ICH M10 Harmonization

JBF point of view for chromatographic assays

Hisanori Hara Novartis Pharma AG
on behalf of JBF

Disclaimer

- The view and suggestions provided in this feedback come from the survey and the discussions in the JBF and might not reflect the entire view from Japanese industry.

Previous discussions of ICH M10 in JBF

Japan Bioanalysis Forum

Expec

- from J

UTC

8th JBF Symp
8 February 2

Yoshiaki Oht
Astellas Pha

AAPS Views on Bioanalytical Method Validation Harmonization

(on Behalf of AAPS Bioanalytical Community)

Faye Vazvaei,
Roche Innovation Center New York

The 8th JBF Meeting, 8-9 February 2017

aaps

Previous discussions of ICH M10 in JBF

1. Common
   Tiered approach, Biomarker assays, Reanalysis, Cross validation, ISR
2. Chromatographic assay
   Internal standard, Recovery, Matrix effect, QC samples in validation and sample analysis, Reintegration
3. Ligand binding assay
   Reference standards, Specificity, Critical Reagent, Parallelism, Total error

URL: http://bioanalysisforum.jp/images/2017_8thJBFS/022_Expectation_on_ICH_M10_from_JBF.pdf

I would like to focus on

Additional input from JBF

1. According to the ICH M10 Survey
   - 1 - Placing of the Mid QC
   - 2 - -20 °C versus -70/-80 °C stability
   - 3 - FDC – comed stability testing
   - 4 - Dilution Linearity and Parallelism
   - 7 - Hemolysed / Hyperlipidemic matrices testing

I would like to focus on

Additional input from JBF

2. Other considerations from JBF point of view

General

- Additional QC or adjusting QCs
- Cross validation

Chromatography

- Definition of re-integration of chromatogram
- Recovery

LBA

- Total Error
- Definition of Critical reagents
- reference standard

1 - Placing of the Mid QC

1. Main area
   a. Small molecules/chromatography; fill in question 2
   b. Large molecules/ligand binding; fill in question 3
   c. Both chromatography and LBA; fill in both questions 2 and 3

A 50%, C 50%, (16)* CRO 2, Generic 2, Pharma 12

*(number of company responded)

2. Chromatography: Placement of calibration standards
   a. If you predominantly use an arithmetical (e.g. 2, 4, 6, 8 …) distribution; fill in Table 1
   b. If you predominantly use a geometrical (e.g. 1, 2, 5, 10 …) distribution; fill in Table 2
   c. If you use both arithmetical and geometrical distributions; fill in both Table 1 and Table 2

B 100% (16)

1 - Placing of the Mid QC

3. LBA: Placement of calibration standards

a. If you predominantly use an arithmetical (e.g. 2, 4, 6, 8 …) distribution; fill in Table 3

b. If you predominantly use a geometrical (e.g. 1, 2, 5, 10 …) distribution; fill in Table 4

c. If you use both arithmetical and geometrical distributions; fill in both Table 3 and Table 4

A 29%, B 43%, C29%

d. Please state whether you ignore or include anchor points when calculating the mean (i.e. do you only consider all calibration points or only the linear portion of the curve?)

ignore 50% (1), include 50% (1)

4. Do you think that placement of QCs should be related to the relative placement of calibration standards or the calibration range?

a. NO. Regardless the relative distribution of calibrators or the extent of the calibration range, QCs should always be in a fixed positions relative to the lowest and/or highest standard.

b. YES. You should use a geometrical distribution of QC levels for geometrically placed calibration standards and arithmetically distributed QCs for a range with arithmetically placed calibration standards.

c. YES. You should use a geometrical distribution of QC levels for large calibration ranges (e.g. > 2 decades) and arithmetically distributed QCs for shorter ranges (< 2 decades)

d. OTHER: ……

A 23% (3), B 62% (8), C 8% (1),D 8% (1)*

* Close to expected concentration of study samples

1 - Placing of the Mid QC

5. Table 2 CHROM: Geometrical (e.g. 1, 2, 5, 10 …) placed calibration standards

Calibration Range	Mid QC at (about) 50% of highest calibrator	Mid QC at (about) the level middle calibrator	Other (indicate the relative level)
Less than 1 decade (if ever)	1	3	
1 to 2 decades (e.g. 1 – 50)	1	10	1 [3, 10, 40]
2 to 3 decades (e.g. 1 – 500)	1	14	1 [3, 30, 400] 1 [Two mid-QCs (geometrically 50% and 30% to 50% of highest calibrator) are applied.]
]3 to 4 decades (e.g. 1 – 5000)	1	12	1 [3, 30, 4000] 1 [Two mid-QCs (geometrically 50% and 30% to 50% of highest calibrator) are applied.]
> 4 decades (e.g. 1 – 20000)	-	7	

2 - -20 °C versus -70/-80 °C stability

Chromatographic assays:

1. How many observations do you have where you tested stability of your analyte at -20ºC and -70ºC /-80ºC?

   from '4' to 'Many'
   depending on the size of the company, mostly 'Many' (16)

2. How many times did you see a difference between the stability at -20ºC and -70ºC /-80ºC, or in other words, how many times did – 20ºC didn't cover the stability for -70ºC /-80ºC?

