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

The Altis Grand Hotel Lisbon,
Portugal September 24-26, 2017

SUMMARY of RECOMMENDATIONS

AAPS/EBF/JBF

Joint Sister Workshop

- Weehawken, NJ workshop (hosted by AAP, Sept 13-15, 2017)
  - with contribution from CBF
  - With global participation (Pharma/CRO)
- Lisbon, Portugal workshop (hosted by EBF, Sept 24-26, 2017)
  - With global participation (Pharma/CRO)

AAPS/EBF/JBF

Joint Sister Workshop

- The Weehawken and Lisbon meetings were organized as synergistic meetings
  - Not all themes were discussed at both meetings
  - Weehawken meeting was organized using a template of the 'Crystal City' meetings (i.e. more strategic in nature)
  - Lisbon meeting was organized using survey data and industry discussions in EBF as a starting point.
  - The resulting recommendations combined aim at providing comprehensive feedback of current industry position on minimum required standards for consideration in a modern science based Guideline

Disclaimer

- *The recommendations in this summary slide deck and the accompanying individual presentations are the result of discussion at the Lisbon meeting, often prepared from industry surveys and discussions in the EBF community and do not necessarily reflect the representative affiliation or company's position on the subject.*

General comment - 1

- The slides in this presentations contain the overall conclusions from the individual presentations from the Lisbon meeting.
- More detailed recommendations can be found in the individual slide decks as presented at the meeting – see next two slides for overview of presentations given. If applicable, detailed recommendations as presented were acknowledged and not repeated in the summary recommendation
- The slides will become available from 10 October on following link: *http://dialogue.europeanbioanalysisforum.eu/previous-meetings/*

Overview of presentations - 1

- 01. Philip Timmerman - Introduction_final.pptx
- 02. Jo Goodman - Issues in Industry with Current Guidance_final.pptx
- 03. Noriko Katori-final.pptx
- 04. Faye Vazvaei - Take Home Messages on Behalf of AAPS.pptx
- 05. Philip Timmerman - Scope_final.pptx
- 06. Morten Kall - ISR revisited - EBF Perspectives_final.pptx
- 07. Joe Stanta - Reanalysis_final.pptx
- 08. Tom Verhaeghe - documentation_final.pptx
- 08b. Faye Vazvaei - Take Home Messages on Behalf of AAPS on session 2.pptx
- 09. Philip Timmerman - PK Criteria - Final.pptx
- 10. Hisanori Hara - ICH M10 Harmonization JBF general_final.pptx
- 11. Steve White - Run acceptance criteria_final.pptx
- 12. Rachel Green - Cross and partial validation_final.pptx
- 13. Stuart McDougall - General principles of stability testing_final.pptx
- 14. Amanda Wilson - EBF Requirements for reference standard NCE_final.pptx
- 15. Marianne Scheel Fjording - Reference standards NBE - final.pptx
- 16. Peter van Amsterdam - MidQC.pptx
- 17. Cecilia Sparr Eskilsson - Hemolized and lipemic samples_Final.pptx
- 18. Timothy Sangster - LTS.pptx
- 18b. Faye Vazvaei - Take Home Messages on Behalf of AAPS on session 4pptx

Overview of presentations - 2

19. Magnus Knutsson - Comed stability_final.pptx
20. Achim Freisleben - Blood Stability_final.ppt
21. Amanda Wilson - processed sample stability.pptx
22. Hisanori Hara - ICH M10 Harmonization JBF Chromatography.pptx
23. Eric Woolf - FB from AAPS/JBF/EBF for Lisbon kopie.pptx
24. Michaela Golob - Selectivity_final.pptx
25. Robert Nelson - Dilution linearity - parallelism_final.pptx
26. Marianne Scheel Fjording - Surrogate matrix LBA_final.pptx
27. Susanne Pihl - critical reagents_final.pptx
28. Heather Myler - EBF AAPS JBF BMVH LBA Summary Lisbon ICH_Final .pptx
29. Magnus Knutsson - interference testing_final.pptx
30. Benno Ingelse - Matrix effect_final.pptx
31. Eric Woolf - AAPS Feedback_Final.pptx
32. Pascal Delrat and Gerhard Paul - Singlet vs Duplicate_final.pptx
32. Pascal Delrat and Gerhard Paul - Singlet vs Duplicate_IQ.pptx
33. Jo Goodman - what should not be in a Guideline_final.pptx
34. Heather Myler - EBF AAPS JBF BMVH LBA Summary Lisbon.pptx

