Tiered Approach to Metabolite Quantification: An Outcome from JBF Discussion Group



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(on behalf of the Japan Bioanalysis Forum)

Discussion Groups (DGs) to date



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2013 (3 trial DGs)
   1) Standard solutions, 2) Partial validation, 3) LBA
2013 (5 full-fledged DGs)
   DG2013-01 Preparation of calibration standards and QC samples
   DG2013-02 Recommendation to prepare standard solutions
   DG2013-03 Tiered approach for bioanalytical methods of metabolites
   DG2013-04 Partial validation (2)
   DG2013-05 LBA topics (critical reagents, ADA, etc.)
2014 (7 DGs)
   DG2014-06 "The Study of Failure" in analytical studies
   DG2014-07 Development of analysis method
   DG2014-08 Quantitative analysis of endogenous substances
   DG2014-09 Tiered approach for the quantitative assay method (2)
   DG2014-10 Partial validation (3)
   DG2014-11 Anti-Drug Antibody (ADA) Assay
   DG2014-12 Quantitative analysis by LBA (PK/Biomarker)
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Currently active DGs



• 2015 (7 DGs)

DG2015-13 Questions and Challenges in Bioanalytical Study - Find the Loadstar -

DG2015-14 Carryover

DG2015-15 Quantitative analysis of endogenous substances (2) incl. biomarkers

DG2015-16 Thinking of scientific validation

DG2015-17 Microsampling

DG2015-18 ADA analysis

DG2015-19 Quantitative analysis by LBA (Method development)

Activities: DG2013-03 & DG2014-09



Survey and Discussion on Tiered Approach

GBC Recommended Workflow
[Discussion / Regional Practice
and Applicability] 2013

GBC, EBF Recommendation
[Recognition Survey] 2014

Urine Analysis (Clinical)
[Discussion and Survey] 2013-2014

NDA Submission of "Tiered" Data [Attitude Survey] 2014

Metabolite Quantitation Strategy [Discussion and Survey] (Early Full Investigation vs Putting off to Post-POC) 2013-2014

Metabolite Reference Stds [Survey] 2013

Retrospective Assay (Left-over Samples)
[Survey] 2014

Survey on Corresponding Items

Survey to Pharma and CROs (in Nov 2014)

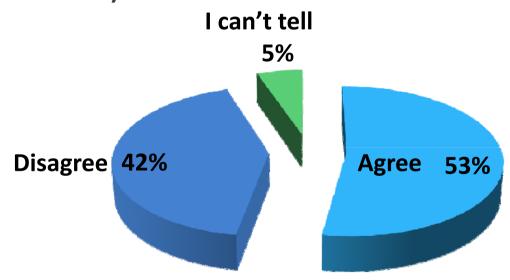


- 1. Have you recognised and utilised "tiered approach" in your daily work?
- 2. How about submission of the data obtained by the analytical methods other than "validated" method for NDA filing?
- 3. Which do you prefer as a strategy, earlier metabolite quantification with validated methods or tiered metabolite quantification with project progress?
- 4. Which "tier" is feasible as the analytical methods for urinary metabolites?
- 5. Is there any possibility of retrospective analysis of human samples in case human specific metabolite is found in later stage?

Q 17 Japanese Nonclinical PK GL



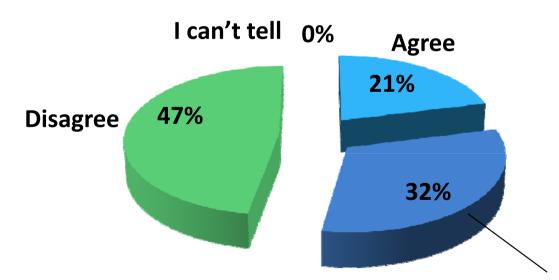
- Q: Do you agree with the following statement?
- Statement: As characterization of analytical method (accuracy, precision, selectivity, LOQ) is required in Japanese nonclinical PK guideline, validated method should be used in nonclinical PK studies, though nonclinical PK is not within the scope of BMV guideline.
- Results (Answers: 19)



