Interference Co-med testing for chromatographic assays

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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

- How to define efficient, consistent and scientific best practices to address interference co-medication testing?

- Expectation in some guidance/guidelines → need to harmonize?

Background – current guidance

- 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."

Background

- In discussion within the EBF community difficulties were encountered to define efficient, consistent and scientific best practice to address co-medication testing

- A team was formed to collect experience from EBF member companies with the aim of providing a recommendation

Background

- Survey performed

1. to understand current practices of co-medication testing within EBF companies
2. frequency of interference testing and the results of these experiments

Background

- 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 frecommendations 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

Definitions in the paper

- *"scheduled co-medication"*
  - all co-administered drugs for which dose, time, and route of administration are defined in the clinical study protocol. Scheduled co-medication may be administered to either the entire study population or to pre-defined sub-groups of the study population
- *"unscheduled co-medication"*
  - all drugs which according to the clinical study protocol are allowed to treat side effects and which are applied to single subjects without having a pre-defined dose, time and route of administration

Practice within EBF companies (n=30)

- *scheduled co-medication*
  - 78% of companies tested
- *unscheduled co-medication*
  - 22% of companies tested

- Most commonly used process
  - Spike QC-samples (typically low QC samples) with a predefined concentration of the co-medication (typically at the nominal concentration of the highest calibration point)

Experience within EBF companies (n=29)

- *scheduled co-medication*
  - tested in 272 studies
- *unscheduled co-medication*
  - tested in 117 studies

  - Data from assays with both Stable isotope labelled and structure analogue IS

- **In none of these 389 studies an interference of co-medication was observed**

Summary of practice and experience from EBF companies

- 78% of companies test interference of co-medication for scheduled co-medication
- In total, experience from 389 studies → in none interference of co-medications was observed
- EBF recommendation

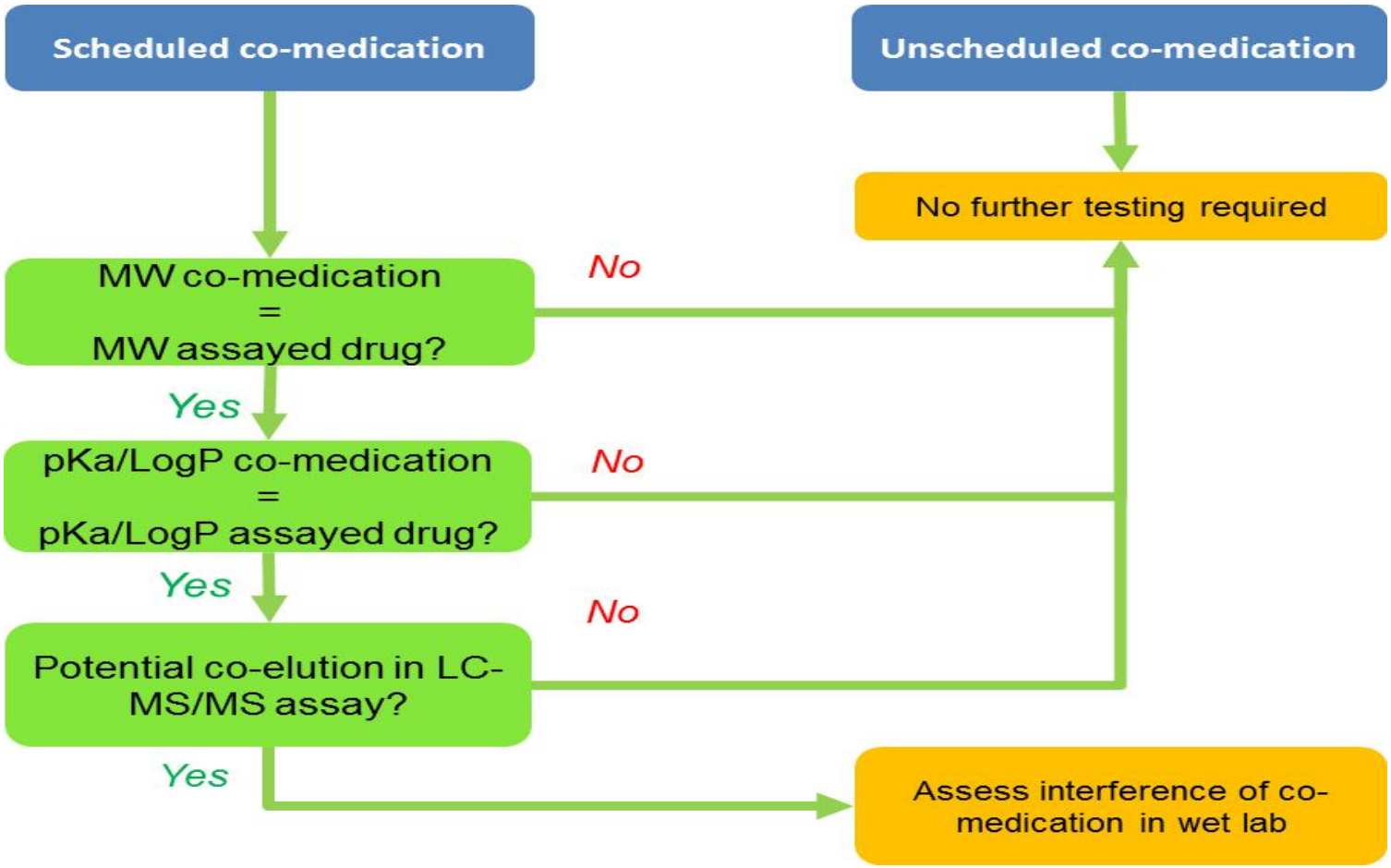
Recommendation - Scheduled co-medication

- If the MW of the co-medication is different from the assayed drug, no further testing is needed.
- If the MW of the co-medication is equal to the assayed drug, identify the pKa and/or log P and assess the potential for chromatographic interference.
  - In case co-elution is not anticipated under the analytical conditions, no further testing is needed.
  - In case co- elution is anticipated under the analytical conditions, we recommend assessing the potential interference of the co-medication in the lab.
  - We would not recommend the need for a CoA for the tested co-medication. Proof of identity should be documented in the raw data, but any certification would not need to be included in the validation or study report

Recommendation - Unscheduled co-medication

- In view of the low likelihood of interference as shown by the survey data (no interference for almost 400 investigated assays), and the difficulties (both logistically and from patient confidentiality perspective) to obtain a list of unscheduled co-medication, no testing is recommended.

EBF recommendation



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

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