General comment - 2

- Throughout the Weehawken and Lisbon sister meetings, there was continuous reflection if the guideline should not focus on BE studies, or at least that BE studies should have the most stringent criteria which cannot and should not apply for any other type of study.
  - A potential solution, in order not to dilute the acceptability of the non-BE studies for our stakeholders, is to provide clear expectations for both areas, by calling out some specific requirements for BE studies (e.g. add *'(for BE studies)'* after some requirements in the guideline or specify some waivers in a Q&A

Recommendation from panel discussion Session 1 – Scope of Guidance/Guideline

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What should be the scope of the guideline and why.

including discussion on studies, development phases or analytes in/out of scope

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Recommendation

- There is no desire to include specific guidelines on alternative validation approaches in ICH M10
- There is no desire to to include list of studies or specify development phase in scope of alternative validation approaches in ICH M10

Recommendation – Scope

- In scope for ICH M10:
  - Quantitative analysis of primary PK analyte
  - Primary matrix
  - The stage of drug development and/or the type of study analyzed should be considered in the scope statements to ensure more scientific freedom at earlier stages of drug development
  - For non-primary analytes/matrices (e.g. early metabolite evaluations (pre- ICH M3 (R2)) or urine and tissues), validation should be performed in line with the anticipated use of the data, using the appropriate/applicable principles described herein. The acceptance criteria and extend of experimental details may vary from those in this document
- Special considerations:
  - Validations for pre-clinical studies may require only a subset of experiments required for clinical (BE-type) PK studies
  - Validation for SAD/MAD studies should be allowed more scientific freedom

Recommendations for Session 2

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06. Recommendations - ISR

- Advise to industry: Limit the number of - and study types in which ISR is performed to those required in current guideline

- Single-sample variation in passed ISR should not call for investigation

- Reduce ISR to 5 % (align with QC) and recommend a minimum and maximum number for ISR analysis

07. Recommendations - Re-analysis

- Guideline should include a reanalysis decision tree, defining acceptance criteria and what is reported value
  - Process for re-analysis should be defined in SOP
- Two types of repeats were identified
  - Analytical repeats (e.g. human error, instrument failure)
    - Should be accepted practice. Reanalysis limited to single samples
  - PK repeats
    - (e.g. positive control, zero mid profile) should be accepted practice. Reanalysis limited to duplicate samples
    - Repeats for PK outliers should be discouraged, especially in for BE studies.

08. Recommendations - Documentation

- Recommendation to use the table from CC III paper as a starting point for ICH M10 discussions on documentation – consider GBC A8 TOC

- Avoid including very detailed information on sample collection/storage/unavailability in the report and keep this in the raw data
  - If this detail is really needed in the report propose to limit to BE/BA type studies

Recommendations and reflection from session 3

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11. Reflection - Harmonized PK run acceptance criteria

- Subject was presented to both Weehawken and Lisbon community to reflect on and discuss the added value of the proposal
- We recognize that change is not a natural characteristic of a BA community, certainly when there is no burning need for change. Nevertheless we feel this proposal has value for the BA community going forward.
- Further reflection and interaction with end users of the data required.

12. Recommendations - Cross Validation

- Note: Discussions did not focus on partial validation
- Cross validation should only be mandatory when data from different methods, or the same method in two different laboratories, are used in the same study.
- No regulatory requirement for cross validation when different methods are used across studies.
- No regulatory requirement for cross validation when different analytical technologies (e.g. LBA vs LC-MS) are used across studies. A comparison of two technologies may be performed to build scientific knowledge but should not be subject to any acceptance criteria.
- Incurred samples are preferred, but spiked QCs are acceptable. Consider informed consent when using incurred.
  - For spiked QCs: 3-6-15/20 acceptance criteria
  - For incurred samples: Minimum of 20 samples; acceptance criteria as ISR, 67% within 20/30% of mean

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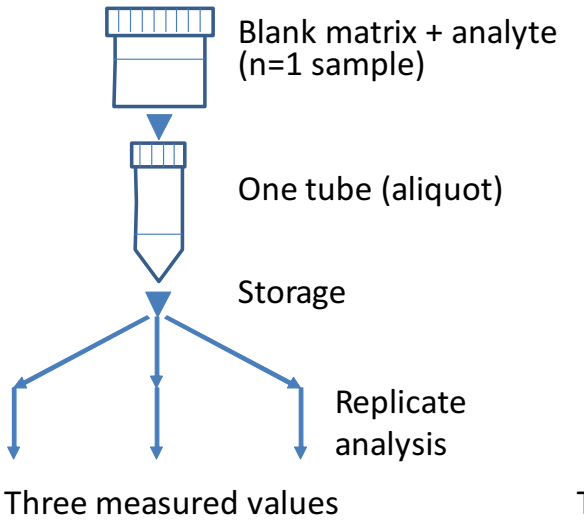
13. Recommendation - Stability testing

