ICH M10 and FDA 2018 BMV Guideline: Feedback from the EBF

Steve White, on behalf of the EBF

10th JBF Open Symposium

13th February 2019

Overview of Presentation

1. EBF activities related to ICH M10
   - To date
   - Planned for 2019

2. EBF activities related to FDA 2018 BMV Guideline
   - Survey to members
   - Discussed during the EBF Year End Members Meeting (YEMM) 2018
   - Summary of "**Practical Implementation of FDA 2018 BMV Guidance"** session during 11th EBF Open Symposium (Barcelona, Spain)

EBF ACTIVITIES RELATED TO ICH M10

EBF activities related to ICH M10

- Two “sister meetings” organised by AAPS/EBF/JBF:
  - Weehawken, NJ USA (hosted by AAPS, Sept 13-15, **2017**)
  - Lisbon, Portugal (hosted by EBF, Sept 24-26, **2017**)
- The resulting recommendations aimed at providing comprehensive feedback of current industry position on minimum required standards for consideration in a modern science based Guideline

EBF activities related to ICH M10

- Agenda and slides from the Lisbon meeting are available via the following link: http://www.e-b-f.eu/fw201709-slides/

- Throughout the Weehawken and Lisbon sister meetings, industry emphasized the importance of defining the scope of the guideline: focus should be on late stage (clinical BE) studies, or at least that BE studies should have the most stringent criteria which **cannot and should not** apply to other studies.

Post Meeting Activities & Publications

- Weehawken and Lisbon sister meetings attended by Industry Expect Working Group members – meeting output available for consideration by the ICH M10 EWG during subsequent discussions
- Multiple industry contributions to a special edition of *Bioanalysis* on the topic of ISR: *Bioanalysis* (2018) 10(21)
  - Includes the EBF article “Incurred sample reproducibility: 10 years of experiences: views and recommendations from the European Bioanalysis Forum”. *Bioanalysis* (2018) 10(21), 1723-1732
- The topic of “**Harmonized PK run acceptance criteria“** was further discussed within the EBF community with a subsequent publication:
  - Toward decision-based acceptance criteria for Bioanalytical Method Validation: a proposal for discussion from the European Bioanalysis Forum. *Bioanalysis (2018) 10(16), 1255-1259*

Future Plans

- In anticipation of Phase 1 sign off and release of the draft guideline for public consultation, EBF plans….
  - Internal survey to understand areas of ambiguity and/or concern
  - Focus Workshop, in collaboration with the AAPS, JBF and CBF:

