Comed stability testing for chromatographic assays

Presenter: Magnus Knutsson,
on behalf of the EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

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Problem statement – Co-med stability

- Unclear regulatory expectation
- Very little is found in existing guidance/guideline
- FDA Form 483 issued despite not in FDA guidance

Co-Med = adminstration of two or more compounds, either as Fixed Dose Combination or co-formulated

Background – current guidance

- Very little is found in existing guidance/guideline.

- EMA 2012: “In case of a multi-analyte study and specific for bioequivalence studies, attention should be paid to stability of the analytes in the matrix containing all the analytes”.
- CFDA 2016: “For multi analyte study, especially for the bioequivalence study, attention must be paid to the stability of each analyte in the matrix”.

- Nothing in the FDA 2001 guidance or the MHLW CHROM/LBA guidelines

Background

- Laboratories have been cited with Form FDA 483 observations proposing that stability experiments should be conducted in the presence of all administered compounds.

- In literature, there are a few references on FDC where, in a CMC setting, there was impact of the combination during stability testing. This is likely one of the reasons FDC stability testing became part of the bioanalytical toolbox.

Background

- However, there are no public data from submitted dossier that suggests that failed method validation stability experiments might be attributed to co-administered drugs.

Background

- Survey performed

1. Frequency of testing
2. Frequency of failure

Survey results – frequency of testing (n=25)

- 60% of companies have tested Co-med stability in addition to test the stability of separately.

- Experience varies a lot, from only one case to tested in 5 programs/year.

Survey results – frequency of failures (n=25)

- For majority of companies, they have never seen any issue in co-medication stability testing.

- In 2-3 cases there were indications of less stability in Co-Med testing, e.g. 150 days LTS compared with 300-400 days LTS when tested individually. No practical impact. Reality or part of normal method variability

GCC paper*

- 56 different combinations of primary compound analyte stability in the presence of one or more co-administered compounds are reported.
- When all data are taken into consideration, they concluded that there was no evidence (within the dataset) that stability of the primary compound was impacted by the co-administered compounds.
- In addition to the observation that all stability values were within ±15% deviation.

* Lowes et al., Bioanalysis (2012) 4(17), 2117–2126

Recommendation

- Based on the data presented before, both EBF survey data as well as the GCC paper, EBF does not recommend that stability testing of Co-medication should be part of the required method validation parameters.

Acknowledgement

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Contact: info@europeanbioanalysisforum.eu