Stability Assessment: Considerations on Fixed Dose Combinations (FDC)

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Disclaimer

This presentation does not necessarily represent the views of EBF. Rather, it is the intent of the author to try to raise concerns expressed by the global bioanalytical community.

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Topic for Discussion

- From M10 Draft:
  - *If multiple analytes are present in the study samples (e.g., studies with a fixed combination, or due to a specific drug regimen) the stability test of an analyte in matrix should be conducted with the matrix containing all of the analytes.*

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Evolution of the Topic

- EMA 2011 Guidance
  - *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*.
- US FDA 2018 Guidance
  - *For drugs administered as fixed combinations, or part of a specific drug regimen, the stability of the analyte should be assessed in the presence of the other drug. The sponsor should also consider the stability of the analyte in the presence of other co-medications that are known to be regularly administered to patients for the indication of the drug under development.*

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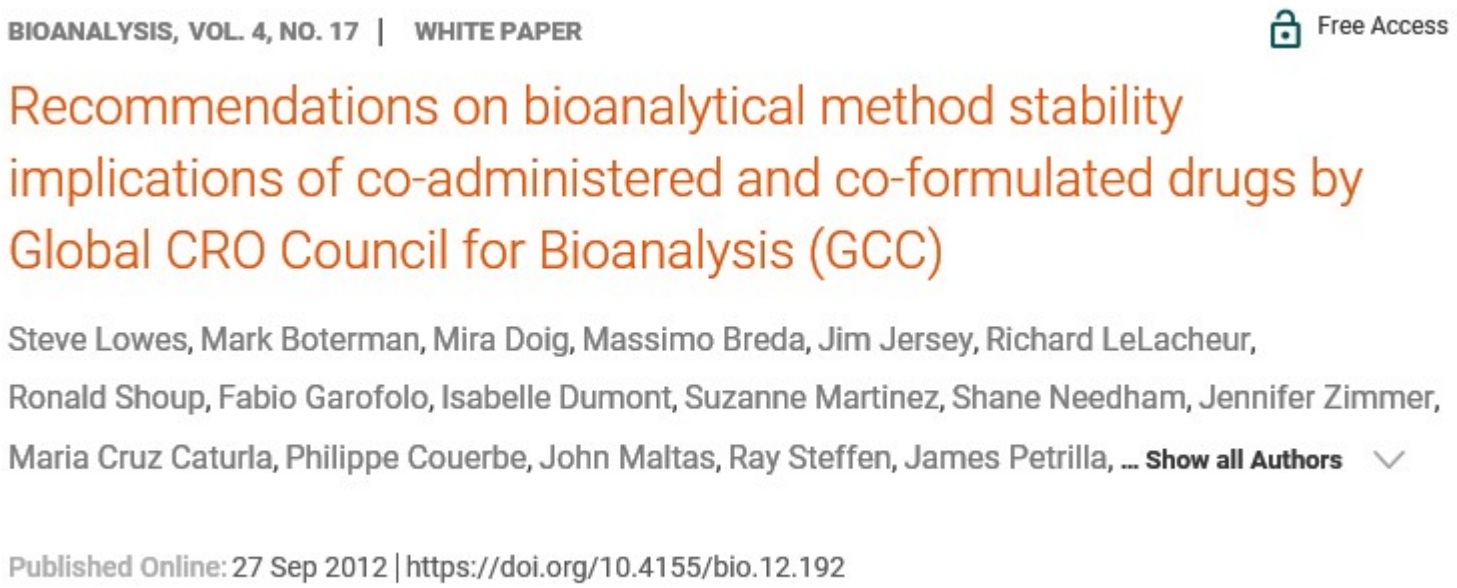
Response of the Bioanalytical Community

- Discussion on topic initiated at the 2010 WRIB meeting and further expanded at the 5th WRIB
  - Proposal made to global CRO community to gather available data on the topic
    - Help inform BA community on the magnitude of the issue



