JBF Feedback

Steering committee of the Japan Bioanalysis Forum (JBF)

Background

- This presentation is opinions from JBF steering committee members, based on the English version of ICH M10 draft guideline.

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

2.1 Method Development

L146

- However, the applicant should record the changes to procedures as well as any issues and their resolutions to provide a rationale for any changes made to validated methods immediately prior to or in the course of analysing study samples for pivotal studies.

JBF It is not necessary to limit the timing of recording before or during testing.

- Change to: "However, the applicant should record any issues and their resolutions during method optimization and method implementation. The necessary changes needed to be made to the validated methods during their life cycles require appropriate justification followed by partial validation."

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 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 quantification even if there is no problem in selectivity. Therefore, our suggestion would be:

- Matrix effect: required (not case by case basis)
- Selectivity: optional

3.2.2 Specificity

L250

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

JBF 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.

3.2.3 Matrix Effect (1)

L273

- The matrix effect should be evaluated by analysing at least 3 replicates of low and high QCs, each prepared using matrix from at least 6 different sources/lots.

Not necessary to evaluate the matrix effect using >3 replicates.

- Requirement in current regional guidance/guidelines appears sufficient.

3.2.3 Matrix Effect (2)

L278

- The matrix effect should also be evaluated in relevant patient populations or special populations (e.g., hepatically impaired or renally impaired) when available.

Two comments

- How many replicates for special populations?
- Does evaluation of special population require matrix effect only? No need for selectivity?

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.

Two comments

- A bit confusing for us. 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.

This may have significant impact on drug development timeline.

- If we find high concentration during clinical sample analysis and then start the long term stability at high concentration, we will hesitate to finalize the sample analysis report until completion of the long term stability test.

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.

Two comments

- Too much burden and not scientifically reasonable. Concomitant medications are numerous and added again and again during the course of drug development.
- Confirmation: If the co-existing substance is not the analyte, then we do not have to add the substance to stability samples. Are we correct?

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.

Two comments

- What action does agency expect if deuterium is used?
- How about the ^{13}C and ^{15}N in the chemical skeletal structure? No need to experiment about isotope exchange?

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.

Two comments

- Two approaches should be acceptable: “exploratory method using blood” and “validated method using plasma/serum”.
- Please do not request to mention method development data in the validation report. They are different studies.

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.

Still we think extract stability and reinjection reproducibility are too prescriptive.

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).

No necessity to re-evaluate the overall measurement accuracy of QC samples that meet the criteria in each batch

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.

Two comments

- No need to change the calibration curve range. If linearity, QC accuracy, and dilution integrity have been evaluated over the concentration range, we are sure the measured values are reliable.
- It is acceptable to add new QCs.

4.2.2 Selectivity

L699

- Selectivity should be assessed in samples from relevant patient populations.

It is not always easy to have samples from relevant patient populations. Do you think it is sponsor's business risk not to include the selectivity assessment in the first method validation study?

4.2.4.1 Preparation of Quality Control Samples

L738

- The QCs should be prepared at a minimum of 5 concentration levels within the calibration curve range: ... at least at 75% of the ULOQ (high QC) ....

JBF Concentration of high QC should be at least one-third of the ULOQ of the calibration curve (no need to change the current regional requirement in Japan).

4.2.6 Dilution Linearity and Hook Effect

L777

- For each dilution factor tested, at least 3 runs should be performed using the number of replicates that will be used in sample analysis

Is it necessary to perform at least 3 different runs? Aren't 3 replicates in a run acceptable?

6.1 Partial Validation

L986

- Change from one matrix within a species to another (e.g., switching from human plasma to serum or cerebrospinal fluid) or changes to the species within the matrix (e.g., switching from rat plasma to mouse plasma)

- Current regional guidance/guidelines require full validation for each species and matrix, except stock/working solution stability.
- Confirmation: Does ICH M10 guideline require less extensive validation in species and matrix changes?

6.2 Cross Validation (1)

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.

Two comments:

- Should be allowed 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 (2)

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.

We are not familiar with Bland-Altman plots or Deming regression. More instruction would be helpful.

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

Following information is not available at analytical sites

- “reasons for missing samples”
- “total duration from sample collection to analysis”

Table 1 Bioanalytical Report

L1267

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

- It is unusual to include SOP texts in a bioanalytical report (in Japan)
- Is it acceptable to write only SOP numbers in Bioanalytical Report?

Actions on ICH M10 Guideline in JP industry

- April-May 2019: Opinion exchange in JBF steering committee
- May-June 2019: Presentations at AAPS and EBF workshop
- July 2019: Internal discussion with JBF members (around 80 scientists) in public consultation period in Japan
- Fall to Winter 2019: Discussion outcome to be published somewhere, and sent to JP regulatory agency

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Thank you for your attention!