EBF Recommendation on testing of co-medications and interaction compounds

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on behalf of the EBF

EBF Open symposium 2013

The Topic Team (TT) – 31

- Aim: **Co-medication and interaction compound testing – best practice and recommendations**
- Formed at the strategic EBF meeting in 2012
- Getting started only in beginning 2013
- Several TCs and 2 surveys about best practice and experience of co-med testing

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Outline

- Background and Goal
- Survey
- EBF-Recommendation
- Future Plans

Background

FDA 2001 and 2013 draft (chapter III, B, 1, selectivity):

…….."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. If the method is intended to quantify more than one analyte, each analyte should be tested to ensure that there is no interference.“

EMA: (chapter 4.1.1 selectivity)

….. "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."

Question:

- How
- How much

EBF Solution?→ form a Topic Team and
→Survey about current practice

Goal

- Evaluate best practice on testing of co-meds and interaction compounds during BMV within EBF
- Evaluate experience and possible threats
- Provide recommondations to BA community

Survey

Defintion of terms:

Co-medication are:

- co-medications (e.g., drug is applied on top of standard therapy)
- interaction compounds (e.g.,DDI –studies)
- fixed drug combinations (e.g., synergistic drugs in a fixed combination)

We distinguish between:

- scheduled co-medications: defined in the study protocol which contains information about dose, route and time of administration and apply to the entire study population or a subgroup of the study

- unscheduled co-medications: are on the list of allowed medications in the study protocol but used to treat side effects as needed and not applied systematically to the entire study population or a subgroup of the study.

Survey

This section belong to chromatography based assays (SMOL)

Q 1. Do you represent Pharma or CRO?
Q 2. Do you test your assay for scheduled co-medication in your company?
Q 3. Do you test your assay for unscheduled co-medications in your company?
Q 4. How do you test the impact of co-medications on your assay?
Q 5. If you test for precision and/or accuracy of QCs, at which level do you test?
Q 6. If you test for precision and/or accuracy, which acceptance criteria do you apply?
Q 7. If you test for co-medications, at which level of co-medications do you test?
Q 8. If you test, then you are testing according to .....
Q 9. If you don't test for co-meds, then (this question is purely focussing on MS)
Q 10. Finally, we would like to ask you if we forgot any major aspect of co-medication testing for the chromatography based assay area?

This page deals with ligand binding assays (IGM)

Q 11. Do you represent Pharma or CRO?
Q 12. Do you test for scheduled co-medications in your company?
Q 13. Do you test your assay for unscheduled co-medications in your company?
Q 14. How do you test the impact of co-meds?
Q 15. If you test for recovery (of QCs), at which level do you test?
Q 16. Which acceptance criteria do you apply for QCs if co-meds were added
Q 17. If you test for co-medications, at which level of co-medications do you test?
Q 18. If you test, then you are testing according to .....
Q 19. At the end, we would like to ask you if we forgot any major aspect of co-medication testing for the IGM area?

Outcome:

Response rate: 30 SMOL (20 Pharma, 10 CRO)
14 IGM (8 Pharma, 6 CRO)

Survey –Results

Q2: Do you test your assay for scheduled co-medication in your company?

	Yes	No
SMOL	85%	15%
IGM	55%	45%

Q3: Do you test your assay for unscheduled co-medications in your company?

	Yes	No
SMOL	25%	75%
IGM	0%	100%

Survey –Results

Q4: How do you test the impact of co-medications on your assay?

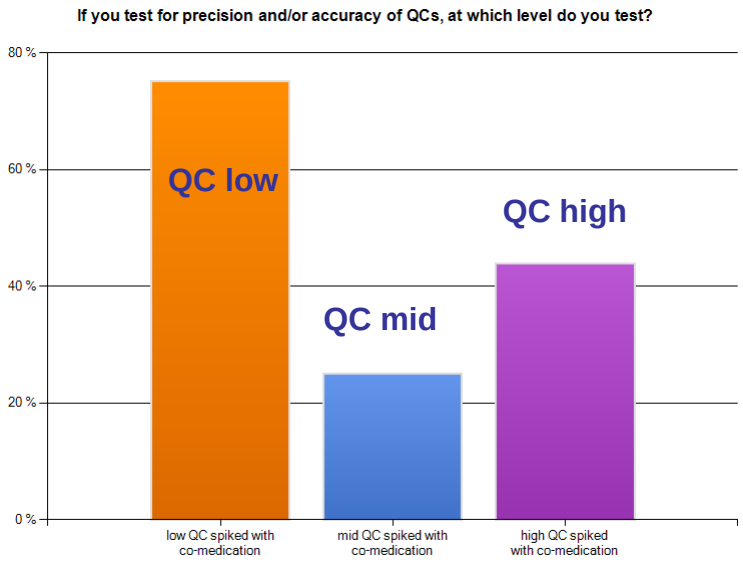
SMOL	
Test for chromatographic interference of pure solutions?	20%
Test for chromatographic interference in spiked matrix after sample preparation?	60%
Test for QC precision and accuracy of the assay analyte?	75%