- One ‘sample’ prepared at each drug level (i.e. QCL & QCH).
- Single aliquot subjected to test condition (temp/time)
- Replicates (≥ 3) analysed from aliquot.
- Fresh calibration (for long-term frozen stability testing) and QC control.
- Mean bias within ± 15% (for chromatographic) and ± 20% (for LBA) of nominal drug concentration.
- Multiple ‘tubes’ will increase cost, potentially require more matrix (unethical) and will not improve data quality



Recommendations from session 4

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14. Recommendation – Reference Standard NCE

- Where the reference item is retested and there is a change of purity, this new purity should apply.
  - However, there will be no retrospective recalculation using the new purity
- Stability of material is in the state it is prepared, i.e. any solution does not expire with the expiry of the test item

15. Recommendation – Reference Standard NBE

- If proper comparison of different batch done in GMP environment there should not be a requirement to use same batch of Ref Std for Cal & QC preparation as the dosing batch
- When having new batch it is not a requirement to revalidated your method.

16. Recommendation – mid QC placement

- Both Chromatographic and LBA methods should use the geometric mean to position the mid-QC.
  - LBA methods anchor-points should not be included in assessing the mid QC level

17. Recommendation - haemolysed/hyperlipidaemic

- Not a routine validation parameter
- Inclusion in relevant patient populations should be scientifically driven, e.g. high-fat populations, CV indications and where there is an impact on red-blood cell
- Affected individual samples will not impact the study outcome

18. Recommendation – 20°C/-70°C

- Documentation of frozen storage stability at one temperature and time validates the use of lower temperatures for storage.
- This is applicable for both LBA and Chromatographic assays

Recommendations from breakout session 5 - CHROM

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19. Recommendation - Co-med stability

- No data are know of co-medication having an impact of stability in bioanalytical matrix
- Stability testing of Co-medication should not be required.

20. Recommendation - Whole Blood Stability (WBS)

- WBS should not be a mandatory experiment during method validation
  - WBS may be required on a case-by-case basis, depending on the structure of the analyte.
- Bioanalytical labs are responsible to guide the sampling procedures. Scientific investigation in this respect may involve assessment of WBS.

21. Recommendation - process sample stability & re-injection stability

- Stability experiments in the context of this slide should mimic the process utilized during sample analysis
  - Consequently, inclusion of fresh calibrators against process samples is not generally required
- If the data can be derived from the P&A experiments, no additional process sample stability experiment is required during method validation
  - If the required PSS during sample analysis exceeds the tested period, additional PSS is warranted

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Recommendations from breakout session 6 - CHROM

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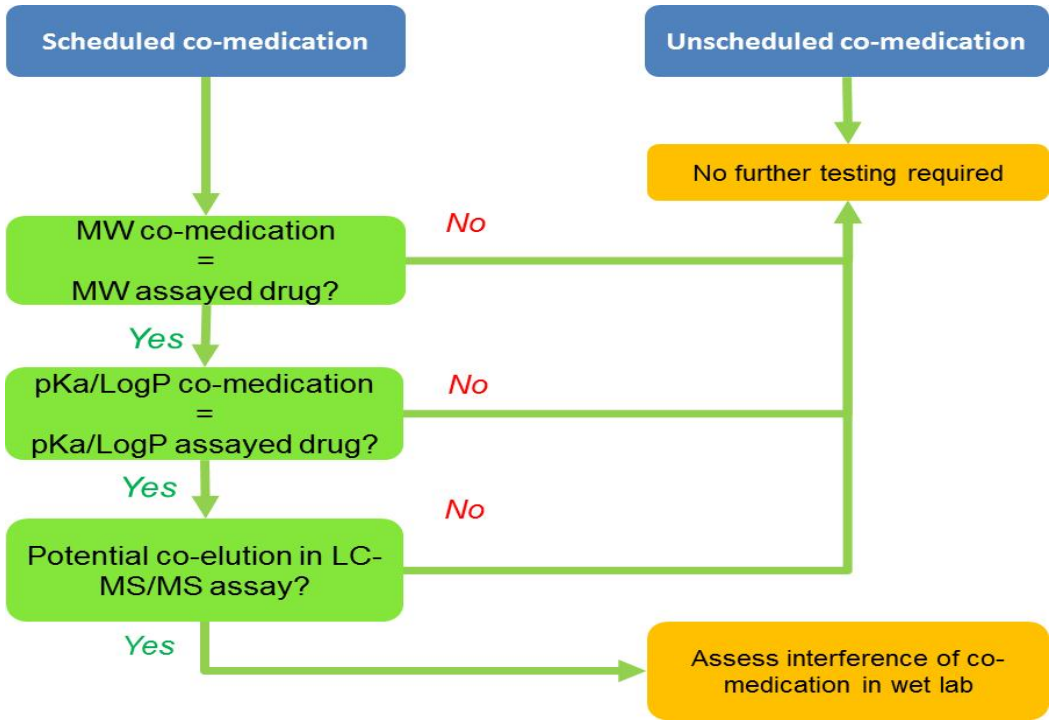
29. Recommendation – Co Med interference

