Building consensus on Bionalytical Guidance in Weehawken
JBF Abstract

ICH took up bionalytical guidance validation for harmonization in June 2016 which was welcomed by the global BA community. The Weehawken Workshop on bionalytical guidance validation was conceived as venue for bioanalytical scientists from all segments of industry, including stakeholders who are not part of ICH, to share concerns, opinions and emerging areas of interest. It grew from an AAPS sponsored event to a global collaboration with EBF and JBF members as part of the organizing committee and as speakers. Its goal was to provide the readout that would available to the community and the ICH 10 EWG during the write-up of the technical document.

The talk will include a summary of the output from this workshop in areas where harmonization may be achievable and those where consensus was not reached. It will also provide some perspective on the many challenges that emerged in our goal to obtain one harmonized guidance as well as a harmonized “interpretation” of the guidance.

Building consensus on Bionalytical Guidance in Weehawken

Lindsay King on behalf of the AAPS

9th JBF symposium - Tokyo

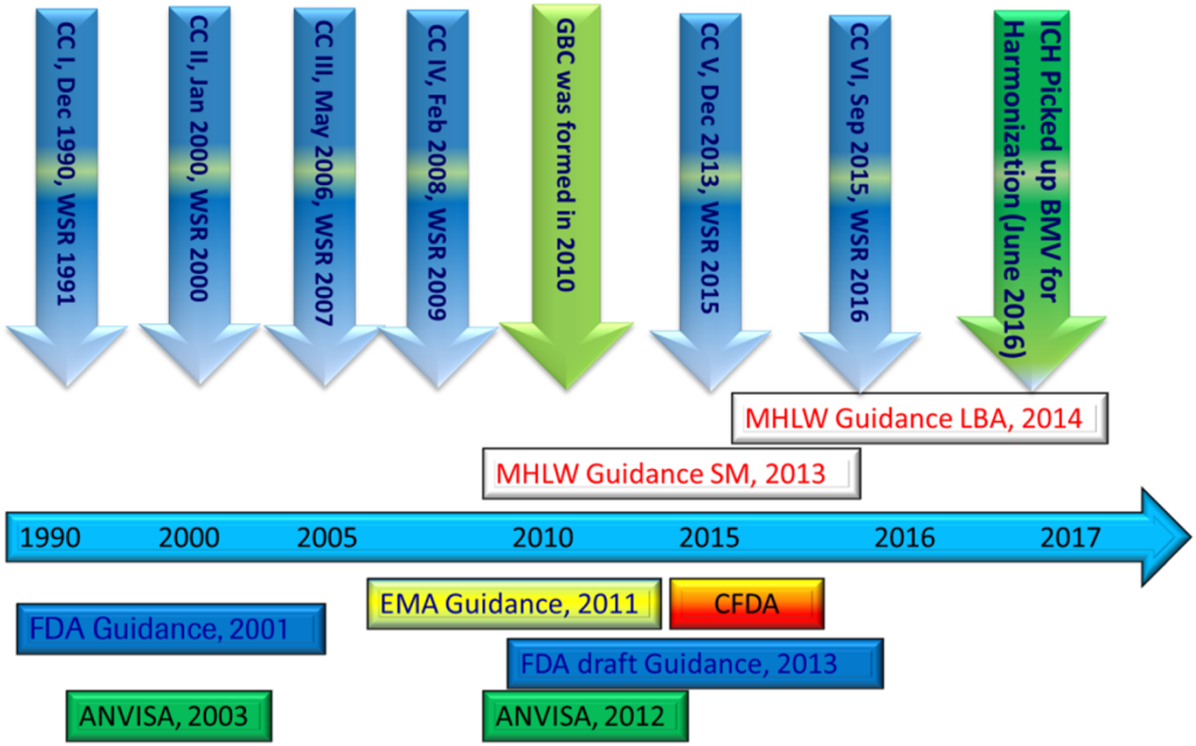
February, 2018

AAPS Background

The American Association for Pharmaceutical Scientists (AAPS) has been actively involved for the last 3 decades in establishing and promoting the best practices in both bioanalytical science and bioanalytical method validation through:

- Crystal City Workshops
- Dedicated focus groups and their associated subteams
  - » Bioanalytical and Ligand Binding Assay Bioanalytical
- Annual and National Biotechnology meetings
- One of the founding member of GBC
- White papers, Open Letters to regulatory authorities and the bioanalytical community
  - » In collaboration with other organizations (EBF, JBF, APA, JBF, CBF, CVG, etc.)
- Other joint activities with EBF & JBF