Q 18 "Voluntary" use of Validated method



- Q: Do you agree with the following statement?
- Statement: Even for the studies outside the scope of BMV guideline, as an applicant's policy, use of validated method should be encouraged for NDA application.
- Results (Answers: 19)

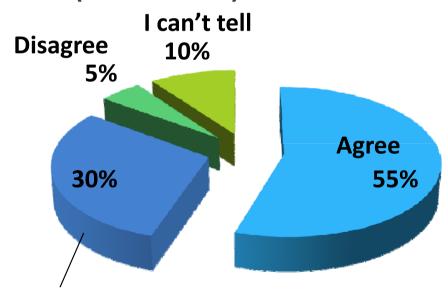


Though scientifically not necessary, we do not take a possible risk and we use validated methods

Q 14 Qualified methods in BMV-GL off-scope study



- Q: Do you agree with the following statement?
- Statement: As for the studies that is not included in the scope of BMV guideline (Toxicokinetics, Clinical Pharmacokinetics and Bioequivalence studies), the data obtained from Qualified method or less characterized method can be included in CTD.
- Results (Answers: 20)



<Comment>

[Agree]

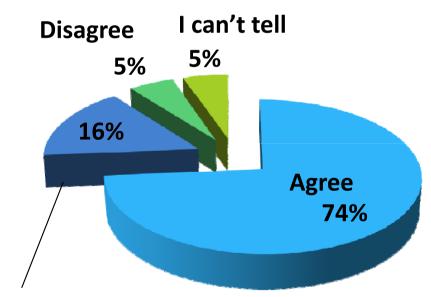
• Ultimately, it will largely depend on the position of such data in CTD.

Agree if Qualified method is used

Q 15 Human "Not important" metabolites



- Q: Do you agree with the following statement?
- Statement: Although clinical pharmacokinetics is within the scope of the BMV guideline, as for the less important metabolite*, data obtained by Qualified method or less characterized method can be included in CTD as supportive information.
- Results (Answers: 19)



Agree if Qualified method is used

<Comments>

[Agree]

- Assuming that the supportive position of the data is clarified in CTD.
- In the first place, not active and less abundant metabolite will not quantified.

[No answer / commentary only]

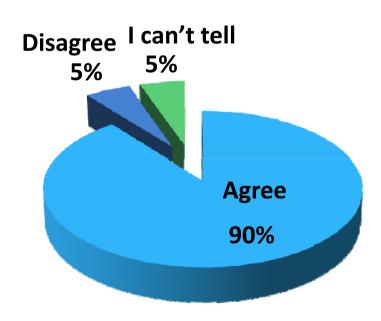
This strategy will not be used.

^{*}less important: Additional nonclinical studies will not required in MIST and CH-M3 perspective.

Q 16 Retrospective Validation in non-GLP study



- Q: Do you agree with the following statement?
- Statement: Even the method is not validated at the time data was obtained, method is consistent and the method is validated a posteriori, the data can be included in CTD in the case of non-GLP study.
- Results (Answers: 19)



<Comments>

[Agree]

- Assuming that the analytical method is not changed at all.
- Personally agree, though regulatory agency do not admit a posteriori validation.

[Disagree]

 Some part of data can be used, while in most part, it is difficult to use such data.

Q 20 Strategy of Metabolite Quantification



Which strategy of metabolite quantification in plasma is basically acceptable?

Quantify metabolites by a validated method as soon as they are found. Research the metabolites ahead of schedule. (Metabolite quantification first)

8

Give priority to early development and proof of concept of the candidate compound. Put off metabolite quantification $\, \, {f 8} \,$

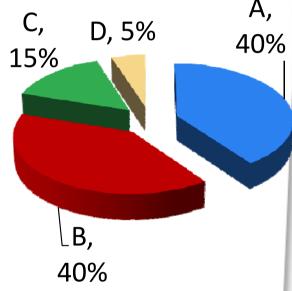
by a validated method. (POC first)

D, 5% 15%

Not fit

No comment

20 Total



Other answers

- It depends on customer's policy (CRO).
- The strategy is different between non-clinical and clinical.
- A: as a person in charge, B: objectively