BIOANALYSIS, VOL. 4, NO. 17 | WHITE PAPER

Free Access

Recommendations on bioanalytical method stability implications of co-administered and co-formulated drugs by Global CRO Council for Bioanalysis (GCC)

Steve Lowes, Mark Boterman, Mira Doig, Massimo Breda, Jim Jersey, Richard LeLacheur, Ronald Shoup, Fabio Garofolo, Isabelle Dumont, Suzanne Martinez, Shane Needham, Jennifer Zimmer, Maria Cruz Caturla, Philippe Couerbe, John Maltas, Ray Steffen, James Petrilla, ... Show all Authors

Published Online: 27 Sep 2012 | https://doi.org/10.4155/bio.12.192

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GCC Survey Results

- Results for a total of 56 different combination of primary compound analyte stability in the presence of one or more co-administered compounds were reported.
  - For frozen sample stability
    - Compounds alone: -12.0 to 13.6% loss/gain after storage
    - Compounds in the presence of co-administered compounds: -11.9 to 15.0% loss/gain after storage

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GBC View on Co-Med Stability

- Topic addressed by A6 team

Stability in presence of co-administered or co-formulated drugs (1/2)

Currently, no formal guidance, but regulatory observations on several occasions

Scientifically questionable, how can the presence of another drug induce instability of an otherwise stable compound?

Practically, it has a relatively large impact

All stability assessments?
All co-administered compounds?
Metabolites of co-administered compounds?

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Global Bioanalysis Consortium
On harmonization of bioanalytical guidance

Stability in presence of co-administered or co-formulated drugs (2/2)

GCC (Global CRO Council) survey early 2011

Results on over 100 non-proprietary and over 60 proprietary compounds were evaluated

No cases seen where there was instability due to the co-administered drug

Bioanalysis (2011) 3(12): 1323-1332

GBC HT recommendation: there is no need.

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Global Bioanalysis Consortium
On harmonization of bioanalytical guidance

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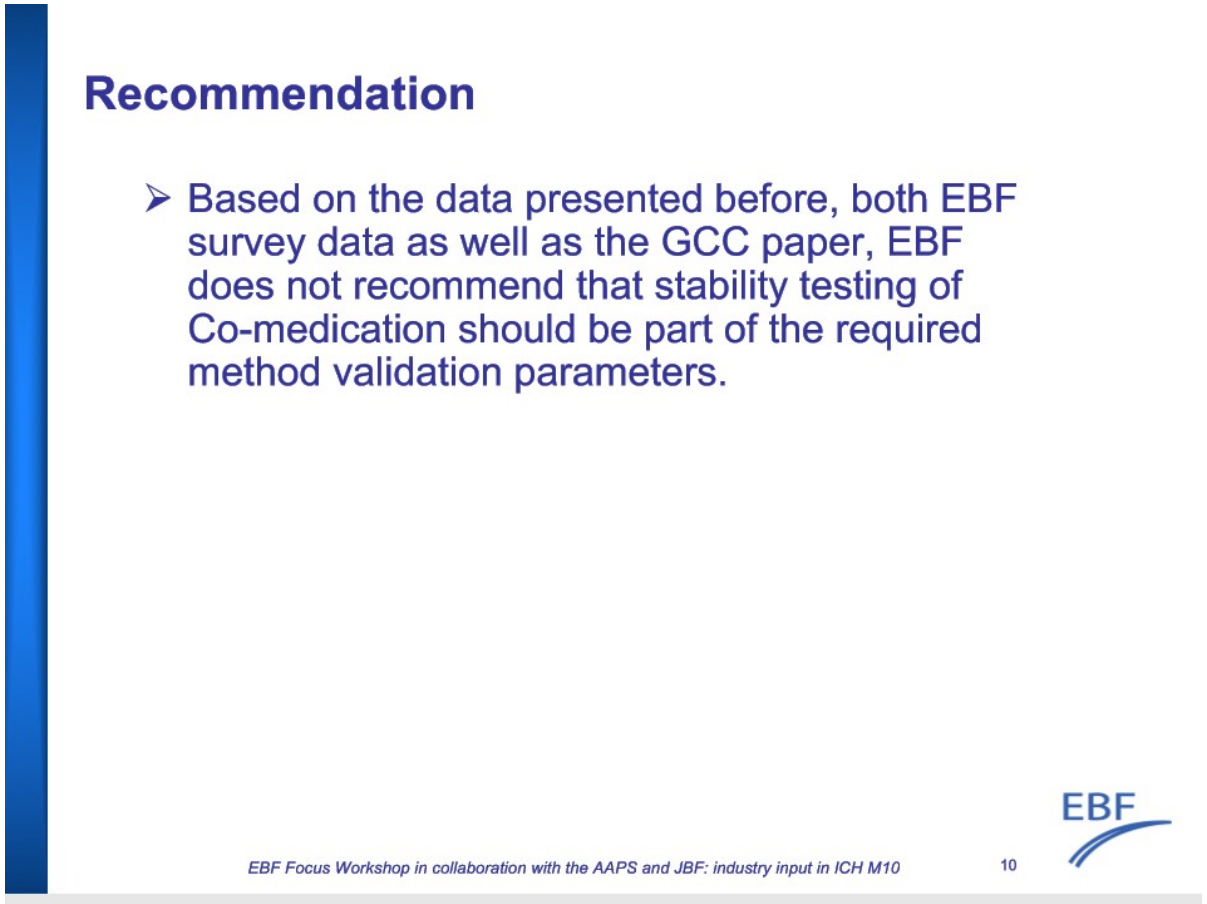
EBF View on Co-Med Stability