History & Regulatory Landscape



AAPS/EBF/JBF

Joint Sister Workshop

Weehawken, NJ workshop was hosted by AAPS in Sept 13-15, 2017

- With contribution from CBF
- With global participation (Pharma/CRO)
  - Recognition that not all BA stakeholders were part of ICH
- Organized using a template of the 'Crystal City' meetings (combine specifies with strategy
- Recommendations as comprehensive feedback of current industry position on minimum required standards for consideration in a modern science based Guideline
- Timing for EWG

Weehawken Meeting

- Co-chairs from both Chromatographic and LBA sciences
- Five sessions (Scope, Harmonization Nuts and Bolts, BA Operations, BA Evolution, Reporting)
- Speakers were asked to present cross-industry views (whitepapers, meeting reports, industry consensus) and not own views or company position
- Speakers will point out to what is already harmonized and what needs more discussion

Session Chairs/ Organizers

- Faye Vazvaei, M.S., Roche Innovation Center New York
- Lindsay King, Ph.D. Pfizer Inc.
- Eric Fluhler, Ph.D., Glenmark Pharmaceuticals
- Lakshmi Amaravadi, Ph.D., Sanofi Genzyme
- Philip Timmerman, European Bioanalysis Forum
- Yoshiaki Ohtsu, Ph.D., Astellas Pharma and JBF
- Eric Woolf, Ph.D. Merck & Co., Inc.
- Heather Myler, Ph.D., Pharmaceutical Product Development
- Marianne Scheel Fjording, Ph.D. Novo Nordisk
- Surendra Bansal, Ph.D. Consultant
- Michaela Golob, Ph.D. Nuvisan Pharma Services

Speakers

Perspectives on a Harmonized ICH BA Method Validation Guidance
CT Viswanathan, Ph.D., CT Viswanathan & Associates, Inc.

Industry Perspectives on a Harmonized ICH BA Method Validation Guidance
Binodh Desilva, Ph.D., Bristol-Myers Squibb Company

Regulatory Perspectives—Differences between Regional Guidance
Yoshiro Saito, Ph.D., National Institute of Health Sciences

China Regulatory Update—Encouraging Innovation and Improving Quality
Fan Jin, M.S., Covance, Inc., China Bioanalysis Forum

Scope and Legal Basis
Surendra Bansal, Ph.D. Consultant

Scientific Validation
Philip Timmerman, European Bioanalysis Forum

Requirements for Reference Standards (incl. Commercial Kits)
Joseph Bower, Ph.D. Covance Laboratories, Inc

Critical Reagents and Continuity
Mark Ma, Ph.D. Alexion Pharma

Calibration Curve, PA, LLOQ, ULOQ
Wenkui Li, Ph.D., Novartis Institutes for BioMedical Research

Selectivity and Matrix Effect (LBA)
Shobha Purushothama, Ph.D. Biogen

Selectivity and Matrix Effect (Chromatographic Assays)
Mark Rose, Ph.D., CHDI Foundation

Stability Assessments (including Co-dosed Medication, Blood Stability, and Tube Number)
Yoshiaki Ohtsu, Ph.D., Astellas Pharma and JBF

Speakers

Pre- and In-Study Validation
Bruce Stouffer, Pharmaceutical Product Development

Instruments/Suitability
Chad Briscoe, Ph.D., PRA Health Sciences

Operational Aspects of Sample Analysis Runs in Chromatographic Assays
Mark Arnold, Ph.D. Covance Laboratories Inc

Operational Aspects of Sample Analysis Runs in LBA
Joanne Goodman, Medimmune

Singlet Versus Duplicate Analysis in LBA
Renuka Pillutla, Ph.D., Bristol-Myers Squibb Company

Incurred Samples Reproducibility
Eric Fluhler, Ph.D., Glenmark Pharmaceuticals
Morten Kall, Ph.D. H. Lundbeck A/S

Assay Life Cycle
Mark Ware, Ph.D. Janssen

Partial Validation and Cross Validation—Industry Perspectives
Eric J. Woolf, Ph.D. Merck & Co., Inc.

Partial Validation and Cross Validation—Regulatory Perspectives
Thais Correa Rocha, M.S., Brazilian Health Surveillance Agency

Documentation and Reporting
Gretchen Dean, M.A, Pfizer Inc.

