Scientific Validation: Feedback from JBF Discussion Group

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On behalf of Japan Bioanalysis Forum (JBF)

Contents

What is JBF Discussion Group

- JBF started in 2011
- JBF Discussion Group (JBF DG) started in 2013
- Similar to EBF topic team,
  - One DG has one selected topic and several (up to 10) experts in JP industry (including pharma and CRO)
  - Discussion and cross-industry survey
  - Outcome is presented within a year (JBF symposium)
  - Several DG per year
- JBF DG members are accountable for their outcome

Currently active DGs

- DG2016-20 Giving consideration to scientific validation (2)
- DG2016-21 Microsampling (2) –Investigation of technical problems
- DG2016-22 Application of mass spectrometry imaging (MSI) to drug discovery and development research
- DG2016-23 The pharma-CRO relationship with a focus on method transfer
- DG2016-24 Questions and challenges in bioanalytical studies – find the loadstar (stability) –
- DG2016-25 Quantitative analysis of endogenous substance – LC/MS: alternative analyte & large molecule endogenous substance –
- DG2016-26 Quantitative analysis of endogenous substance – validation studies for the analysis of endogenous substance by LBA –
- DG2016-27 Quantitative analysis of endogenous substance – other analytical methods for endogenous substances: flow cytometry, Luminex, and PCR –

JBF DG activities on scientific validation

- Started in 2013 as “tiered approach” DG
- Publications
  - Niwa, Makoto, et al. "Tiered approach to metabolite quantification: regional practices reviewed by Japan Bioanalysis Forum discussion group." *Bioanalysis* 7(8) (2015): 935-938.
  - Niwa, Makoto, et al. "Survey on the tiered approach for Japanese bioanalysts operated by Japan bioanalysis forum DG2014-09." *Bioanalysis* 8(2) (2016): 93-98.
  - In addition, one Japanese publication
- In 2015, AAPS/EBF/JBF joint survey
- Presented the outcome in EBF Open Symposium 2015

DG2015-16

- Today's presentation is based on outcome of this DG
- Members

Hiroko Ashizawa
(Kaken Pharmaceutical)

Takuho Ishii
(Sunplanet)

Takahide Uchimura
(Chugai Research Institute for Medical Science)

Nozomu Koseki
(Kyorin Pharmaceutical)

Akiko Toda
(Shin Nippon Biomedical Laboratories)

Kuretake Soejima
(Toyama Chemical)

Naoko Nakai
(Daiichi Sankyo)

Naohiro Nishimura
(Sumika Chemical Analysis Service)

Tsuyoshi Mayumi
(Zensei Pharmaceutical)

Yutaka Yasuda
(Toray Research Center)

Makoto Niwa
(Nippon Kayaku)

Yasuhisa Sano, as observer
(Sunplanet)

DG2015-16

- The DG shared the following EBF article within DG members and had discussion
  - Timmerman, Philip, et al. “Tiered approach into practice: scientific validation for chromatography-based assays in early development- a recommendation from the European Bioanalysis Forum.” *Bioanalysis*, 7(18) (2015): 2387-2398.
- Most of the EBF article is understandable for the DG.
- Today, the feedback and questions will be presented

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COA in metabolite assay in plasma

EBF article:

Purpose of the assay	COA
Relative exposure among species	No COA is needed
Quantification for pharmacological effect	COA with identity, purity and retest date

JBF DG: regional practices reviewed by DG2014-09

Relative exposure among species

Step 1) Use analytical instrument signals for comparison (no use of reference materials)

Step 2) Obtain small amounts of metabolites, analyze the samples after multiple dosing using a qualified assay

↓

Step 2 is important because

- the data will be used to judge which metabolite(s) will be monitored on a routine basis
- the data may be used in order to demonstrate that the metabolite is not important

↓

Documentation with at least purity would be recommended for step 2.

Selectivity in the presence of co-medication

In support of DDI studies

EBF article:

Category	Test in pre-study method validation
Metabolites in plasma (ICH-M3)	No
Urine	No
Tissue homogenates	No
Early development clinical studies	No
Early development preclinical studies	No

JBF DG:

- Agree with the EBF article in most cases
- Experiences of having interferences (survey is ongoing)

↓

- Would take case-by-case approach.

Freeze-thaw stability

EBF article:

Category	Test in pre-study method validation
Metabolites in plasma (ICH-M3)	No, consider incurred sample stability
Urine	Yes, 1 cycle
Tissue homogenates	Yes, 1 cycle
Early development clinical studies	Combined stability experiment to cover unknown samples
Early development preclinical studies	Same above

JBF DG:

- Agree that combined experiment is a good approach
- For metabolites, DG members prefer to test
- For urine and tissue homogenates, is 1 cycle a good option? more cycles?

Sample stability in a freezer

EBF article:

Category	Test in pre-study method validation
Metabolites in plasma (ICH-M3)	Yes (acceptance criteria of 20%)
Urine	No
Tissue homogenates	No
Early development clinical studies	Combined stability experiment to cover unknown samples
Early development preclinical studies	Same above

JBF DG:

- Agree that combined experiment is a good approach
- Agree with the EBF article in most cases
- When urine is important in mass balance studies, frozen stability should be established

Protocols and reports

EBF article:

Category	Protocols	Reports
All	At minimum SOP or short protocol summarizing scientific parameters to be tested	At minimum a document summarizing scientific parameters tested

JBF DG:

- Agree to keep them brief and relevant
- However, documentation in the EBF article appears a bit concise than what they have in mind.

→ Concrete proposal from JBF DG?

→ JBF DG found inter-company/individual differences within the team

→ Could not reach an agreement within the team

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IS variability

- EBF article: use IS variability for assessment of matrix effect, including hemolysed and lipidemic plasma
- JBF DG: No standard acceptance criteria for IS variability in Japan. Is it reasonable to use IS variability for the assessment?
- Question: EBF published an article on IS variability. Do you use this in your lab?

Inter assay variability

- EBF article: use scientific judgment based upon P&A of 1-run validation
- Question: I am not familiar with scientific judgment in this context. Any good examples?

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Conclusion

- JBF DG agree with most of EBF recommendations.
- This presentation provided viewpoints on metabolite COA, co-medication selectivity, F/T stability, frozen stability, documentations.
- JBF would very much appreciate it if EBF could act as a partner and/or collaborator to promote the concept of scientific validation to the industries/authorities.
- JBF continue to discuss scientific validation. DG2016-20 will present the outcome in 8th JBF symposium in Feb 2017 in Tokyo, Japan.

Acknowledgment

- Past and present DG members for scientific validation
- Makoto Niwa (leader of the above DGs)
- JBF steering committee members
- EBF

Thank you for your attention.

Next JBF symposium

8-9 Feb 2017, Tokyo

- DG outcome
- Regulatory session (incl. industry expectation for ICH)
- Collaborative session with Japan Society of Quality Assurance (JSQA)
- ADA, biomarker, large molecule LC-MS