State of BMV in Japan and Some Comments on Questions from Industry

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Topics

- New Drug Application in Japan
- Japan Bioanalysis Forum
- Regulatory Findings from Audits/Inspections (Results of discussion in JBF meeting)
New Drug Application in Japan

Application Systems and GLP

Work Flow of Drug / Device Development

R & D → Non-Clinical Study → Clinical Trial → Application → Post-marketing

GLP Inspection → GCP Inspection → GMP/QMS Inspection → GPSP/GVP Inspection

Review

Post-marketing Safety Operations

R&D Promotion

National Institute of Biomedical Innovation (Established in April 2005)

Pharmaceuticals and Medical Devices Agency (PMDA, Established in April 2004)

NIHS

MHLW (Health Policy Bureau)

MHLW (Pharmaceutical and Food Safety Bureau)

Pharmaceutical Affairs and Food Sanitation Council (PAFSC)
Responsibilities of MHLW and PMDA

[MHLW]
Making political agenda and enforcement of administrative actions such as approval, execution of administrative order, etc. based on laws

- Making decision on approval.
- Conducting withdrawal and directions of releasing emergent safety information.
- Adopting emergent safety measures in significant cases

[PMDA]
Review and examination before administrative actions to be taken, implementation of data analysis, etc.

- Review of pharmaceuticals, GMP/GLP/GCP inspections, clinical trial consultations
- Acquisition, examination, analysis, assessment and provision of ADR information
**Reporting GLP Inspection Results (PMDA)**

**Inspectors’ Findings**
Agreed by both the inspection team and the test facility at the closing meeting

**Inspection Report**

**The GLP Evaluating Committee**
(Consisting of External Experts)

**Inspection Result Notification to the Test Facility**
(by PMDA Chief Executive)

**Toxicokinetic Study in non-clinical tests and GLP**

- Development of analytical method
- Analytical method validation
- Toxicity studies
- TK study
- Summary reports of analytical method validation, raw data
- Selectivity, trueness, precision (repeatability, inter-mEDIATE), calibration, LOQ, range, stability, dilution effect, recovery, etc.

**GLP**
- Toxicity studies
- TK study
- Administration, sampling (blood, urine), identification, labeling, storage, etc.

**non-GLP**
- TK test
- Weight of sample
- Sample processing (extraction, derivatization, etc.)
- Pre-measurement: system suitability, calibration
- Measurement: QC sample, (incurred sample)
- Acceptance or rejection of raw data
- Calculation of TK parameters
- Statistical calculation
- Reports
- Storage of sample and data
New Drug Application in Japan

The History of GLP and Analytical Method Validation in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>Japan</th>
<th>Other Countries</th>
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<tr>
<td></td>
<td>The Guideline for Pharmacokinetic Test (1991)</td>
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<td>The Guidance for Analytical Validation (ICH Q2A,B, 1997)</td>
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<td>Non clinical test practice standard for drug safety (Ordinance of MHW, 21th, 1997) GLP</td>
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<td>Guideline for Bioequivalence Studies of Generic Products (Q&amp;A, 1998)</td>
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<td>General Considerations for Clinical Trials (ICH E8, 1998) GCP</td>
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<td>2001</td>
<td>Clinical Pharmacokinetics of Pharmaceuticals (iyakushin#796, background information for ICH E8)</td>
<td>FDA, Guidance for Industry (Bioanalytical method validation)</td>
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<td>2007-2009</td>
<td>Symposium for the AAPS/FDA White Papers (MASS2008, Tsukuba, Japan), Dr. Viswanathan was invited.</td>
<td>AAPS/FDA White Paper (2007 - )</td>
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<td>General procedure of audit for GLPs of pharmaceuticals and medical devices (Ordinance of PMDA, #0815008, 2008)</td>
<td>WHO GCLP (2009, Japanese version, introduced by JQA)</td>
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Guideline for Bioequivalence Studies of Generic Products (Q&A, 1998)

Q-27. What is the specific method for carrying out an analytical validation?

(Answer) It should be needed to do as described below.

1. Pre-analysis validation (development)
   - Stability in a matrix (include frozen/thaw cycle)
   - Trueness (recovery)
   - Precision (repeatability & intermediate variation)
   - Specificity (using matrix coming from multiple individuals)
   - Calibration curve
   - LOD

   *The summary of these validation results should be described in a report.

2. Routine validation
   - Acceptance criteria for analytical data
   - Criteria for reanalysis

   *The results of the routine validation need not be included in a report.

