Workshop

Towards harmonised implementation of the ICH M10 Guideline

Chapter 7 (AOB), Chrom

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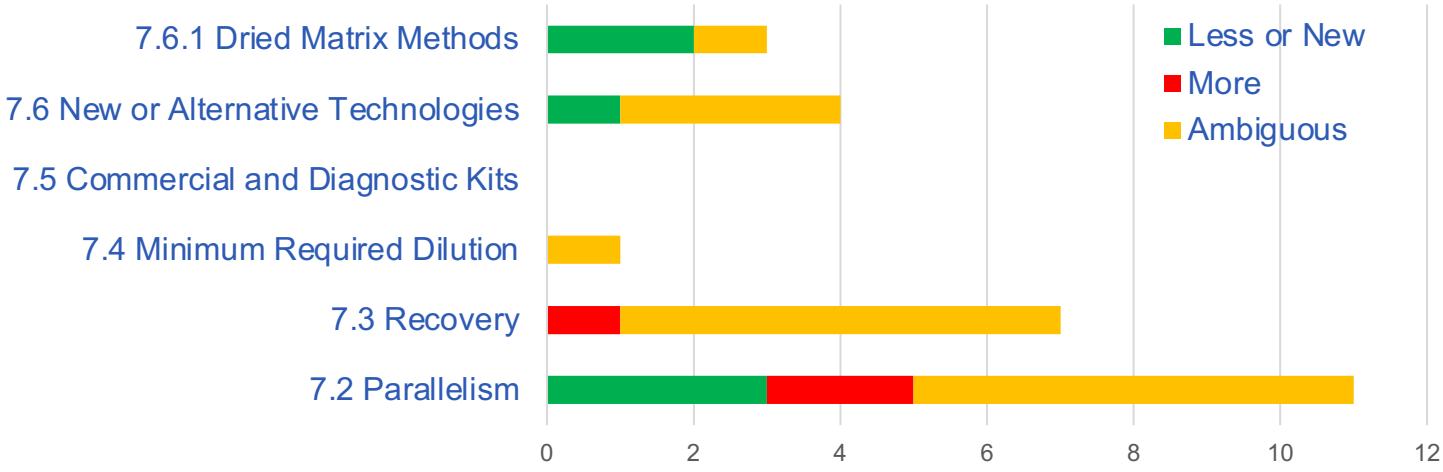
Flow of the session (7. Chromatography - AOB)

- What is explicitly stated in the Guideline
- Comments and questions raised by us
- Discussion and our consensus understanding
- Action and follow-up

ICH guideline M10 on bioanalytical method validation

Themes and Areas of Commentary



- Three main themes of Parallelism, Recovery and New Technologies inc. DMM

Parallelism required for LBA and Chromatography

7.1.3. Parallelism for methods for analytes that are also endogenous molecules

Parallelism assures that observed changes in response per given changes in analyte concentrations are equivalent for the surrogate and the authentic biological matrix across the range of the method. Parallelism should be evaluated in the Surrogate Matrix and Surrogate Analyte Approaches, taking into account that parallelism is assessed differently in LBA and chromatographic methods.

- Expectation that parallelism is addressed

7.2 Parallelism

7.2. Parallelism

Parallelism is defined as a parallel relationship between the calibration curve and serially diluted study samples to detect any influence of dilution on analyte measurement. Although lack of parallelism is a rare occurrence for bioanalytical methods for PK evaluation, parallelism of LBA should be evaluated on a case-by-case basis, e.g., where interference caused by a matrix component (e.g., presence of endogenous binding protein) is suspected during study sample analysis. Parallelism investigations, or the justification for its absence, should be included in the Bioanalytical Report. Some methods may demonstrate parallelism for one patient population, but lack it for another population. Generally, these experiments should be conducted during the analysis of the study samples due to the unavailability of study samples during method development or validation. A study sample with a high concentration (preferably close to Cmax) should be diluted to at least three concentrations with blank matrix. The consistency of the back calculated concentrations between samples in a dilution series should not exceed 30% CV. However, when applying the 30% criterion, data should be carefully monitored as results that pass this criterion may still reveal trends of non-parallelism. In the case that the sample does not dilute linearly (i.e., in a non-parallel manner), a procedure for reporting a result should be defined *a priori*.

7.2 Parallelism – Chromatography Methods

- "lack of parallelism is a rare occurrence for bioanalytical methods for PK evaluation … Parallelism investigations, or the justification for its absence, should be included in the Bioanalytical Report."

Less work

We do not have to do parallelism per default, is a case by case.

