ICH M10 Harmonization

JBF point of view for general topics +LBA

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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
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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

- 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

- 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)

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

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

Overall summary:

1. Many Japanese companies conduct the both -20°C and -70/-80°C stability assessments.

2. There are several results which showed instability in -20°C but better stability in -70/-80°C.
   The other way round has not been observed.

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.

- 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

Overall summary:

1. Chromatographic assay:
   Many company have conducted FDC co-med stability assessments.
   There has been no observation for instability of analytes among them.

2. LBA:
   The frequency of the FDC co-med stability assessments in the LBA area is much less than that of Chromatographic assay.
   There has also been no observation for instability of analytes among them.

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

Overall summary:

Hemolysed matrix testing

- Hemolysed matrix testing is widely conducted in Japan.
- The judgement is done visually.
- Hemolysed matrix is prepared by adding blood or purchased commercially.
- Some companies adjusted the analytical method due to hemolysed matrix.

Hyperlipidemic matrix testing

- Hyperlipidemic matrix testing is less frequent in Japan.
  One of the reason is that the definition of hyperlipidemic matrix is still unclear.
- The judgement is done visually.
- Most of the companies prefer to purchase hyperlipidemic matrix commercially.

7 - Hemolysed / Hyperlipidemic matrices testing

Free comments:

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.

If Hemolysed and / or Hyperlipidemic matrices give impact on the PK, I would have a partial method validation. If the partial method validation does not meet the acceptance criteria, the results will be asterisked and reported separately.

If the preclinical and clinical studies are for the disease area of hyperlipidemia, I would use hyperlipidemic matrix from the beginning of the validation to the end of the studies.

Other considerations from JBF point of view

General:

Placing additional QC or adjusting QCs according to the range of measuring the values

It seems that the EU and US scientists have already accepted the request by FDA and EMA. However, certain number of Japanese scientists have not been convinced the value of the additional QCs and adjusting QC levels according to the range of measuring unknown samples, because the quality of the measured data should be able to be assured by the original QCs from the validation in the entire range of the validated dynamic range. JBF wants to have the clear rationale for the values of placing additional QC or adjusting QC levels.

Cross validation

JBF feels that the cases which require a cross validation have ambiguity and would like to have clarification in which cases we need to have a cross validation.

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.

Other considerations from JBF point of view

LBA:

Total Error

The precision and the accuracy can be expressed as the bias and the CV. The total error is redundant and should be removed from the ICH M10. If we keep the total error, we should come back to the item later and assess if it is really important and necessary to show the assay performance.

Definition of Critical reagents

We would like to have clear definitions for the critical reagents and the reference standard. Some people (e.g. QA) believe that the critical reagent should be handle as equal level of the reference standard.

Recommendation for the same batch of reference standard

We understand that it is a recommendation. However, I am afraid that it is difficult to use the same batch for all studies. With the reason, we prefer to remove the recommendation.

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