IGM	
Test for difference in recovery of pure solutions?	0.0%
Test for difference in recovery in matrix after sample preparation (dilution)?	100%

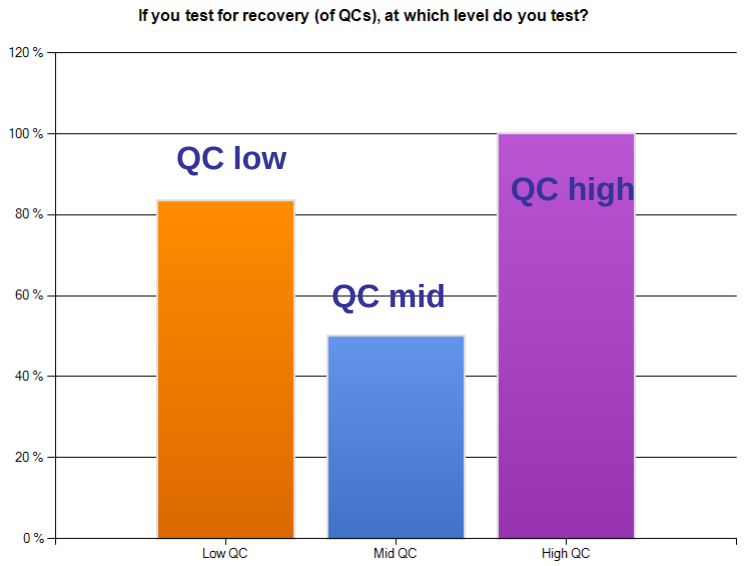
Survey –Results

Q5: If you test for precision and/or accuracy of QCs, at which level do you test?

SMOL



IGM



Survey –Results

Q6: If you test for precision and/or accuracy, which acceptance criteria do you apply?

SMOL	
Simple testing, one level, few replicates, applying 85-115%	82,4%
More extensive testing, multiple levels, multiple replicates, applying 4/6/15 rule	17.6%
IGM	
Simple testing, one level, few replicates, applying 80-120%	83.3%
More extensive testing, multiple levles, multiple replicates, applying 4/6/20 rule	17.7%

Q7: If you test for co-medications, at which level of co-medications do you test?

SMOL	
Cmax of co-med	95%
Same as QC	5%
IGM	
Cmax of co-med	100%
Same as QC	0%

Survey –Results

Q8: If you don't test for co-meds, then (this question is purely focusing on MS)

SMOL

A) You are following the argumentation that mass spec is so specific that interference could be ruled out (30%)

B) You are following the argumentation that mass spec is so specific that interference could be ruled out but only in case you are using a stable isotope internal standard (SIL) (70%)

Survey –Results

Q9: If you test, then you are testing according to SOP and/or study plan.

SMOL and IGM:

Testing is always guided by either SOP or Study Plan

Q10: Finally, we would like to ask you if we forgot any major aspect of co-medication testing for the chromatography based assay and ligand binding assay area?

→ comments

Survey 2 – co-medication testing

Second survey (5 questions)

- was asking for experience made during the recent two years (25 responders)

- 203 studies for scheduled co-meds tested
- 180 SMOL, 23 IGM;118 CRO, 85 Pharma

- 7 studies for unscheduled co-meds tested
- All from CRO

- Not a **single study** was failing
  - none for IGM,
  - none for SMOL with SIL
  - none for SMOL with structural analoque as IS

Best Practice - EBF recommendations

We believe and we have evidence that co-med testing is not needed and we would recommend to follow a tiered approach.

Consider physico-chemical properties of the drug and the co-med and decide on this basis if interference is likely or not.

If interference is likely or could not be ruled out, then:

- Test in matrix samples
- Test for accuracy of QCs SMOL 85-115%, IGM 80-120%
- Test at **low** and **high** QC level, 2 replicates
- Test at Cmax of co-med

Future plan

Collect more data on survey 2:

- Consolidate survey 2
- Publish the results and recommondations

Acknowledgements

- The topic team
- EBF members for providing the data for the survey and the discussions in our meetings
- All of you !!