

Survey results and perspectives on analytical validation in Japan

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Description on endogenous compounds in PK GL of Japan

“GL on BMV in Pharmaceutical Development” for LC/MS

In Q&A (Q15)

This guideline does not cover the validation of an analytical method for an endogenous substance (e.g., vitamins, amino acids) in biological samples, even though it is administered as drugs.

“GL on BMV (LBA) Validation in Pharmaceutical Development”

In Q&A (Q1)

This guideline is applicable to a drug having an amino acid sequence identical to an endogenous substance. Selection of a blank matrix requires special precautions, such as the use of a surrogate matrix or a matrix that has been depleted of the endogenous substance concerned.

For submitting companion diagnostics (CDx)

Analytical validation for companion diagnostics

Should be clarified following items

- ✓ Accuracy
- ✓ Precision (Parallelism, Intra- & Inter-labo, etc.)
- ✓ Specificity (Cross-reactivity, Interference, Anticoagulant, etc.)
- ✓ Calibration range, Lower limit of quantification, Linearity
- ✓ Analytical cut-off value
- ✓ Reference standards
- ✓ Sample collection, treatment and storage condition
- ✓ Assay condition

No assessment criteria

Past activity in Japan (JBF)

Point to consider for quantitative analysis of biomarkers in drug development (JBF task force, 2015.2)

Scope:

- Endogenous compounds used for biomarkers
- LC or GC with/without MS, LBA
- Points to consider on assay validation in late clinical trials when biomarker is used as primary or secondary endpoint and included in application package.
- In nonclinical stage and early clinical trials, fit for purpose approach is expected for assay validation.

1. Preface
2. Scope
3. Matrix
4. Reference standards
5. Selectivity
6. Calibration curve
7. Lower limit of quantification
8. Accuracy, Precision
9. Stability
10. Commercial kit

Current activity in Japan-1

AMED Research group “BMV: Biomarker WG” chair: Y Saito

2015-2017:

- **Performed a questionnaire survey to pharmaceutical companies on the current status of biomarker assay validation in Japan**

Answered by 37 companies (26 domestic, 11 foreign)

Brief overview is follows

2018-2020:

- **Making points to consider document based on the survey results and scientific consideration**

Quantitative measurement of biomarkers

Were quantitative measurements of biomarkers **performed in clinical trials in 2012 or after?**

Yes: 23, No: 14 companies

Is the data on quantitative measurements of biomarkers **included in the application dossier?**

**Yes: 12, No: 24 companies
(Unable to answer: 1)**

Questions from regulatory authority

Did you receive questions on biomarker assay or its results from the regulatory authority?

**Yes: 2, No: 27 companies
(unable to answer: 6,
unanswered: 2)**

Presence of SOP

Was SOP for biomarker measurements set in clinical trials?

Yes: 12, No: 25 companies

If Yes, was SOP for biomarker assay validation (items, criteria) set?

Yes: 6, No: 5 companies (unanswered: 1)

If No, do you think SOP for biomarker assay validation is needed in the future?

Yes: 17, No: 7 companies (unanswered: 1)

Quantified biomarkers

82 biomarker molecules

What is the purpose of biomarker measurements?

Exploratory: 24, Decision making: 29,
In application: 27, Others: 2

What is the used platform?

LC/GC w/wo MS: 17, LBA: 51, Others: 14

Did you set the assessment criteria for the assay validation?

Yes: 43, No: 13, Unanswered: 26

Validated items-1

%	LC/GC(MS)	LBA
Selectivity	81%	65%
Specificity	6%	47%
Calibration curve	100%	100%
LLOQ	100%	91%
ULOQ	75%	94%
Accuracy	88%	78%
Precision in surrogate matrix	56%	44%
Precision in authentic Matrix	94%	72%

LC/GC(MS): n=16, LBA: n=30-32

Ohtsu et al., *Bioanalysis* 11 : 55-60 (2019)

Validated items-2

%	LC/GC(MS)	LBA
Matrix effect	63%	33%
Carry-over	69%	10%
Stability in matrix	94%	81%
Dilution linearity	56%	83%
MRD	0%	13%
Parallelism	0%	17%
Stability in standard soln.	38%	17%

LC/GC(MS): n=16, LBA: n=30-32

Ohtsu et al., *Bioanalysis* 11 : 55-60 (2019)

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- AMED Research group “Biomarker assay validation WG” members

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