

Co-med stability and interference testing

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Feedback from the AAPS/EBF/JBF sister meetings

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on behalf of EBF*

10th EBF Open Symposium
10 – A New Journey Begins
NH Collection Barcelona - 15 to 17 November 2017

AAPS/EBF/JBF sister meetings

AAPS workshop

Towards Global Harmonization of Bioanalytical
Method Validations

Weehawken, NJ, USA - Sep 13-15 2017

EBF focus workshop

Industry input into ICH M10 - Experimental data as
the cornerstone for a science driven bioanalytical
guide

Lisbon, Portugal - Sep 24-26 2017

Scope of this presentation

- Give feedback from the workshops on 2 chromatographic based topics
- Co-med stability
- Co-med Interference testing

Background – Co-med stability

- Unclear regulatory expectation
- Very little is found in existing guidance/guideline
- No public data that suggests that failed method validation stability experiments might be attributed to co-administered drugs.
- FDA Form 483 issued despite not in FDA guidance

Regulatory expectations – Co-med stability

- 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

EBF survey data – Co-med stability

- 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.

EBF survey data – Co-med stability

- 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* – Co-med stability

- 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 $\pm 15\%$ deviation.

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

AAPS meeting – Co-med stability

- Should not be required.
 - Data has not been presented to demonstrate that stability in samples with co-meds is different from that of the individual analytes

Recommendation – Co-med stability

- No data are known of co-medication having an impact of stability in bioanalytical matrix
- Stability testing of Co-medication should not be required as a standard validation parameter

Background – Co-med interference

- How to define efficient, consistent and scientific best practices to address interference co-medication testing?
- Expectation in some guidance/guidelines → need to harmonize?

Background – Co-med interference

- US-FDA 2001: “.....each blank sample **should be tested for interference**, and selectivity should be ensured at the lower limit of quantification (LLOQ). Potential interfering substances in a biological matrix include endogenous matrix components, metabolites, decomposition products, **and in the actual study, concomitant medication** and other exogenous xenobiotics.
- EMA 2012 requests to **consider the potential impact of interferences on the drug assay**: “....It may also be necessary to investigate the extent of any interference caused by metabolites of the drug(s), interference from degradation products formed during sample preparation, and **interference from possible co-administered medications**. Co-medications normally used in the subject population studied which may potentially interfere should be taken into account at the stage of method validation, or on a study specific and compound specific base.”

EBF paper – Co-med interference

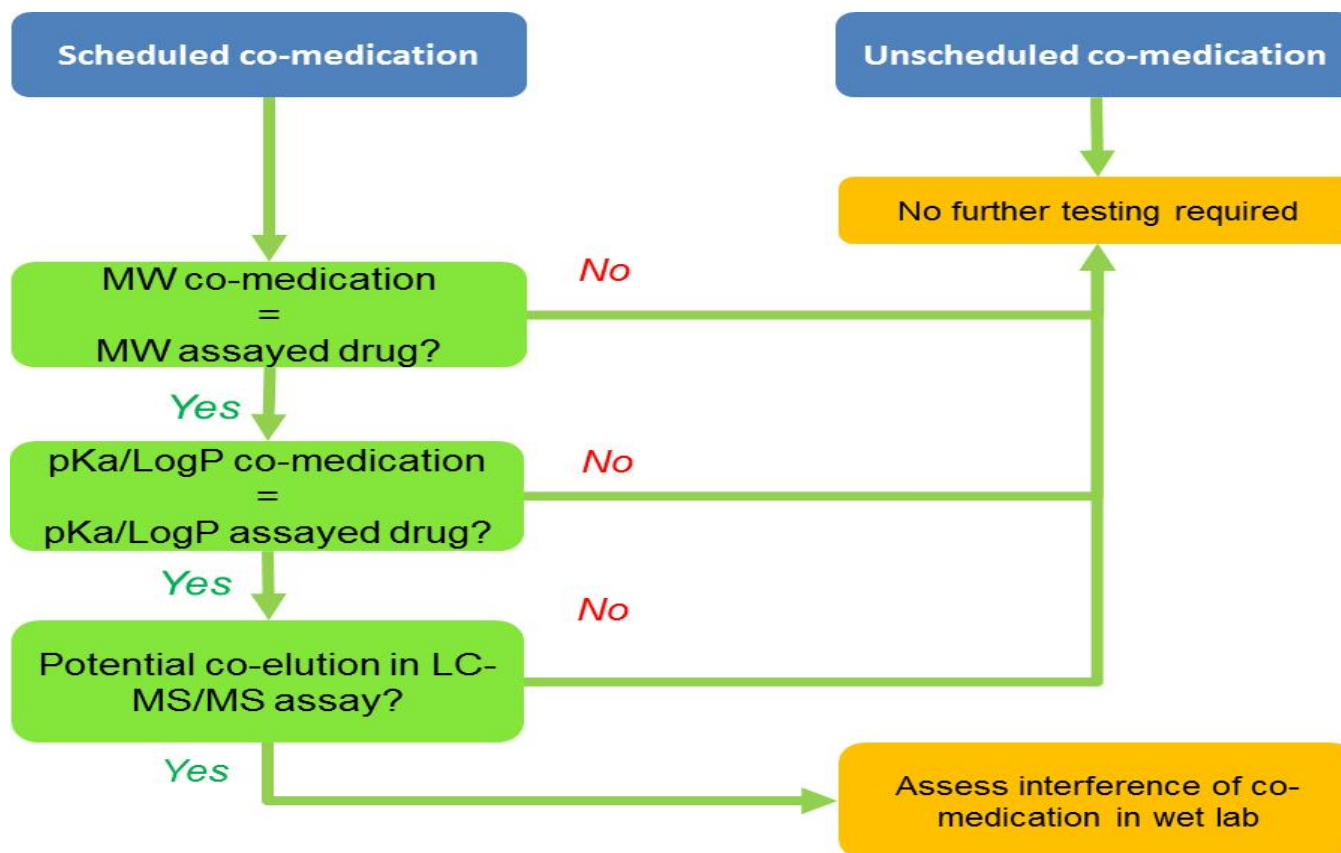
- Based on survey results and discussion within the EBF community the team came up with a recommendation

Co-medication and interference testing in bioanalysis—
Feedback from EBF discussions and recommendations how
to comply with regulatory requirements

Marcel de Zwart, Berthold Lausecker, Susanne Globig,
Daniel Neddermann, Bruno Le Bras, Alberto Guenzi,
Stephen White, Marianne Scheel-Fjording and Philip
Timmerman

Bioanalysis (2016) 8(19), 2065–2070

EBF paper – Co-med interference



Picture taken from de Zwart et al. *Bioanalysis* (2016) 8(19), 2065–2070

AAPS meeting – Co-med interference

- Recommend a “paper” assessment of potential for interference of anticipated co-meds.
 - Based on molecular weight of analyte of co-med
 - Follow up with actual experiment if molecular weights are close
- Recommend collection of pre-dose samples in studies in patients to demonstrate lack of interference for co-meds at steady state

Recommendation – Co-med interference

- No routine validation for scheduled/non-scheduled comedication should be required. Consider principles of paper evaluation as per figure on previous slide, with appropriate scientific nuance pKa/LogP being similar vs. identical, prior to wet lab experiments

Acknowledgement

- EBF TT-31 for the work on Co-med interference testing
- EBF companies for their input to the surveys