More work

Justification for absence of parallelism investigation should be included in the Bioanalytical Report

Ambiguous

Is there a risk for "increasing the bar" and that parallelism will be included "just in case"? On the other hand the test may be helpful in assays/drugs where we have limited experience

Discussion –

When is it appropriate to carry out/not carry out a Parallelism assessment?

7.2 Parallelism – **Ambiguity**

- "A study sample with a high concentration (preferably close to Cmax) should be diluted to at least three concentrations with blank matrix."
- "consistency of the back calculated concentrations between samples in a dilution series should not exceed 30% CV. However, when applying the 30% criterion, data should be carefully monitored as results that pass this criterion may still reveal trends of non-parallelism."

Based on the text parallelism (if relevant) should only be verified using 1 study sample, correct?

Still no acceptance criteria for assessing "Trends"

Acceptance criteria of 30% are not sufficient as authors indicated. However the method for monitoring parallelism is not defined and a subjective assessment is implied. In this case why do we have 30% criteria at all?

7.2 Parallelism – Ambiguity

- “A study sample with a high concentration (preferably close to Cmax) should be diluted to at least three concentrations with blank matrix.”
- “consistency of the back calculated concentrations between samples in a dilution series should not exceed 30% CV. However, when applying the 30% criterion, data should be carefully monitored as results that pass this criterion may still reveal trends of non-parallelism.”

Discussion –

How many samples from how many populations should used in a parallelism assessment?

How are trends of non-parallelism identified when the set criterion of ±30% is met? What action is taken?

Parallelism in Chromatographic Bioanalysis

- Current EBF perspectives based on Biologics and Biomarker fields
  - EBF TT-61 Non-parallelism in Biomarker Assays, 2016 OS, 2019 FW
  - Practical approach recommended that goes beyond dilutional linearity
  - Proper parallelism assessment for biomarker assays during development and validation enables appropriate data interpretation.
  - If non-parallelism is encountered, there are a number of analytical strategies to explore that may address the issue.
  - If parallelism cannot be demonstrated, then a quasi-quantitative or qualitative approach should be taken.

7.3 Recovery

7.3. Recovery

For methods that employ sample extraction, the recovery (extraction efficiency) should be evaluated. Recovery is reported as a percentage of the known amount of an analyte carried through the sample extraction and processing steps of the method. Recovery is determined by comparing the analyte response in a biological sample that is spiked with the analyte and processed, with the response in a biological blank sample that is processed and then spiked with the analyte. Recovery of the analyte does not need to be 100%, but the extent of recovery of an analyte and of the IS (if used) should be consistent. Recovery experiments are recommended to be performed by comparing the analytical results for extracted samples at multiple concentrations, typically three concentrations (low, medium and high).

7.3 Recovery

Ambiguous

Replicates? and limits of consistency?
Unsure if should do in method development or validation
Is protein precipitation also considered to be extraction, or only methods like SLE or SPE?

More Work

Is the recovery of SIL required

Discussion –

What is the design of an appropriate Recovery experiment? Does this include SIL internal standards?

Should recovery be carried out for protein precipitation methods?

What does consistent mean?

7.6 New or Alternative Technologies

7.6. New or alternative technologies

When a new or alternative technology is used as the sole bioanalytical technology from the onset of drug development, cross validation with an existing technology is not required.

The use of two different bioanalytical technologies for the development of a drug may generate data for the same product that could be difficult to interpret. This outcome can occur when one platform generates drug concentrations that differ from those obtained with another platform. Therefore, when a new or alternative analytical platform is replacing a previous platform used in the development of a drug it is important that the potential differences are well understood. The data generated from the previous platform/technology should be cross validated to that of the new or alternative platform/technology. Seeking feedback from the regulatory authorities is encouraged early in drug development. The use of two methods or technologies within a comparative BA/BE study is strongly discouraged.

The use of new technology in regulated bioanalysis should be supported by acceptance criteria established *a priori* based on method development and verified in validation.

7.6 New or Alternative Technologies

Ambiguous

What cross validation would be required and is there acceptance criteria expectation? It already states that the data generated may be difficult to interpret

Ambiguous

x-validation of new/alternative platform vs previous platform is only feasible if exactly the same analyte fraction (total/free/active/target-binding competent) is detected with both methods.

Discussion –

Do we have experience (yet) of cross-validation between platforms?

7.6 Dried Matrix Methods

7.6.1. Dried matrix methods

. . .

- DMM sample collection for ISR
  - Care should be taken to ensure sufficient sample volumes or numbers of replicates are retained for ISR
  - Should be assessed by multiple punches of the sample or samples should be taken in duplicate

Ambiguous - Duplicate sample for ISR - is this really the same sample?

Discussion –

With reference to ISR and other aspects: does ICH M10 alter DMM strategies?

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