Blood Stability Testing

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on behalf of the EBF

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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Current challenges with blood stability testing

- Current regulatory guidance does not strictly require blood stability testing in all cases, leaving room for scientifically justified strategies
- Surveys have demonstrated lack of acute problem with blood stability tests due to low mismatch rate vs. plasma stability (≤ 5%)
- **In reality**, however, blood stability is routinely run as a method validation item in many pharma companies
- Significant driver seems to be CRO SOPs
- Is industry on the right track?

Regulatory landscape

- FDA 2001 and 2013 (draft) are pretty similar
  - „Stability procedures **should evaluate** the stability of the analytes during sample collection and handling“
  - Remaining documend is silent
- CC-V White Paper
  - Silent
- EMA 2012
  - **Sufficient attention** should be paid to the stability of the analyte in the sampled matrix directly after blood sampling of subjects and further preparation before storage, …
  - A demonstration of this stability may be needed on a case-by-case basis, **depending on the structure of the analyte**.
- PFSB 2013 and ANVISA
  - Very general, not specifically mentioned

→ **Opportunity for science-driven processes**

Recap of 2008 – 2011 Discussions: Survey Results

- Incidence of mismatches between plasma and blood stability was reported to be low (<5%)
- Testing warranted as incidence is low, but not zero
- Parallel or tiered approach recommended
- Plasma stability considered as acceptable surrogate or data covered by other DMPK studies
- Mismatches explained by
  - Higher enzyme activities in blood vs plasma
  - Cpd classes where reductive mechanisms involved

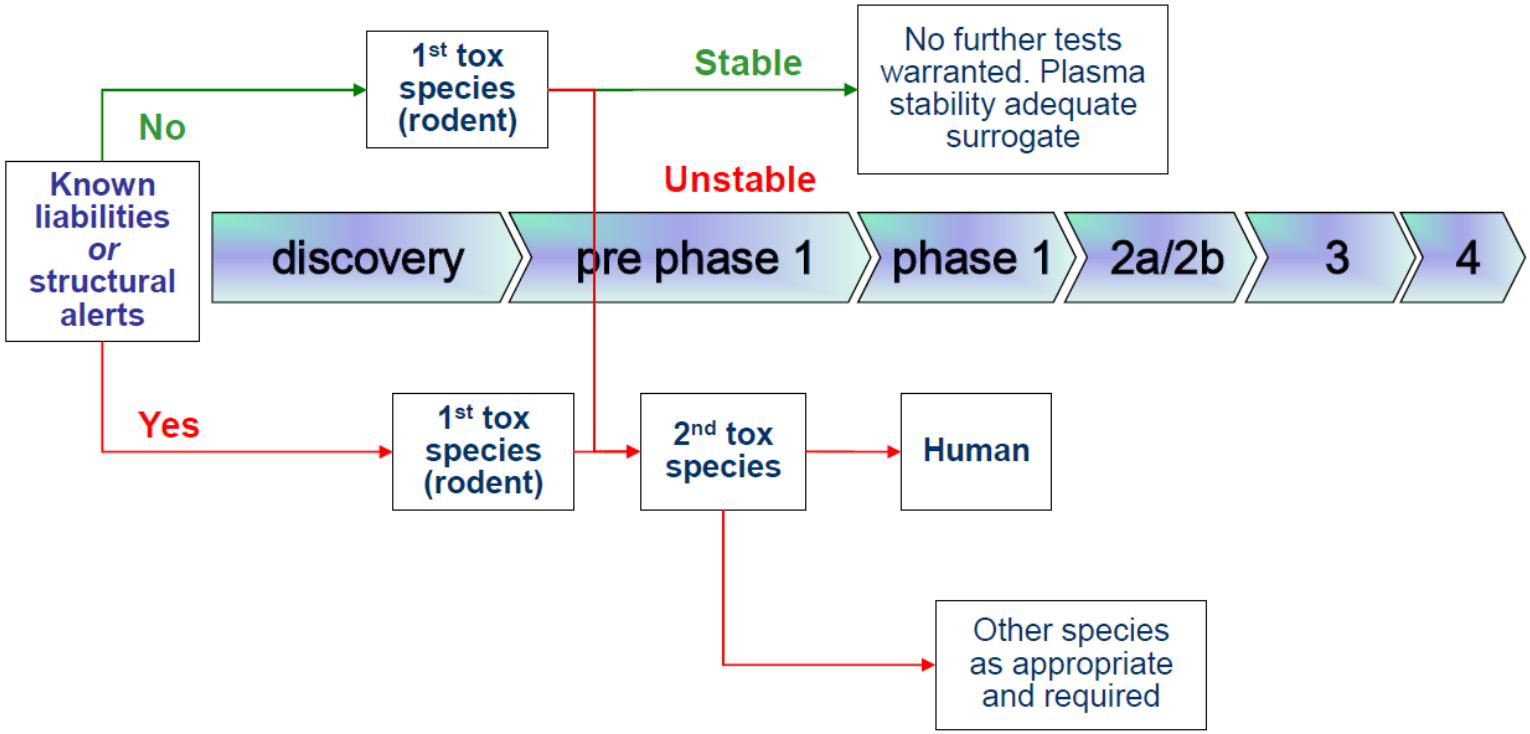
Recap of 2008 – 2011 discussions: EBF recommendation #1

EBF Current Thinking on WBS - summary

1. Test at least one species, preferably rodent
2. Analyse whole blood – not plasma
3. Recommended to use a qualified assay
4. Data available as part of filing documents
5. Further investigations required once instability is observed
6. Incurred samples might be considered in special cases

Recap of 2008 – 2011 discussions: EBF recommendation #2

Proposal for Tiered Approach



Situation 2017 – FoP and follow-up discussions

- Out of 20 Pharma, only 6 **do not** run whole blood stability (WBS) experiments routinely in validation
- Out of the remaining 14 Pharma
  - 7 do clinical and non-clinical
  - 7 do only clinical
- Most CROs routinely run WBS as part of the validation SOP, i.e. in **all validation studies**
- Availability of fresh blood (defined as being <24 hours old) still seems to be a concern
  - Raises questions about the appropriateness of the WBS experiment
  - Added value over plasma stability?

Outlook #1

Summary

- Compared to number of mismatches between blood and plasma, **high incidence of validation work** for blood stability
- More validation work done in **human** as opposed to non-clinical (i.e. the more ‚early work')
- In essence, tiered or parallel approaches are **not common practice**

Outlook #2

Proposed recommendation

- Blood stability is **not required as a routine validation item** but focus should be on selected experiments based on incidence and knowledge on compound classes

  → **Tiered/parallel approach**

- Focus on the right experiment at the right time (i.e. in early development, pre-GLP) with matrix as well controlled as possible. **Blood stability should not be a tick-box experiment**

- **Appropriate documentation** is needed to support filings

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