   (in total) 25

3. If the answer in 2 is larger than zero, can you provide background and/or scientific rationale of why there was a difference

   a. Erroneous experiment, after repeat the issue was solved 1

   b. Scientific reason – please provide some details: 23*

   * -20°C less stable but -70°C stable, no other case reported

2 - -20 °C versus -70/-80 °C stability

Free comments:

- Due to some examples of differences in stabilities, we think the both assessment of stabilities at -20 °C and at -70/-80 °C is mandatory. We conduct them in the method development.

- Although I do not think we do need to have -70/-80 °C stability assessment for small molecules if we have -20 °C data, it is not a big deal for having the both stabilities at -20 °C and at -70/-80 °C . I believe that the procedure of freezing, the material, the size and the shape of the tube can give much more impact on the stability than that of at -20 °C or at -70/-80 °C

- We conduct the short term stability assessments at -20 °C and at -70/-80 °C during the 3 analytical batches of the method development.

3 - FDC – comed stability testing

Chromatographic assays:

3. Frequency of testing:

a. How often did your lab test the stability of drug combination (FDC or comed)?
'Never' (4) to 'always' (1)
Generic company tends to do more.

b. For how many of those did your lab also test the stability of (one of) the drugs separately as part of prior validations?
'Never' (3) to 'always' (2)

4. Frequency of failure:
No failure is reported.(8)

5. Frequency of repeat: how many times did you have to repeat stability testing of a known stability part of the validation of the single analyte in order to include a FDC or drug combination:
'0' or '3' times(1)

3 - FDC – comed stability testing

Free comments:

(Limited experience of comed stability testing.) No effect due to co-existence and change of the ratio of the compounds. However, stability of the compounds was affected due to co-existence in the tablet.

We believe that the individual stability testing is enough and the comed testing is not necessary. The concentration of the compounds can be high enough to trigger physical or chemical interaction in the FDC drugs, e.g. in tablet etc., however that in the biological matrix is much lower.

The effect of co-existence of the analytes to the stability is very unlikely. Since the biological matrix can contain lots of metabolites, the testing with only unchanged is meaningless.

The comed stability testing is not so important. I believe that the impact of endogenous compounds and the pH of the matrix for the stability of analytes is much greater than the co-existing compound from FDC.

7 - Hemolysed / Hyperlipidemic matrices testing

Identify yourself:

3. Pharma/ CRO
   Pharma 75% (12), Generic 13% (2), CRO 13% (2)

4. How does your lab defines “Haemolysed” matrix?
   Judging by colour with printed picture as a colour chart 6% (1)
   Judging by colour 94% (15)

5. How does your lab defines “Hyperlipidemic” matrix?
   Judging by colour with printed picture as a colour chart (1)
   Judging by colour (1)

7 - Hemolysed / Hyperlipidemic matrices testing

Chromatographic assays:

6. **Frequency** of testing (including test in validation study) and **Failure** rate.
   Please add average number of validation studies per year, and average number of failed test in validations per year.

	Hemolysed sample tests	Hyperlipidemic sample tests
Number of clinical validations including hemolysed /hyperlipidemic samples conducted yearly	From '0' to 'many' (in total 16)	From '0' to 'many' (in total 16)
Number of failed hemolysed /hyperlipidemic sample tests in clinical validations yearly	No issue observed (15) Ca. 5% of method modified due to hemolysed sample (1)	No issue observed (16)
Number of pre-clinical validations including hemolysed /hyperlipidemic samples conducted yearly	'0'	'0'
Number of failed hemolysed /hyperlipidemic sample tests in pre-clinical validations yearly	N/A	N/A

7 - Hemolysed / Hyperlipidemic matrices testing

8. Feasibility to do the test(s)

a. Do you have access to in-house blood facilities (Yes/No):
Yes 70% (7), No 30% (3)

b. Do you use a commercial supplier for
Hemolysed matrix (Yes/No):
Yes 40% (4), No 60% (6)

Hyperlipidemic matrix (Yes/No):
Yes 80% (8), No 20% (2)

