assessed by Bland-Altman plots or Deming regression. Other methods appropriate for assessing agreement between two assays (e.g., concordance correlation coefficient) may be used too.

Statistical methods are shown as evaluation of cross validation, but criteria are unknown.

Table 1 Sample tracking

L1266

- Records that indicate how samples were transported and received. Sample inventory and reasons for missing samples
- Storage: total duration from sample collection to analysis

- "reasons for missing samples" are not usually available at only the analytical site.
- "total duration from sample collection to analysis" is not available at only analytical site.

Table 1 Bioanalytical Report

L1267

- SOP for reintegration, as applicable
- Reanalysis SOP, if requested
- SOP for ISR†† (if requested)

It is unusual to include these SOP texts in the analytical report(in Japan). We understand that SOPs should be available to only browse at the analysis site.

- SOP number can be written in the document

JBF M10 Workshop

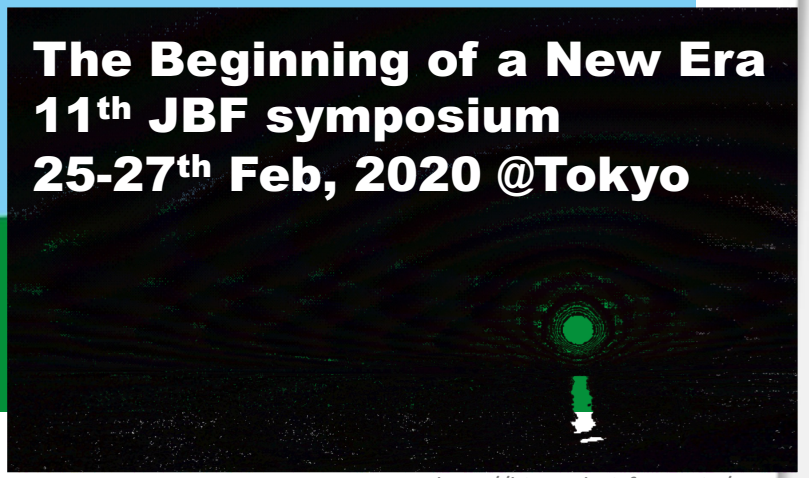
- 25th July at Kyoto
- Internal discussion with JBF members (around 80) in public consultation period
- using the Japanese translated version of ICH M10 draft document
- Summary will be published

Acknowledgement

- European Bioanalysis Forum
- JBF steering committee members

Thank you for your attention!

JBF M10 Workshop
25th Jul, 2019 @Kyoto



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