Wenzhe Lu, Ph.D. Roche Innovation Center Shanghai, China
Bioanalysis Forum

Disclaimer: the recommendations in this summary slide deck are based on individual presentations and the result of discussion at the Weehawken meeting, prepared from industry surveys and discussions in the bioanalytical community and do not necessarily reflect the representative affiliation or company's position on the subject.

Some Feedback slides have been annotated/ reorganized/condensed and/or abbreviated

Industry United

Where was consensus straight forward?
Where was consensus not reached?

Request for harmonized “interpretation” of the guidance

What level of detail is needed in guidance?
When do exceptions become the rule to be safe?

What elements are regulatory, business risk decisions or scientific?

Can we find balance between “Best practices” vs minimum expectations?

CRO vs Pharma. Are we on the same team?

Guidance as specifics. How and what to do when?
Scientific Validation Debate

Ambiguity= risk= what are consequences?

How would 20% vs 15% CV impact quality of data?
Context of how the data is used
Eg Safety margins based on AUC

BA scientists are not customers/users of the data they generate

Guilty until proven innocent?

Overall Industry Request to EWG

- One harmonized guidance with clear and simple expectations (**not an additional guidance**)
  - Simple guidance, clarity in the scope, flexibility, harmonization in interpretation (by industry & regulatory)
  - Encompassing with no need for any appendices by countries – any appendices should only cover non-technical issues such as language requirements
  - M10 to replace regional guidance Regional appendices should not add additional technical requirements
- Prospective guidance – Acknowledgement of advances in new technologies and emerging of new modalities – Accommodation for innovation
- Let us think science and reflect on decision to be made (or how the data will be used)
- Best practices should not become expectations by the inspectors

Feedback from the Weehawken

Specific Issues and Positions

Guidance Format Request

For readability/Compliance purposes separate sections for chromatographic and ligand binding assays—Complete sections with no cross references

Scope Request

- Complete, discrete sections without cross references; for chromatographic and ligand binding assays, respectively
- Clarify scope to include:
  - Quantitative analysis of primary PK analyte
    - only metabolite(s) required by ICH M3 (R2) in scope once determined
  - Primary matrix
  - The stage of drug development and/or the type of study analyzed should be considered in the scope statements to ensure appropriate compliance at required stages
    - no desire to include list of studies, alternative validation approaches or specify development phase in scope in M10

Scope

- Request to exclude from M10
  - Urine and tissue analyses, unless these are the primary matrices used to characterize PK
  - Early metabolite evaluations
  - “Non-major” metabolites
- Method development out of scope

Specifically cover above points (exclusions) in scope statement

Scope – Additional Consideration

- Non-clinical – only a subset of experiments needed for clinical validation
- GLP and GCP principles
  - To avoid the confusion between GLP and GCP in EMA guidance, follow the FDA verbiage
  - Sample management and analysis based on study protocol – (out of scope of guidance)
  - Not in scope for performing validations

Additional Considerations

- MHRA guidelines are applicable to EU counties
- EMA reflection paper adds confusion – Should be out of scope for M10
- The GCP oversight authority and inspection process in different countries is not clear for BA labs

Issues and Positions

- Enforcement of Draft Guidance
  - This was identified as an issue for the industry
    - Eg FDA Draft 2013 Guidance
- Retroactive application of guidance updates to previously performed studies/validations
- Adoption of new ICH guidance; how will this work?
  - Historic studies “should” be supported by validations meeting requirements in place at the time of the study
  - New studies must meet contemporary guidance

Issues and Positions

New Modalities

- Request: Add a brief section that acknowledges that this area is still evolving and, therefore, use in regulated BA should consider general principles of PK assays recognizing the unique challenges related to new modalities in setting validation parameters/criteria

New Technologies: A brand new platform or new practical application of an established platform that is not well characterized nor widely utilized in the current regulated BA community.

- Request implementation of new technologies does not need to be supported by data from established technology
- Recommend use in regulated BA should be supported by acceptance criteria established apriori based on MD and verified in validation.
- Includes Hybrid" and Surrogate Peptide based LC/MS Assays

Issues and Positions

Singlicate vs. Duplicate Analysis in LBA

- Singlicate is acceptable if the method is validated as such, use language in FDA Guidance

Feedback from the Weehawken

Specific Validation Experiments

Cross Validation

- Required when multiple assays are used in a single study or when assays on different platforms (e.g., LC/MS and LBA) are used within a program
  - Different platforms may yield different results
    - Not a show stopper
    - Conducted to determine if data from multiple platforms can be aggregated
  - No need to cross validate LBA assays and MS assays if only LBA assays are used in a program
- Independently validated assays used across a program do not require cross validation