If you use a commercial supplier, why? What is the main reason?
Easy to obtain (1), Ethical reason (in-house volunteers) (1)

c. Prepare samples in-house by spiking erythrocytes into plasma (Yes/No):
If No, Other?
Yes 80% (8), No 20% (2)

d. Prepare samples in-house by spiking plasma with triglycerides (Yes/No):
If No, Other?
Yes 10% (1), No 90% (9)*

*Commercial supplier (7), Generic company (2)

7 - Hemolysed / Hyperlipidemic matrices testing

9. Procedure

a. Do you access the Hyperlipidemic and Hemolysed sample tests in connection with the 6 individuals or do you prepare a separate experiment?

in connection with the 6 individuals 33% (3)
a separate experiment 67% (6)

b. Do you use pooled samples or do you use individual samples for these test?

individual 78% (5)
Pool 22% (2)

c. At what levels do you spike your Hemolysed matrix?

LLOQ High Mid Low Other (mark in yellow), If Other: What level?

High & Low 62% (5)
Low & LLOQ 13% (1)
LLOQ 25% (2)

d. At what levels do you spike your Hyperlipidemic matrices?

LLOQ High Mid Low Other (mark in yellow), If Other: What level?

High & Low 62% (5)
Low & LLOQ 13% (1)
LLOQ 25% (2)

7 - Hemolysed / Hyperlipidemic matrices testing

10. Acceptance criteria

Hemolysed sample tests

a. We follow the acceptance criteria as defined in EMA Guidance (Yes/No):
Yes 75% (6), No 25% (2)

b. If No: What criteria do you use?
With LQC and HQC, >2/3 within +/-15%
Undefined for Hemolysed sample tests(generic)

Hyperlipidemic sample tests

c. We follow the acceptance criteria as defined in EMA Guidance (Yes/No):
Yes 75% (6), No 25% (2)

d. If No: What criteria do you use?
With LQC and HQC, >2/3 within +/-15%
Undefined for Hyperlipidemic sample tests(generic)

7 - Hemolysed / Hyperlipidemic matrices testing

11. In case of failure in testing hemolysed and/or hyperlipidemic matrices what do you do:

a. For Hemolysed failed tests, we usually;

No failure (6)

We will re-develop bioanalytical method. (3)

Comment: If the test is failed only in severe hemolysis in a MV, we would use a color chart for degree of red color when analysing real samples and omit severe hemolyzed sample.

b. For Hyperlipidemic failed tests, we usually;

No failure (4)

We will re-develop bioanalytical method. (3)

7 - Hemolysed / Hyperlipidemic matrices testing

12. Do you measure the Lipid content of your real samples? (Yes/No):
    If Yes, How do you do that?
    No 100% (8)

13. What is the average % of Hyperlipidemic samples you find in Clinical Trials?
    No information (only visually checked) 100% (6)

14. What is the average % of Hyperlipidemic samples you find in Pre-Clinical studies?
    Only Hyperlipidemic model animal (1)
    not known or no information

15. Do you use a colour chart for degree of red colour when analysing your real samples? (Yes/No):, If No, what do you do instead?
    Yes 33% (3)
    No 67% (6)
    Comment: Just visually checking if hemolyzed or not, do not care the degree of the hemolysis

7 - Hemolysed / Hyperlipidemic matrices testing

16. What is the average % of Hemolysed samples you find in Clinical Trials?
    Up to 10%, 10% (1)
    Up to 1%, 30% (3)
    No statistical information, 60% (6)

17. What is the average % of Hemolysed samples you find in Pre-Clinical studies?
    ca. 5%, 12% (1)
    2-3%, 12% (1)
    maximum 1%, 12% (1)
    No statistical information 64% (5)

Free comments (Chromatographic assays):

The definition of hemolyzed samples is relatively well-established. However that of Hyperlipidemic is not. I believe that the assessment of Hyperlipidemic matrix in the method development (not an item in the method validation) is enough as a part of risk assessment. If we need to mind hyperlipidemic matrix, I think there are many factors, e.g. impact by another ingredients from food which we may have to also mind.

Other considerations from JBF point of view

Chromatography:

Definition of re-integration of chromatogram

JBF would like to have a clarification on the re-integration. If the integration parameters from the defined ones or from the method validation do not work in an analytical run and need to have adjustment, is it a re-integration? We would like to have examples which showed a manual integration was accepted by FDA or by EMA, since we feel the interpretation may be different by the health authorities.

Recovery

It is still controversial in JBF if the recovery is really mandatory in the validation items. JBF feels that the two levels of QCs, i.e. Low and High are enough for the recovery.

Thank you for your attention.
I welcome your comments and questions.