ICH M10 - BMV

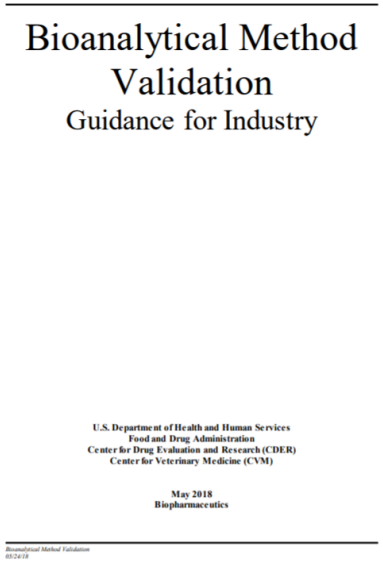
Public Consultation & Industry Feedback

Towards a Science based Global Bioanalytical Guideline

20-22 May 2019 - Hesperia Tower, Barcelona, Spain

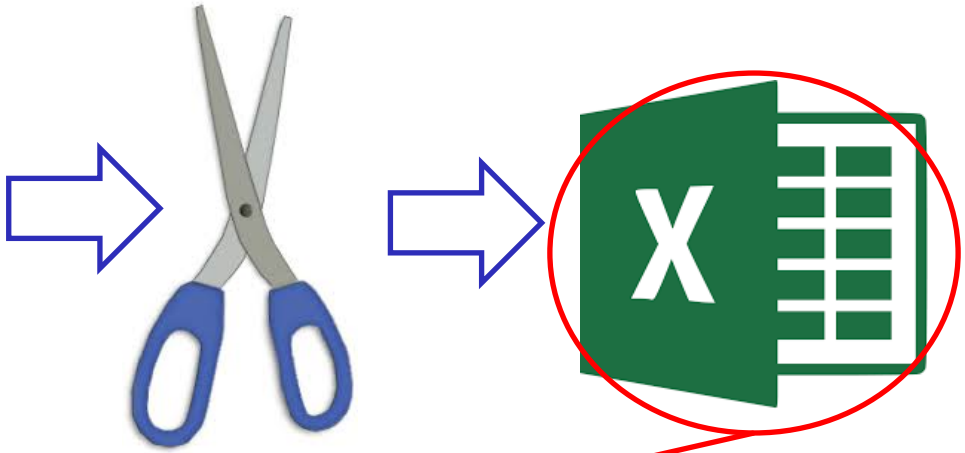
EBF ACTIVITIES RELATED TO FDA 2018 BMV GUIDELINE

All Good Things Start With a Survey


Bioanalytical Method Validation
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

May 2018
Biopharmaceutics



I have <u>difficulties in implementing</u> this paragraph because it is **ambiguous** (meaning "I don't understand what I need to do here")	I have <u>difficulties in implementing</u> this paragraph because it is **in conflict with another guideline** (mention conflicting guideline in brackets)	I think this is good paragraph which clarifies an earlier (conflicting or ambiguous) requirement

Looking at the Data

- Took the **top 5-8 topics**
- Asked for examples of how EBF member companies have implemented

Reviewed Case Studies and Discussed F2F at the Year End Members Meeting (YEMM)

1. Use of Fresh QCs
2. Fit for Purpose (FFP)
3. Documenting Method Development
4. Cross Validation
5. What is pivotal for ISR?
6. Fixed Combinations and Specific Drug Regimens

Taking the YEMM discussions to the Open Symposium

- Organising Team summarised the discussions from the YEMM in preparation for the Open Symposium…

Day 3-02 Auditorium: Practical Implementation of FDA 2018 BMV Guidance

Session chair: Philip Timmerman (EBF)

In this session, we plan to focus on Industry's first experience of bringing the 2018-FDA BMV Guidance into practice. From a recent survey, EBF delegates will present their current experience or share the ambiguities they have on 6 themes areas. We have invited FDA- and US industry experts to help us implement the 2018-FDA Guidance as harmonized as possible.

Presentations from Sriram Subramaniam (CDER-FDA) and Lakshmi Amaravadi (Shire/AAPS) – Feedback from the US bioanalytical community

EBF Case studies/survey results including panel discussion
Presented by Joanne Goodman, Johannes Stanta, Michaela Golob, Magnus Knutsson

Panel Discussion

Organising Team:

Jo Goodman, Magnus Knutsson, Johannes Stanta, Michaela Golob, Philip Timmerman

⇒ Sriram-Subramaniam (FDA)

Lakshmi Amaravadi (Shire/AAPS)

⇒ EBF Case Studies

Framing the Discussion

- Focus on Industry's first experience of bringing the 2018 FDA BMV Guidance into practice
- How are the community implementing?
- EBF gathered relevant experience from their member companies on their interpretation of the guidance and what areas bring challenges
- No intention of polarisation

For this Session ….

- Presentations on each of the 6 topics
- Share the summary of the internal EBF discussions
  - Interpretation
  - Challenges
  - Areas that need clarification and further discussion

Not for this Session ….

- Areas of agreed disagreement
  - Interference testing
  - Almost expired reference standards
  - Biomarkers

Topic 1: Use of fresh QCs

- **FDA:**

  "The sponsor should use freshly prepared calibrators and QCs in all A & P runs. Use of freshly prepared QCs in all A & P runs is preferred; however, if this is not possible, the sponsor should use freshly prepared QCs in one or more A & P runs."

- **EMA:**

  "For the estimation of precision and accuracy QC samples should not be freshly prepared, but should be frozen and treated the same way as for the analysis of study samples."