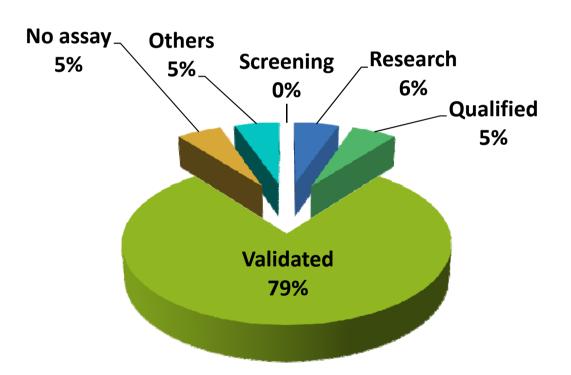
→Strategy A : Strategy B

= 50:50

Q 39 Tiered Level for Metabolite in Urine



- Question: What kind of tiered level is suitable for metabolite assay in urine in the clinical study?
- Results (Answers: 19)



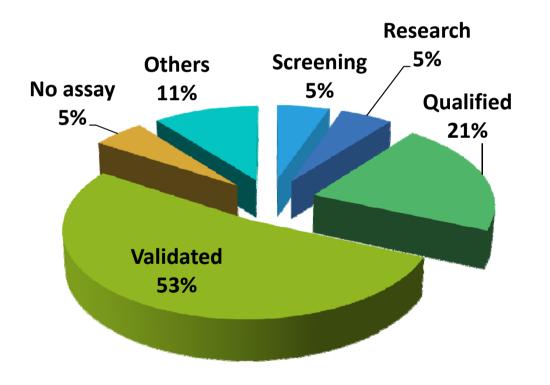
Comment:

- First in man study: Research method, Human ADME study: Validated method
- → Main answer is validated method.

Q 42 Future Tier for Urine Metabolites



- Question: Which tiered level do you accept on urine metabolite assay in the future clinical studies?
- Results (Answers: 19)



Comments:

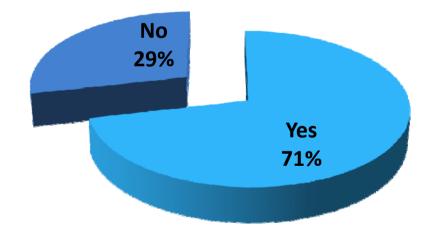
- Validated method is used as no early clinical studies are performed by our company.
- First in Man study: Research method, human ADME study: Validated method.
- → Major answers are validated method, but some are qualified method.

Q 43 Future Submission

(using other than Validated Method for Urine Metabolites)



- Question: To who selected answers other than validated method in the previous question, will you submit the data in the NDA files in the future?
- Results (Answers: 7)

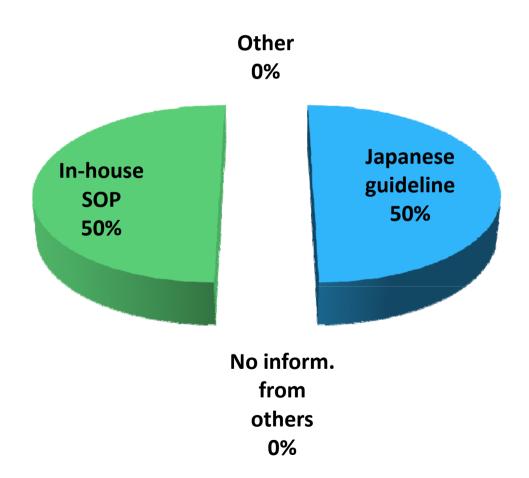


→ Positive opinions on submission of data obtained under non-validated method are obtained in the future.