Partial Validation

- Partial Validation NOT Required For:
  - Anti-coagulant counter-ion change
  - Change in gender
    - Unless analyte is impacted by gender
  - Minor mobile phase changes to adjust retention
  - Change between very similar instruments
    - MS with same ionization source

Reference Standard

- For large molecules it is not required to use the same lot of reference standard for CAL and QC preparations if it conforms to the same quality specifications stated in CoA
- No CoA is required for Internal Standard—demonstrate suitability
- Standards and QCs could be spiked using the same stock solution if the accuracy has been verified

Reference Standard Stability

- If the reference standard is within its expiration date when the stock solution is prepared, there is no need to prepare a new stock solution when the reference standard expires (CC III)

Precision and Accuracy

- P&A LC/MS
  - 3 QC levels (L, M, H), and LLOQ*, 5 replicates, 3 runs
  - Mid QC: near geometric mean
- P&A LBA
  - Curve, ±25% at LLOQ **and ULOQ**
  - 3 QC levels and LLOQ* and ULOQ*, 6 runs
  - Mid QC: near geometric mean

* during validation only; extrapolation may be needed

Stability

- Assess with fresh or freshly frozen calibrators when feasible.
  - Acceptance: match QC acceptance criteria
- The process for reinjection reproducibility/processed sample stability should mimic the processes followed during sample analysis
- Stability assessment of SIL IS solutions should not be required

Stability

Long Term Stability

- A property of the molecule
- Independent of assay and site

-20°C vs -70°C

- If matrix stability for an analyte is established at higher temperature, stability is assumed at lower temperature.

No requirement for multiple tubes

- There is no scientific rationale that increasing the number of tubes impacts stability conclusion

Stability

Co-Med Stability is not required.

- There is no scientific evidence that presence of co-medication impacts stability conclusion

Assess whole blood stability when scientifically indicated

- Pro-drugs and other analytes known to be unstable
- This can be assessed during method development

Selectivity vs Specificity (General)

- Harmonize definitions of selectivity and specificity
  - Selectivity: ability to measure analyte in presence of matrix components
  - Specificity: ability to measure only the analyte in presence of closely related compounds
    - E.g. metabolites

Selectivity (Chromatographic Assays)

- Lack of interference from endogenous components of the matrix (both visible and invisible to the detector)
  - Visible interference
    - Evaluate specificity using blank matrix samples obtained from at least 6 individual sources, the absence of each analyte and IS should be confirmed.
    - **Acceptance Criteria :** Response of interfering peak at the retention time should be lower than 20% of the response of LLOQ samples and lower than 5% of the IS response.

Selectivity (Chromatographic Assays)

- Invisible interference (matrix effects on ionization)
  - Calculations of matrix factors add no value to validation
    - Internal standard normalized matrix factors can be used as diagnostic tool

Selectivity (Chromatographic Assays)

- Assess both visible and invisible interference through precision and accuracy assessments in multiple lots of matrix.
  - Analyze control and LLOQ samples in multiple matrix lots
    - Lack of peaks in controls – visible selectivity
    - Precision of LLOQ results – demonstrate lack of matrix effects (invisible selectivity)
- Selectivity assessment in hemolyzed and lipemic plasma should be issue driven

- Do multiple lots need to be assessed for pre-clinical work?
- Does the use of stable label internal standards eliminate the need for matrix effect assessments in multiple matrix lots?

Specificity (Chromatographic Assays)

- Recommend a “paper” assessment of potential for interference of anticipated co-meds.
  - Based on molecular weight of analyte of co-med
  - Follow up with actual experiment if molecular weights are close
- Scientific mitigation could include, collection of pre-dose samples in studies in patients demonstrating lack of interference for **co-meds** at steady state

Selectivity (LBA)

- **Selectivity**
  - Evaluate using 10 individual sources at blank and LLOQ QC levels
  - May consider including relevant patient population
  - Assessment in hemolyzed and lipemic matrices should be issue driven not routine
  - Blank samples, ≥80%: below LLOQ
  - Accuracy: ≥80% of samples ≤±25% at LLOQ

- **MRD**
  - MRD should be determined in MD and should not be a validation experiment
  - MD is out of scope of guidance

Specificity (LBA)