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Given the Totality of the Data the Industry has Provided, Why Does this Topic Persist?

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Recent Regulatory Experience

- From a Clarifax received from Health Canada in 2018 in conjunction with submission of a fixed combination tablet

5. As stated in the EMA *Guideline on Bioanalytical Method Validation* (which has been adopted by TPD), for multi-analyte bioequivalence studies, "attention should be paid to stability of the analytes in the matrix containing all the analytes". Please provide the results of studies demonstrating the matrix stability (i.e., long-term frozen stability, freeze-thaw stability, and bench-top stability) of both [redacted] in QC samples containing both analytes at concentrations reflective of those observed in subject samples.

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Response to Clarifax

We acknowledge the recommendation in the EMEA bioanalytical method validation guidance that "attention should be paid to stability of the analytes in the matrix containing all the analytes." We agree that a requirement to generate explicit stability data is scientifically justified when it is expected that multiple analytes may interconvert; examples include assays for pro drugs/active species or assays for molecules and their active metabolites.

In the case of chemically un-related and relatively stable species such as [redacted] and [redacted] it is hard to conceive of a mechanism whereby one could influence the stability of the other in a biological matrix where both are present at ng per mL concentrations. As noted in section 2.7.1.1.5.1 of the submission, the stability of [redacted] in plasma is 628 days (-20°C) and that of [redacted] is 753 days (-20°C). The longest period between sample collection and analysis from samples in the studies in this submission was 105 days.

A recent survey of bioanalytical laboratories (Bioanalysis 4(17) 2117) found no cases where the stability of multiple chemically unrelated drugs in a single matrix was significantly different then the stability of the compounds alone in the same matrix. More recently, this finding was replicated in a survey by the European Bioanalytical Forum (http://dialogue.europeanbioanalysisforum.eu/wp-content/uploads/2017/10/19.-Magnus-Knutsson-Comed-stability.pdf).

Given the above historical findings, the stability of [redacted] and [redacted] in the samples containing both analytes was not considered to be significantly different from that in samples containing the individual analytes and therefore explicit stability assessments were not conducted.