Q 45 Reason of Not-Submitting Non-Vali Data



- Question: To who answered "no" in question 43, why will you not submit?
- Results (Answers: 2)



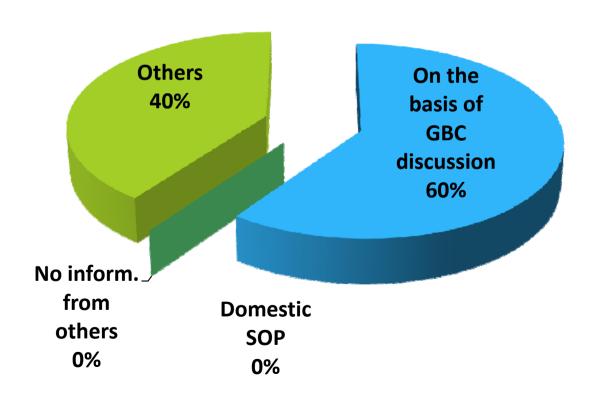
Comment:

- On the basis of the previous experience
- →The reason why data generated by non-validated method will not be submitted is a traditional form in NDA filing.

Q 44 Reason of Submitting Non-Vali Data



- Question: To who answered 'yes' in previous question, why will you submit?
- Results (answers: 5)



Comments:

- Based on the importance of the data, it can be included in NDA files as reference materials.
- The data are used only as reference materials for NDA because validated method are available in human ADME study.
- → Discussion in GBC about tiered approach has a positive effect.

Key Findings from DGs (on Tiered Approach)



Items	Findings	
GBC Recommended Workflow	Different from Current Regional Practice but Adoptable	
Recognition of GBC, EBF Recommendation	Half of the Entire Community Responded / Well Recognized in this Population	
Urine Analysis (Clinical)	Currently Validated but Moving to SV	
NDA Submission of "Tiered" Data	Dependent on Description in CTD	
Metabolite Quantitation Strategy	Early Full Investigation / Putting Off to Post POC = 50/50	
Metabolite Reference Standard	Abbreviated Quality Documents Prepared to Fulfill BMV GL Requirements	
Left-over Samples Assay	Not Performed as Stability is Unknown	

M. Niwa et al., Tiered approach to metabolite quantification: regional practices reviewed by Japan Bioanalysis Forum discussion group. Bioanalysis 7:8, 935-938 (2015)

M. Niwa et al., Survey on the tiered approach for Japanese bioanalysts operated by Japan Bioanalysis Forum DG2014-09. Bioanalysis, accepted.

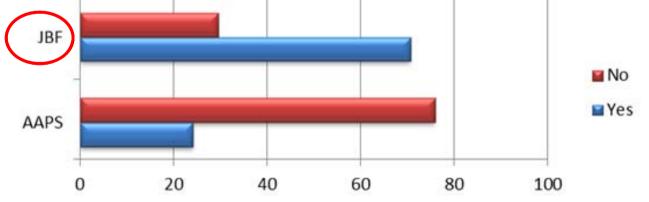
AAPS Survey / Japan-Specific Findings and Comments



- Regional Demographics
 - Survey Panel: Company Basis, 38 Companies
 - 21 Responses Collected
 - Pharma: 17
 - CRO: 4

 As a sponsors would you require your vendors to use validation as per guidance, wherein you would allow an alternative approach when analyzing the study in

