Co-stability assessment for fixed dose combinations: an additional burden to bioanalytical method validation

Tom Verhaeghe, Janssen Research & Development

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Introduction

- Current trend to develop fixed dose combinations (FDC, n-in-one pill), eg for HIV or hepatitis treatment
- Complicating factor: often drugs are developed by different companies and analyzed in different labs → separate assays
- Regulators requesting data to prove matrix stability in presence of co-administered drugs
- Uncertainty around background for these requests

Example #1; 483 observation

- BE study to compare the FDC of Janssen1, Drug2 and Drug3 to the administration of the individual compounds
- Janssen1 analyzed at Janssen's preferred CRO, Drug2 and Drug3 analyzed at co-developer's CRO
- April 2011: inspection in Janssen's preferred CRO
  483: "Failure to demonstrate the long term stability of Janssen1 in human plasma in presence of Drug2 and Drug3 for the duration of sample storage (51 days) at – 20 °C"

Example #1: mitigation

- Performed LTS experiment for Janssen1 at -20 °C and -70 °C in the presence of 600 ng/ml Drug2 and 2400 ng/ml Drug3

Example #1: mitigation

conc. Janssen1	storage (days)	temperature (˚C)	deviation
3 ng/ml	11	-20	-7.5 %
	11	-70	-3.5 %
	61	-20	+1.3 %
	61	-70	+1.9 %
1600 ng/ml	11	-20	-2.3 %
	11	-70	-3.6 %
	61	-20	+1.2 %
	61	-70	+0.9 %

No effect from co-administered drugs on LT stability of Janssen1

Example #2

- Phase 1 multiple dose study to evaluate the relative bioavailability and PK of Janssen2 when co-administered with Drug4
- Janssen2 analyzed at Janssen's preferred CRO, Drug4 analyzed at co-developer's CRO
- February 2013: inspection in Janssen's preferred CRO 483: "Failure to evaluate long term stability at -70 °C for Janssen2 in the presence of Drug4. Specifically, subjects were co-administered by Janssen2 and Drug4 for 10 days, plasma samples collected and stored in the freezer contains both the drugs"
- Important note: drugs were administered as separate doses, no FDC!

Example #2: mitigation

- Performed LTS experiment for Janssen2 at -20 °C and -70 °C in the presence of 2500 ng/ml Drug4

Example #2: mitigation

conc. Janssen2	storage (days)	temperature (˚C)	deviation
15.0 ng/ml	62	-20	-5.3 %
	62	-70	-2.9 %
8000 ng/ml	62	-20	0.0 %
	62	-70	-1.5 %

No effect from co-administered drug on LT stability of Janssen2

Regulatory guidelines

- EMA: “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”
- FDA: not explicitly mentioned; not even in 2013 draft

Consequences

- What is a “multi-analyte study” ? → Not only co-formulated drugs but also co-administered drugs like in DDI studies?
- Looks like FDA only asks for LTS, while EMA mentions “stability” → Applicable to bench top and F/T as well?
- If we go down that route this may have a huge impact on workload for additional validation work

Are we the only one faced with this issue?

- GCC conducted survey and collected existing stability data for non-proprietary compounds[1]
- 56 different combinations listed; mix of benchtop, F/T and LTS
- No evidence that stability is impacted by co-administered compounds
- GCC recommends to conduct benchtop and F/T co-stability experiments for FDC. If these fail perform LTS as well.

1. S. Lowes et al., Recommendations on bioanalytical method stability implications of co-adminstered and co-formulated drugs by Global CRO Council for Bioanalysis (GCC), Bioanalysis (2012), 4(17), 2117-2126

Conclusion

- No scientific rationale why co-administered drugs would impact stability
- No experimental data (both Janssen data and data from GCC survey) providing evidence of any impact of co-administered drugs on stability of individual analytes
- Stability data generated for the individual analytes should be applicable for multi-analyte studies (under the assumption that all other collection and storage parameters remain identical)
- Recommend against generating co-stability data if stability data are already available for individual analytes!

Poll