- **Specificity**
  - Blank and QC samples should be spiked with related substance (as appropriate) to demonstrate that the related substance is not detected in the assay and that the assay is specific to the analyte of interest.
  - Accuracy: ≤±20% of nominal. (≤±25% at LLOQ, ULOQ)
- **Interference**
  - Target, ADA, etc. interference or tolerance discussions ongoing
  - Current thinking is to test these parameters in MD and verifications not needed in MV

Instrument Related Considerations

- Carryover
  - Should be minimized and assessed for impact if appropriate.
  - A prescriptive % not needed. Range of technologies prevents single criteria
- System Suitability
  - Strike “system suitability” as an assay requirement
  - State that system preparation should be specified in the method.
- Instrument Qualification
  - Out of scope. Suggest no mention as requirements are outlined in other guidance’s and regulations.

Recommendation for ISR

- ISR, based on low failure rate (~2%)
  - 1st GLP study/species, FIH study, all BE studies, others as scientifically justified
  - 5%, minimum of 6 (GBC recommendation)
  - Selection, based on GBC rec, high/low, driven by primary active entity.
  - Individual failures – no investigation required

Operational Aspects of LC/MS Sample Analysis

- Failed runs – Do not included failed run stds or QCs in study statistics, not representative of valid data
- For passing runs include stats with and w/o individual failed QCs (outliers)
- Failed run for multi-analyte run, collect all m/z channels, only integrate analytes needed.
- Reanalysis for PK reasons alone is not allowed in BE studies
- BE studies should use auto-integrations only, although may be preferred for all studies, process does not need to be prescriptive/mandatory
- Dilution QC's not required for production runs
- Interference testing of LM on LC/MS should be conducted only as needed.
- R^2 should not be used as an acceptance criteria or reported.
- If concentrations in QC samples have to be close to those in study samples, limit the requirement to BE studies
- Extraction recovery should not be required in validation

Operational Aspects of Sample Analysis for LBA

- ULOQ – 25%
- Avoid the use of “top and bottom” for standards given anchor points
- OK to truncate calibration curve as long as you still have 3 QCs within curve
- Placement of mid QC – Geometric mean of calibration curve (log scale), (excluding anchors)
- No prescription on placement of QCs on plate
- Remove reference to additional QC for data in narrow range
- Remove the request to run samples from 1 subject on a single plate
- BE study reanalysis for PK reasons is not allowed.

Dilutional Linearity and Parallelism

- **Dilutional Linearity**
  - Hook effect to be assessed in validations using a dilution QC

- **Parallelism**
  - Parallelism should not be a mandatory requirement
  - It can be used as an investigation in study when needed

Critical Reagents

- **Critical Reagents**
  - Identify critical reagents (eg capture and detection antibodies) in the bioanalytical method and manage them appropriately to ensure consistent analytical performance of the method.

Documentation and Reporting

- Clarity on what should be archived/documented in the lab records vs. in the reports (validation and bioanalytical).
  - Crystal City 3 report is a good start for the harmonized guidance
  - Need global consistency for the BA reports in
    - Attachments/appendices to reports, e.g. study plans, SOPS, COAs, etc.
    - Reporting of failed data
    - Number of chromatograms attached to reports
    - Level of method development details

Documentation and Reporting

- Exact sample collection details (date/time) are available only in the clinics not in bioanalytical records. Not appropriate to be reported in BA reports
- Too prescriptive guidance on writing of BA reports may conflict with other ICH guidance on reporting (e.g., eCTD)
- Requirements for specialized reports/forms in addition to required BA reports defeats harmonization purpose. Such forms should be minimized and referred to only in the regional guidance required in module 1 of eCTD, not in the bioanalytical reports or documentation
- In light of increasing electronic submissions, a high level of harmonized guidance for the reports would help. Suggestions/requests for paper records (e.g. stamped records in Chinese submissions) should be eliminated or minimized

Harmonization Goal

- Important: The industry wants **<u>one harmonized guidance</u>** (not yet an additional guidance)
- The industry also wants a harmonized “interpretation” of the guidance
- Request to ICH EWG; lobby your EWG from industry (PhRMA, BIO, EFPIA, JPMA, IGBA) & regulatory (FDA, MHLW/PMDA, EC, ANVISA, Health Canada, etc.) to consider our collective views and emphasize the need of only one guidance (M10) – no additional regional based requirements
- Request to the regulatory agencies; lobby your region’s regulatory agency to consider industry views and get involved in these types of discussions—We need their support!

Bioanalytical Utopia

☺

Perfection Imagined:
One global BMV guidance
interpreted the same by all