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Response to Response – Another Clarifax

2. Item #5 of the request for clarification dated January 25, 2018 requested data demonstrating the matrix stability (i.e., long-term frozen stability, freeze-thaw stability, and bench-top stability) of both [redacted] and [redacted] in QC samples containing both analytes at concentrations reflective of those observed in subject samples.

In your response, you have cited the results of retrospective surveys of bioanalytical laboratories, which found no examples in which the stability of a primary compound was affected by a co-administered compound. While the results of retrospective surveys contribute to the overall body of information regarding this issue, such study designs are known to be subject to several sources of bias. In addition to those associated with retrospective studies in general (e.g., selection bias), possible sources of bias particularly relevant here are that significant stability interactions between coadministered compounds may result in a bias in reporting, as well as a bias in the likelihood that a combination product may succeed in development to the point that such stability studies would be undertaken. While the survey results do suggest that stability interactions between coformulated medications are likely not common, they do not provide a level of evidence sufficient to rule out such an interaction between [redacted] and [redacted]

Aside from highlighting the results for the stability studies of the individual drug substances alone in plasma, you have not provided a scientific justification directly supporting the particular situation for [redacted] and [redacted] administered in combination. These data are required: in their absence, the reliability of the results of the clinical sample bioanalyses, and thus the results of the comparative bioavailability studies, are undermined.

If well designed matrix stability studies are not available, DBE is willing to consider other relevant scientific data (e.g., based on the physiochemical characteristics of [redacted] and [redacted] the results of incurred sample reanalyses for clinical samples stored under conditions and duration supportive of those applicable to those from Studies [redacted] and [redacted].

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Hypothetical Concerns

- Enzyme replacement therapy
  - Higher concentrations of enzyme in samples may impact stability of any analytes that are enzyme substrates
- Drugs that impact chemical properties of the matrix
  - Compounds that alter urinary pH co-administered with drugs whose urine stability is pH sensitive

No actual data reflecting the above scenarios have been shared by regulators

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Suggested Edit for M10

- Place focus primarily on those studies for which PK is a primary objective
  - If multiple analytes are present in the samples (e.g., studies with a fixed combination, or due to a specific drug regimen) *from a study whose primary objective is PK assessment*, the stability test of an analyte in matrix should be conducted with the matrix containing all of the analytes.

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Objectives from a Recent Oncology Study Protocol

- Primary Objectives
  - Objective: To evaluate overall response rate (ORR) as assessed by X per Y, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.
- Secondary Objectives
  - Objective: To evaluate progression free survival (PFS) as assessed by X per Y, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ
  - Objective: To evaluate the duration of response (DOR) per X, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by Y
  - Objective: To assess safety and tolerability of treatment with X in combination withY.
  - Objective: To characterize the population PK of X when co-administered with Y.

PK is Secondary Objective; Co-med Stability Would be Out of Scope per Proposal

Practical Aspects to Consider

- From GBC A6 Recommendations (*AAPS J, 16 (3) 392-399*)
  - "*For multi-analyte assays, it is most practical, although not scientifically required, that all analytes are added to the samples used for stability assessment*."
    - For studies where multiple analytes are being assayed (even with separate assays), consider using QCs that contain all analytes
- Health Canada has suggested using incurred sample stability assessments as surrogate for explicit stability studies
  - Time between initial and repeat analysis must be greater than time between collection and analysis
- CMC data (stability of fixed dose combination tablets) has been accepted by at least one regulatory authority as rationale for why stability assessment was not needed

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Conclusions

- Despite data driven efforts by the bioanalytical community to convince regulators of unlikelihood that co-medication impacts the stability of co-administered analytes in matrix, the requirement for co-med stability persists in the M10 draft and will likely be contained in the final version
- Efforts by the bioanalytical community should focus on clearly defining the situations in which such assessments are required
  - Consider studies where PK is a primary objective.
    - Better yet: Limit to bioequivalence studies of fixed dose combinations

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THANK YOU