If we prepare for global filing we have contradictory requirements when applying FDA guidance rather than EMA

Topic 1: Use of fresh QCs

- The EBF community would like to understand the background of this requirement as QCs should mimic study samples and all study samples are frozen?
- If mandatory, there are 3 possible ways to manage…
  - Qualification run using freshly prepared QCs – then step into A&P with freshly prepared but one time frozen QCs
  - First A&P run using fresh QCs, other A&P runs using frozen QCs
  - Use fresh QCs for A&P, and for all additional validation parameters use frozen QCs (run acceptance QCs)
  - No consensus in EBF

Topic 1: Use of fresh QCs

Panel Discussion Summary:

- Appears that the FDA BMV wording is designed to mitigate the stability risk during validation A&P runs
- If frozen QCs are used during one or more A&P runs, then sufficient stability must be demonstrated
  - Generating stability data after conducting A&P using frozen QCs is a business risk

Topic 2: FFP - what does it mean, and do we align on which studies are in scope?

- "The fit-for-purpose (FFP) concept states that the level of validation should be appropriate for the intended purpose of the study. The key questions listed above should be evaluated relative to the stage of drug development. Pivotal studies submitted in an NDA, BLA, or ANDA that require regulatory decision making for approval, safety or labeling, such as BE or pharmacokinetic studies, should include bioanalytical methods that are fully validated. Exploratory methods that would not be used to support regulatory decision making (e.g., candidate selection) may not require such stringent validation. This FFP concept applies to drugs, their metabolites, and biomarkers."

Topic 2: Fit For Purpose Validation

- Great interest among EBF companies to apply FFP/SV approaches
- Inclusion of FFP in the FDA BMV Guideline is very welcome
- Further discussion needed and clearer guidance appreciated
- Industry interprets scope differently from the regulatory perspective, i.e. regulators see the filings, whilst industry over-regulates on all phases regardless of whether the data used are filed to support pivotal decisions

Topic 2: Fit For Purpose Validation

Example: Company A

- Interpret “candidate selection” in the context of progression to patient studies
- All FTIH (volunteer) studies are supported using FFP/SV assays by first intent
- Where FTIH = FTIP (oncology) we would typically adopt Full (BMV) assay validation
- Validation Plan written to document nature of the validation, and rationale

Example: Company B

- Pleased that FFP is acknowledged by FDA for the first time but are unsure for what studies it can be applied and what level of validation is necessary.
- PK FFP is and will remain applicable only to Non-regulated pre-clinical work; work not in scope of guidance may use FFP e.g. non-primary matrices such as tissue and urine.

Topic 2: Fit For Purpose Validation

- Show of hands during EBF YEMM (approximately 50 companies)

- Approx. ⅓ are having similar FFP scope interpretation as Company A
- Approximately ⅔ are having similar FFP scope interpretation as Company B

Topic 2: Fit For Purpose Validation

Panel Discussion Summary:

- The wording in the FDA BMV Guideline is intended to give industry the freedom to use best judgement
- No clear direction on when the use of FFP validation is deemed appropriate

Topic 3:
Documentation of Method Development

- **FDA:**

Bioanalytical method development does not require extensive record keeping or notation. However, the sponsor should record the changes to procedures as well as any issues and their resolutions during development of the bioanalytical method to provide a rationale for any changes during the development of the method.

- **Other regions:**
  - Not mentioned in any other guideline

Topic 3: Documentation of Method Development

Case studies shared during Year End Members Meeting:

- Development summary in the Validation report which includes experiments not performed in the validation such as:
  - MRD
  - Specific critical reagent selection and their concentrations
  - Blood stability

Topic 3: Documentation of Method Development

We discussed as a community and propose:

Documentation of the method development should be left to the discretion of the company, unless for late stage clinical methods (e.g. BE studies) but ensure traceability

For certain parameters that are only conducted during the method development phase, a short synopsis should be included in the validation report

It is not necessary to include a detailed description of all method development data in the validation report

This is consistent with Crystal City V discussions

Booth, Arnold et al. (2015)

Topic 3: Documentation of Method Development

Panel Discussion Summary:

- Intended to capture the evolution of the assay during the life-cycle of an asset (i.e. a synopsis of the assay revision history)
- In line with the proposal from EBF members (see previous slide)

Topic 4: What triggers cross validation? How do we define ‘different’ methods?