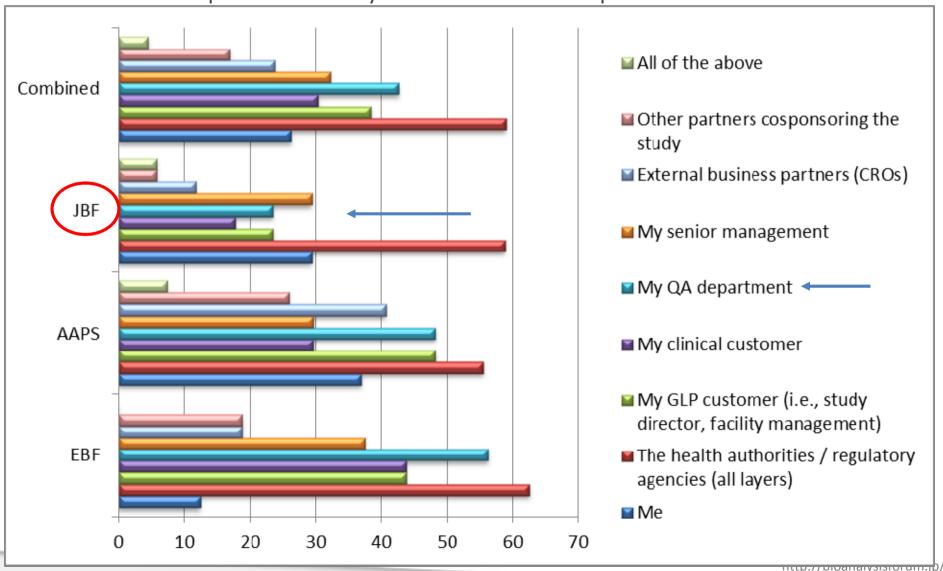




Japanese companies tend to require validation to CRO even when they would allow an alternative in house

AAPS Survey / Japan-Specific Findings and Comments

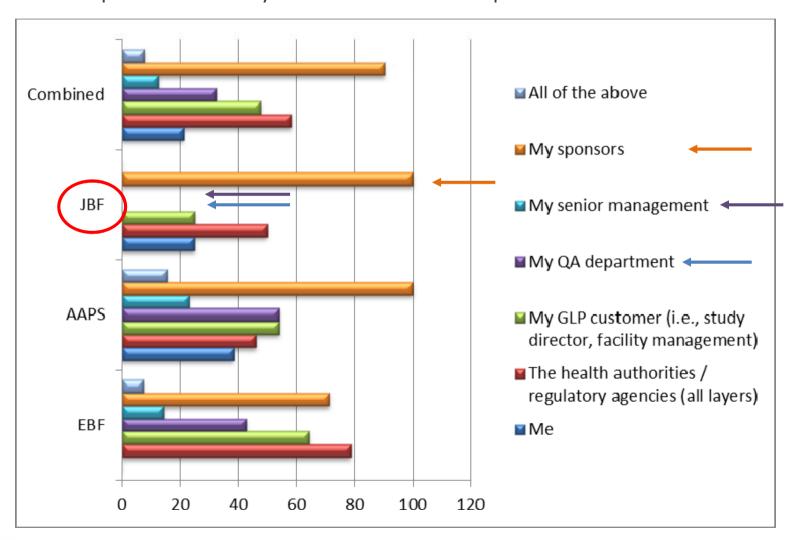
(as a Sponsor) which stakeholders are least likely to apply scientifically driven standards to the studies in scope instead of fully validated standards as per BMV Guidance?



AAPS Survey / Japan-Specific Findings and Comments



• (As CRO) which stakeholders are least likely to apply scientifically driven standards to the studies in scope instead of fully validated standards as per BMV Guidance?



DG2015-16 (Scientific Validation)



- Trend analysis of the survey, and discussion about high priority issues (e.g. metabolites, non-plasma matrix, in vitro samples) for 1.5 y
- 2 Interim report of the above discussion and open discussion with attendees at the 7th JBF symposium in Mar 2016 (They want to see EBF members there to share some perceptions)
- 3 Presentation of our position on SV at 8th JBF symposium (Mar 2017) and publication on scientific papers

<oct 2015=""></oct>	<mar 2016=""></mar>	<aug 2016=""></aug>	<mar 2017=""></mar>		
①Trend Analysis & Discussion (e.g. metabolites, non-plasma matrix, in vitro samples)					
	26th JBF Sympo	(BMAS sympo)	37th JBF Sympo		

Conclusion



- Current position of most of bioanalysts in Japan tends to be passive, and BMV Guideline is the best cornerstone for us.
- However, the concept of Scientific Validation has become widespread to us from some reasonable points of view (e.g. cost, time, other resources).
- We are driving forward this consensus through discussion at DG and presentation at the 7th JBF symposium.
- We would very much appreciate it if EBF could act as a partner and/or collaborator to promote the concept of SV to the industries/authorities.

Acknowledgment



- DG2013-03&DG2014-09 members
- Dr. Makoto Niwa (leader of the above DGs)
- Respondents to the surveys
- JBF steering committee members
- EBF

Thank you for your attention.