LBA- Considerations for Reference Standards and Key Reagents

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Outline

- Summary from ICH M10
- Changes to current guidance (FDA, EMA, MHLW, China)
- Impact on our industry – Cost
- EBF position on the subject from publications/Lisbon-2017
- Feedback from you and EBF members
- Feedback from EBF Strategy /Suggested changes to ICH M10 draft

Summary from ICH Guideline-released 16-Mar-19

- Ligand Binding assays

  - The Reference standard should be well characterized and documented. It is recommended that, **whenever possible,** the batch of drug substance used to support bioanalysis is **derived** from the same batch that is used for dosing

  - Critical reagents should be identified and defined in the assay method. Reliable procurement should be considered early in method development. Changes may need additional validation experiments

Review from Current Guidelines*

Agency (year)	Definition of critical reagents	Recommendation for lot-to-lot changes	Recommendation for reagent stability
EMA (2012)	Binding proteins, Conjugates, Antibodies Aptamers	Verification of method performance	Storage conditions and maintenance should be documented
FDA (2018)	Reference standards, Antibodies, Labeled analytes, Matrices	Evaluate binding and re-optimize assays Verify performance with a standard curve and QCs Evaluate cross-reactivities	Storage conditions should be defined
MHLW (2014)	Conjugates, Antibodies Components with performance impact	Perform partial validation when minor changes are made to an analytical method that has already been fully validated	Storage conditions should be used that ensure consistent quality
Major Gap	No formal definition	No practical recommendations	Limited recommendations

*Adapted from Pihl, et.al. Bioanalysis (2018) 10(19), 1557-1565

Impact on our Industry

- Cost to Implement
  - Conjugation and characterization
    - ~1 week of FTE time (for a 50mg batch ~$12-15K)
- Cost of failure to implement (at CRO)
  - 6-10 days of MD ($24-30K)
  - Investigation/troubleshooting costs about $20-60K
  - Qualification of new reagents: 2-3 days ($6-9K)
- Examples:
  - Water source was a critical reagent in an enzymatic PK assay
  - Aliquot size impacting stability
  - Incorrect concentration
  - label incorporation variance and aggregate
  - Incorrect clone

What if we don't get this right?- Case 1

- No characterization performed on reagent labeling #1
- Labeling #1 used for MD, Val, and sample analysis
- Labeling #2 did not match Labeling #1
- Labeling #3 did not match Labeling #1 nor #2
- Investigation (~3 days) Partial validation (~5 days)
- Total loss from not characterizing reagent labeling #1 ~10 days and delayed an interim data transfer
- $2200 and $3000 per diem = $22-30K loss

What if we don't get this right?- Case 2

- Transferred assay showed high background
- Troubleshooting (~2 days) identified the reagents as the source
- prepared the 16 (small batches) labels (~1 day)
- 2 days of MD to identify the best pair
- Scale up of selected pair (~1 day)
- Optimized for concentration of the new reagents
- Total time of about 7 days and missing a timeline. ~$15-21K loss

EBF WS Lisbon 2017: Recommendations for ICHM10 *

- Identify the critical reagent and clearly document
- Identify the noncritical reagents and monitor during routine sample analysis
- Ideally, ensure enough material is available to support an entire study and/or drug development program
- Use GBC definitions to evaluate what constitutes a minor or major change:
  - Minor: expected to have minimal effects on assay performance and may therefore be implemented without any deleterious effect on data production
  - Major: require the most extensive reagent qualification
- Where one single lot cannot be sourced for the entire period of use, retain enough material of the old lot for head-to-head comparison with new lots

** http://www.e-b-f.eu/fw201709-slides/*

EBF WS Lisbon 2017: Recommendations for ICHM10 cont'd

- Evaluate lot-to-lot changes of critical reagents using the CoA and test in the PK assay using *a priori* criteria
- Application of re-test dates instead of expiry dates to monitor and evaluate reagent stability
- Monitor QC and assay data during the assay life cycle
- Document reagent identity, lot-to-lot changes and evaluation/extension of re-test dates in the relevant paperwork for the method
- For commercial kits that are used for PK purposes, secure sufficient kits of the same lot number. If this is not possible then test new batches when available

EBF WS Lisbon 2017: Recommendations for ICHM10 cont'd

Reference Standard new biological entities (NBE)

- If proper comparison of different batch done in GMP environment there should not be a requirement to use same batch of Ref Std for Cal & QC preparation as the dosing batch
- When having new batch it is not a requirement to revalidated your method

Feedback from you and EBF members

Line 647

Which additional validation experiments are needed when major changes occur?

Line-710, add:

...is derived from the same batch **or from an batch which has shown analytical comparability**

Line 735-

Would clarify to use the same wording as in GLP OECD (4.4 reagents): "The expiry date may be extended on the basis of documented evaluation or analysis."

Line 727, remove:

minor and major changes and use EMA wording (§7.1.1.12) since it's simpler and clearer and covers all the cases for critical reagents.

A lot of time the old reagent expired and it is impossible to have a direct comparison of the new and old reagent.

Line 737-

Ambiguity concerns the general guidance for reagents storage conditions. Would it be possible to specify which is the guidance to refer to?

Line 731, rephrase:

Ideally, assessment of changes will compare the assay with the new reagents to the assay with the old reagents directly.

Suggested Comment to EMA/EWG-Ref. Std.

Current text in draft M10	Suggested Changes
Line 626 If the reference standard batch used for bioanalysis is changed, bioanalytical evaluation should be carried out prior to use to ensure that the performance characteristics of the method are within the acceptance criteria.	If the reference standard batch used for bioanalysis is changed, bioanalytical evaluation should be carried out prior to use to ensure that the performance characteristics of the method are within the acceptance criteria and to ensure consistency of results between batches in case of change during bioanalysis of samples from a given nonclinical or clinical study
Line 627 .. bioanalytical evaluation should be carried out ..	.. bioanalytical evaluation (e.g. qualification of QCs prepared by new batch against std prepared with original batch) should be carried out
	Include additional information on how to proceed if analytical comparability has been proven between two drug substance batches (for example with different formulation buffer) and CMC only releases one drug substance batch as reference batch

Suggested Comment to EMA/EWG- Reagents

Current text in draft M10	Suggested Changes
Line 633 Critical reagents bind the analyte and, upon interaction, lead to an instrument signal corresponding to the analyte concentration. The critical reagents should be identified and defined in the assay method	~~Critical reagents bind the analyte and, upon interaction, lead to an instrument signal corresponding to the analyte concentration.~~ The critical reagents should be identified and defined in the assay method
Line 636 Reliable procurement of critical reagents, whether manufactured in-house or purchased 636 commercially, should be considered early in method development.	~~Reliable procurement of critical reagents, whether manufactured in-house or purchased commercially, should be considered early in method development~~.
Line 645 If the change is minor (e.g., the source of one reagent is changed)…	Misconstruing definition for minor change

Suggested Comment to EMA/EWG- Reagents cont'd

Current text in draft M10	Suggested Changes
Line 646 If the change is major, then additional validation experiments are necessary.	Add minimum validation parameters that should be assessed and indicate if a validation amendment would be the appropriate way to document it
Line 652 Retest dates and validation parameters should be documented in order to support the extension or replacement of the critical reagent.	Specifying where to document. The restest date updates may be documented in a data sheet or RoA, while validation experiments may be documented as part of the validation report

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Preguntas?

Further questions to info@e-b-f.eu before 31 May 2019

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