- **FDA:**

Cross validation is a comparison of validation parameters of two or more bioanalytical methods or techniques that are used to generate data within the same study or across different studies. Also, cross validation is necessary when sample analyses within a single study are conducted at more than one site or more than one laboratory. In such cases, cross validation with shared matrix QCs and nonpooled subject samples should be conducted at each site or laboratory to establish interlaboratory reliability. Pooled incurred samples can be used when insufficient volume exists. An SOP or validation plan should define the criteria a priori.

- **EMA:**

Similar language

Topic 4: Cross validation

Feedback from EBF Member Companies:

- When?
  - Different detection systems concerning specificity (e.g. MS and UV detection)
  - Different analytical techniques
  - Different laboratories **within a study**
- How?
  - Spiked samples – mean bias from nominal conc. at each level within ±15%/20% for each assay/lab
  - Incurred samples (minimum of 20 non-pooled samples), ISR type of evaluation (2/3 of samples within 20%/25% of mean)
  - Some Informed Consent concerns

Good consensus across EBF member companies

Topic 4: Cross validation

Panel Discussion Summary:

- No significant comments of discussion beyond what was presented as the EBF consensus (see previous slide)

Topic 5:
How to interpret pivotal in the context of ISR

- **FDA**:

ISR should be conducted in all studies submitted in an NDA, BLA, or ANDA that provide pivotal data for the approval or labeling of the product, regardless of the matrix.

For instance, ISR is expected for all *in vivo* human BE studies in ANDAs, or all pivotal pharmacokinetic, pharmacodynamic, and biomarker studies in NDAs or BLAs. For nonclinical safety studies, the performing laboratory should conduct ISR at least once for each method and species.

Topic 5: How to interpret pivotal in the context of ISR

- **EBF Interpretation and discussions:**
  - Currently guidance creates confusion
  - Results in a significant increase in the number of ISR studies where there are data to support less
  - Desire to continue with EMA guidance
  - Special issue in Bioanalysis on ISR

Topic 5: How to interpret pivotal in the context of ISR

Panel Discussion Summary:

- It was discussed and accepted that conducting ISR is not always practically possible
- However, there remains a difference of opinion on the appropriate “scale” of when ISR should be performed
- EBF continues to challenge the extent to which ISR is conducted

Topic 6:
Fixed Combinations and Specific Drug Regimens

- **FDA:**

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.

- **EMA:**

Similar language

Topic 6: Fixed Combinations and Specific Drug Regimens

EBF looked at this new requirement in the FDA guidance and discussed interpretation between EBF member companies

=>*How do we bring fixed combinations and specific drug regimens in practice*

Outcome of the discussion:

- *Clarity on scope for studies to which this applies creates confusion*
- *Stability of fixed dose combination (one pill with more than one drug) should be established*
- Stability of the analyte in the presence of other co-medications that are known to be regularly administered is considered not feasible. *Co-medication should be considered, if there is strong reason for specific concern but not in general.*

Topic 6: Fixed Combinations and Specific Drug Regimens

Panel Discussion Summary:

- Fixed Dose Combinations – pretty clear cut: demonstrate stability
- Co-meds:
  - Where administered as part of the therapy (e.g. Oncology)
  - No need to look at what's irrelevant
- There remains a difference of opinion on the scale of the problem/unclarity
- EBF continues to challenge this requirement in the absence of data showing this to be an issue

Overall Summary

- Experiences shared in dealing with the new guidance over the last 6 months
- Presented the 6 areas with the greatest concerns/ambiguity around implementation for the EBF community
- Good correlation between the “hot topics” highlighted by EBF and those from the AAPS community
- Some clarity gained on certain topics during the panel discussion, while dome differences of opinion remain on others
- Industry awaits to see how our interpretations of the 2018 FDA BMV Guideline are received

Acknowledgements

- EBF community (survey input and discussions)
- Team preparing EBF Survey and summaries:
  - Jo Goodman
  - Magnus Knutsson
  - Johannes Stanta
  - Michaela Golob
  - Philip Timmerman