Bioanalytical Methods

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Outline

1. The FDA guidance-our philosophy in the revision and our feedback

2. Questions from the JBF

3. FDA Revision Efforts-the Next Steps

FDA BMV Guidance

- Some old issues, some new issues
  - Some new concepts e.g. biomarkers
  - Some old concepts clarified
  - Some things carried forward from old Guidance
  - Some topics not mentioned

FDA BMV Guidance-Philosophy

Non-prescriptive/conceptual (Issues)

- Describes the issues that need to be satisfied for a validated method and the minimum standards
  - Allows for scientific judgment
  - Prescriptive may be too restrictive
  - Cannot conceive & capture all situations

- Not intended to be an extensive treatise on method validation or analytical platforms

FDA BMV Guidance

Our feedback (docket, CC V)…

Conceptual >>>>>Prescriptive

Many comments to include issues we don't think we need to comment on…

- E.g. Statements about anticoagulants with differing counterions

Bioanalytical Guidances

- MHLW Draft Guideline on
  Bioanalytical Method Validation (Ligand Binding Assay)
  Validation in Pharmaceutical Development-2014

- FDA Guidance for Industry: Bioanalytical Method validation-2013

- MHLW Guideline on Bioanalytical Method Validation
  in Pharmaceutical Development-2013

- ANVISA-Bioanalytical guidance-2012

- EMA-guideline on Bioanalytical Method Validation-20111/2012

Harmonization

There is extensive harmonization of the guidances/guidelines

- Chromatography, LBA, essentially the same
- WRIB, AAPS, APA, LOL, EBF, JBF, etc

Differences…..

Biomarkers, Diagnostic Kits

What are the criteria and parameters that should be followed?

DBS, and other new technologies

should be crossvalidated with prior standard methods to interpret data

Cross-/Partial validations

What are the criteria and parameters that should be monitored? In what situations?

Future Issues…..

ADCs, LC/MS of large molecules

What are the criteria & parameters that are needed for these methodologies?

Questions from the JBF

Q1. Cross-validation (L122-123)
Does “The comparisons should be done both ways.” mean comparing the data analyzed by both 2 methods using same samples? In case that the reference method is not available, how should we handle this?

A little grammatical clarity is needed in the Guidance.
Crossvalidation is a comparison of (at least) two methods.
QCs and samples should be used, by analysis with both methods.

What are the appropriate acceptance criteria?
EMA: 15% for QCs, 20% for samples
MHLW: 20%

Questions from the JBF

Q2. Recovery (L238-240)
Is Low and High sufficient? We think there's no need to add Medium.

Thank you. We will discuss this during our revision.

Questions from the JBF

Q3. Calibration (L284-295)
In case 75% of non-zero standards except the ULOQ met the criteria, is the standard curve accepted? If it is accepted, the quantitation range would narrow except the ULOQ or keep original range ?

ULOQ is defined by the highest concentration on the standard curve. If you dropped the highest concentration, the next highest concentration would define the top end of the calibration curve.

Questions from the JBF

Q3. Calibration (L284-295)
What does the sentence "Excluding an individual standard should not change the model used." mean?
1) When any of the concentration points fell outside the criteria, the calibration curve should be re-constructed without that point.
2) The calibration curve avoid the need to re-construct. The model (weighted least-squares regression method, weighting and other) should not change.

Correct. Loss of one calibrator should not alter the mathematical model used to fit the curve
(if it does, that is indicative of a problem with the method).

Questions from the JBF

Q4. QC samples (L399-408)
We hope to delete the sentence “e.g., capacity limit of 96-well... analysts”, because this provision makes the pretreatment more troublesome.

This is a difficult issue. Without inclusion of QCs on separate plates etc, it is difficult to monitor analytical performance adequately.

Questions from the JBF

Q5. Carry-over during sample analysis (L438-439)
In routine bioanalysis, should the carryover be included into acceptance criteria of an analytical run as well as accuracy of a calibration curve and QC samples?

Carryover needs to be assessed as part of your method. Ideally, it will be corrected. But if some carryover persists, you will need to monitor it during study sample analysis. If it becomes problematic during a run, you may need to reject the run and re-assess/correct the issue.

Questions from the JBF

Q6. Change of counter ion on an anticoagulant
Based on the discussion in CC-V, I understand that a change of counter ion on an anticoagulant does not require a partial validation. Please confirm that additional stability data is not also required with the 'new' counter ion.

It does **NOT** require a partial validation,

nor a stability assessment.

Questions from the JBF

Q7. Re-integration (L459-463)
Do criteria for reintegration mean rationale for reintegration? Could you present example of criteria for reintegration?

Yes, the criteria for reintegration is another way of saying what is the rationale for the re-integration.

A shoulder peak on the analyte could be a legitimate reason, defined *a priori*, as the basis for re-integrating the peak of interest.

Questions from the JBF

Q8. ISR (L752-783)
We hope the number of ISR samples is harmonized among JP MHLW, EU EMA and US FDA.

The FDA is agreeable to MHLW and the EMA accepting 7%

Questions from the JBF

Q8. ISR (L752-783)
Does that mean not all PK study should do ISR evaluation? We need to confirm what studies we don't need to do ISR. Does PD marker need ISR?

ISR is intended to be a “spot check” of the method. It should be applied to Studies that support regulatory actions. This would include biomarkers and PD assays, if they were to be used for this purpose.

e.g. Studies that need ISR

- PK study to support labeling
- BE studies

Studies that may not need ISR

- early BE studies changes in formulation (not the final formulation)
- exploratory studies of PK
- exploratory studies of biomaker (e.g. Phase 1)

Questions from the JBF

Q8. ISR (L752-783)
We think that the acceptance criteria for ISR (20% for small molecules or 30% for large molecules) should also be defined based on the difference of measurement principle (Chromatographic assay or Ligand binding assay), not molecular size.

Generally, small molecules equates to chromatographic methods (20%)

And LBA equate to large molecules (30%)

What about LC/MS (chromatography) of large molecules? –20%?

Questions from the JBF

Q9. Inspection
Please indicate clearly which item will be applied for future inspection/investigation retrospectively, if there are any. It is unfair to apply some rules against old projects/ studies retrospectively.

Some new things aren't new…e.g. LBA criteria, which have been used since 2006.
Other things are too new…..

When the final Guidance is posted, it will describe when/how things will be in force.

FDA Guidance Revision-Update

Draft Guidance posted in Sept 2013
Ninety-day comment period-closed Dec 2013

Feedback on the Guidance

- AAPS-FDA: Crystal City V
- Emails
- Comments submitted to the docket

FDA Guidance Revision-Update

Docket:
> 640 pages of comments;
•from around the world.
•Individuals and consortia
•Basic types of comments
- Grammar/clarification/semantics
- Scientific suggestions/recommendations
- Unsubstantiated comments

FDA Guidance Revision-Update

Completed database of comments

- Next: sort and codify
- Revise text and structure
- Re-circulate within FDA

When will this be completed?-Unclear

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