Critical reagents

Susanne Pihl,
on behalf of the EBF

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Why are we discussing critical reagents in LBA?

1. There is no clear definition
2. No specific guidance from regulators including no recommendation on how to deal with a change of lot
3. No unified approach can be used due the variation of types of critical reagents and platforms
4. High variability in the approaches described in the current literature, leaning towards being very extensive
5. Challenge with lack of communication or warming from commercial suppliers, when reagents are changed

Agenda

- Current guidelines
- Recommendation from Lisbon ICHM10 workshop
- Best practice

Keep in mind

Critical reagents are not reference standard

ICH M10: Only PK assay

Steps for critical reagents

- Critical reagents during assay development
  - Selection
  - Characterisation (only to be included during assay development)
  - Commercial availability vs custom-produced

- Critical reagents throughout the lifecycle of the assay
  - From validation and onwards
  - What is covered by the guideline

Critical reagents throughout the lifecycle of the assay

- To ensure the analyte concentrations in study samples are comparable during the assay's lifespan

  - Validation
  - Change of critical reagents
    - Run partial validation, if required
  - Monitoring of the assay over time
    - Including long-term stability
  - Ongoing study sample analysis

EMA (2011): 7.1.1.12. Reagents

- **Critical reagents, including binding reagents** (e.g. binding proteins, aptamers, antibodies or conjugated antibodies) **and those containing enzymatic moieties have direct impact** on the results of the assay and therefore **their quality must be assured**. Accordingly, when **changing reagent batches** during validation or sample analysis the analytical **performance of the method must be verified** to ensure that it is not altered compared with the original or previous batch.

- **Conditions guaranteeing the maintenance of the stability** of both non critical reagents (e.g. buffers, diluents or acidification reagents) and more importantly of the critical reagents should be documented in order to ensure that the performance of the method is not affected over time.

FDA (draft 2013): Key Reagents

- **Key reagents**, such as **reference standards**, antibodies, tracers, and matrices **should be characterized appropriately and stored under defined conditions**. **Assay reoptimization** or validation may be important when there are **changes in key reagents**. For example:
- Labeled analytes (tracers)
  - Binding should be reoptimized
  - Performance should be verified with standard curve and QCs.
- Antibodies
  - Key cross-reactivities should be checked.
  - Tracer experiments above should be repeated.
- Matrices
  - Tracer experiments above should be repeated.

Japan (LBA, 2013): 6.5. Critical reagents

- **A critical reagent is the one that has a direct impact on the results of an LBA-based bioanalytical method** and usually includes, but is not limited to, binding reagents (e.g., unlabeled or labeled antibodies).

- A critical reagent should be selected by considering the specificity for the analyte and **should be stored under conditions that ensure consistent quality**. The quality of critical reagent should be appropriately maintained throughout the period of use in analytical method validation and study sample analysis. **Partial validation is in principle required when the critical reagent lot is changed**.

Proposal to ICH M10: *Topics NOT to be included in the critical reagent section for LBA*

- Reference standard
  - Not classed in scope as critical reagent for PK assay
- Selection of critical reagents
  - Part of assay development, which is not part of the guideline
- Level of characterization of critical reagents
  - Risk based approach
  - Different possibilities for commercial available and customized reagents

Recommendation from Lisbon workshop on ICH M10

- Critical reagents should be identified and defined for each assay method
- Should be monitored through the life cycle
- Assess for lot to lot changes and consider the impact of the change on the assay
- Documentation: source origin and storage condition by CoA or technical datasheet
- It is possible to extent the stability beyond the expiry/retest date as long as it is monitored

Best practice: change of critical reagents

EBF suggestion to follow GBC paper on critical reagents*

- Definition of minor and major critical reagents
- ”Minor reagent changes are defined as those that are expected to have minimal effects on assay performance and may therefore be implemented without any deleterious effect on data production”.
- Major changes: ”This is the most extensive reagent qualification level and is directed primarily towards the replacement of critical reagent where the original source of a reagent is no longer available”

** King et al: Ligand binding assay critical reagents and their stability: Recommendations and best practices from the global bioanalysis consortium harmonization team, The AAPS Journal Vol. 16, No. 3, May 2014*

Best practice: Lot-change of critical reagents – Minor change

EBF suggestion for minor changes:

Minor change:

- New purification of the same lot
- Relabelling
- Change of standard reagents

<u>Change of standard reagents:</u>

One qualification run with standards and 3 QC levels

If normal run acceptance criteria are fullfilled, then the new batch is accepted – min requirements

To be documented in relevant paperwork for the method

<u>New purification or relabelling of the same lot:</u>

One qualification run with standards and 3 QC levels including the original lot if possible

If normal run acceptance criteria are fullfilled within the same lot, then the new batch is accepted – min requirements

To be documented in relevant paperwork for the method

Best practice: CoA (or technical datasheet)

EBF recommendation for CoA:

- CoA (or technical datasheet) for the new reagent should at a minimum include:
  - Name of reagent
  - Lot nº
  - Catalogue no (for commercial reagents)
  - Concentration, if applicable
  - Retest date (expiry date)
  - Manufactoring date
  - Storage recommendation

Best practice: Stability and Documentation

- EBF recommendation on Stability:
  - Stability testing should be based on performance in the assay, rather than expiry dates from supplier, and retest dates can be set from experience and generic table for recommendation of suggested re-test periods

- EBF recommendation on Documentation:
  - Requirements for documentation of source and origin of critical reagent by CoA or technical datasheet
  - Characterization and selection to be part of development
  - Lot-changes and reagent stability testing should be documented in relevant paperwork for the method

Future

- Discuss best practice in further details for:
  - PK assay
  - Immunogenicity assay
  - Biomarker assay

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