- No routine validation for scheduled/non-scheduled co-medication should be required. Consider principles of paper evaluation as per figure below, with appropriate scientific nuance pKa/LogP being similar vs. identical, prior to wet lab experiments



30. Recommendation – Matrix Effect for LC-MS

- Matrix factor is not adding value
- Matrix effect assessment should be evaluated using a QC-type experiment.
  - Number of QC-levels, replicates: 6 lots (clinical)
  - Consider leaner experiment for pre-clinical species
  - Mean Bias & precision should be ≤ 15%
- SIL-IS recommended
- Downstream matrix effects during sample analysis
  - Individual haemolysed / hyperlipidemic samples covered by SIL or deemed not having impact on data conclusions
  - Disease state/special populations: consider additional ME (in study) investigations

Recommendations from breakout session 5 - LBA

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24. Recommendations - Selectivity and Interferences LBA

- Harmonised definition of selectivity and specificity to be included in the guideline for both chromatography and LBA
- MRD/interference is not a validation parameter as it belongs in method development
  - Summarize in method validation report
- Minimum requirements for selectivity as validation parameter
  - 10 sources of individual HV and/or relevant matrix (if scientifically driven)
  - Spiked at or within 2x LLOQ
  - Acceptance
    - 80% of tested blank sources <LLOQ
    - 80% of spiked sources within 25% RE

25. Recommendations - Dilution Linearity and Parallelism

Dilutional Linearity

- Blank matrix sample spiked at or above anticipated Cmax or at highest feasible concentration
- At least one concentration >ULOQ (to evaluate hook effect) and 3-5 dilutions within assay range
  - Dilution scheme should reflect that used for study samples
- Acceptance: within 20% RE for all in-range diluted samples
  - Evaluate trends that may have meaningful impact on the study data

Parallelism

- Not a routine validation parameter
- If scientifically relevant, incurred samples tested at multiple dilutions (above and within assay range)
  - Individual samples preferred, pooled with justification
  - Consideration of assay format (e.g. free, total, bound), drug modality, binding partners, reagent specificity
  - Evaluate trends that have impact on the study data (e.g. %RE vs lowest dilution in range)

26. Recommendations - Surrogate Matrices

- For rare matrices and high endogenous counterpart, alternative matrices rather than sample matrix may be used for calibrators
- QCs should be reflective of sample matrix where possible

27. Recommendations - Critical Reagents

- Critical reagents should be identified and defined in the assay method
- Should be monitored through the life cycle
- Assess for lot to lot changes and consider the impact of the change on the assay
- Documentation: source origin and storage condition by CoA or technical datasheet
- It is possible to extent the stability beyond the expiry/retest date as long as it is monitored

Recommendations from breakout session 6 - LBA

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31-33: Session feedback Regulatory ambiguities in LBA

- Flexibility is allowed in the guidance for single replicate analysis
- Immunogenicity, biomarkers, method development, MRD, parallelism, chromatography creep should be removed
  - Full list can be consulted on slide 42: *Summary of Industry Request for Exclusions* of the Weehawken Feedback slide deck

Misc. - Follow up items post-Lisbon

- Following up on JBF discussions, we plan to recommend to EWG on re-integration practices. Starting point for the recommendation = GBC S1-2-3
- Following up on the FB from Weehawken, a fresh look (*there was challenge on generalizing the position when indirect assays are used*) may be required on when and why LTS should not be repeated
- Following up the final panel discussion an industry position on Dilution QCs was requested

Acknowledgment

- The organizers want to thank
  - all presenters and delegates to both Sister Meetings (Weehawken & Lisbon)
  - The organizers of the Weehawken meeting
  - The AAPS/JBF/EBF leadership
  - The EBF community

Contact

For any questions or comments

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