3. References
   - Analytical validation
   - Acceptance criteria for data
     - ISO 5725-6 Accuracy (trueness and precision) of measurement methods and results - part 6: Use in practice of accuracy values
     - JIS z 8402

New Drug Application in Japan

Relationship between Japan and Other Countries
**Relationship between Japan and Other Countries (NDA)**

ICH

USA  Japan  EU

MRA (GLP, GCP, GMP)

MAD

OECD

WHO

GCLP (2009)

MRA: Mutual Recognition Agreement
MAD: Mutual Acceptance of Data
GCLP: Good Clinical Laboratory Practice

**Relationship between Japan and Other Countries (TK)**

**MAD**
(Mutual Acceptance of Data)

OECD (Countries)
AUS, AU, BE, CAN, CZ, DK, FIN, FR, GER, GR, HU, ICL, IRE, IT, JP, KO, LU, MEX, NL, NO, NZ, PO, PT, SK, SP, SWE, SWI, TU, UK, USA

Non-members
South Africa 2003
Slovenia 2004
Israel 2005


MOU with EC, Switzerland and USA*

MOU: Memorandum of Understanding
*Only pesticides program

India, Singapore, China, Russia, Brazil, Argentina, Chinese Taipei, Thailand, etc.
Japan Bioanalysis Forum (JBF)

The developing process of the JBF.

- Jan. 12-13, 2011, The First Asia Pacific Conference on Recent Issues in Regulated Bioanalysis (Shanghai, China),
- Jan. 27, 2011, Mailing list group was made,
- Feb. 18, 2011, The first configuration of this forum was proposed,
- Feb. 21, 2011, Prof. Kurokawa was recommended for GBC-SC by the Pharmaceutical Society of Japan,
- Mar. 10, 2011, The meeting of the delegates of JBF with Dr. Garofolo was held.
Foundation Members of JBF

GBC-Steering Committee
- Kurokawa, Tatsuo (Prof., Keio Univ.)

University
- Haginaka, Jun (Prof., Mukogawa Women's Univ.)
- Masujima, Tsutomu, (Prof., Hiroshima Univ.)

Company
- Pharmaceutica!
  - Hara, Hisanori (Novartis Pharma AG, Switzerland)
  - Jinno, Fumihiro (Takeda Pharmaceutical Co., Ltd.)
  - Kobayashi, Nobuhiro, (DaichiSankyo Co., Ltd.)
  - Kondo, Takahiro (Takeda Pharmaceutical Co., Ltd.)
  - Mabuchi, Masanori (Mitsubishi Tanabe Pharma Co.)
  - Matsumaru, Takehisa (Nippon Boehringer Ingelheim Co., Ltd)
- Nakayaka, Akira (Ajinomoto Pharmaceuticals Co., Ltd.)
- Ohtsu, Yoshiaki, (Astellas Pharma Inc.)
- Osumi, Takahiko (Otsuka Pharmaceutical Co., Ltd.)
- Tachiki, Hidenao (Towa Pharmaceutical Co., Ltd.)
- Yahata, Kenji (Sanofi-Aventis)
- Yoneyama, Tomoki, (Takeda Pharmaceutical Co., Ltd.)

CRO
- Inoue, Noriko (JCL Bioassay Co., Ltd.)
- Taniguchi, Masahiro (Sumika Analysis Service, Ltd.)

Regulation
- Katori, Noriko (National Institute of Health Sciences)

Regulatory Findings from Audits/Inspections
(Results of discussion in JBF meeting)
Results of the discussion in JBF meeting

The JBF is now the only association for regulatory bioanalysis in pharmaceutical area in Japan.

- Japan has no guidance for bioanalytical method validation.
- The answers in these slides are the results of the discussion in the JBF kickoff meeting on March 30.

Regulatory Findings from Audits/Inspections

1. Alternate detectors (AMS, High Resolution MS, ICPMS)
   - Which guidance to follow for method validation and sample analysis?
2. It seems that different auditors interpret the guideline in different ways:
   - Is it possible to create consistency amongst inspectors?
3. Batch failure:
   - What is an acceptable level of batch failure 10%, 20%, 50%, more?
4. Whole blood stability evaluation:
   - What are the Agency’s recommendations for this evaluation?
5. Effect of counter-ion anticoagulants:
   - Is it real or just a matrix effect when we analyze multiple plasma lots?
   - What are the Agency’s recommendations for this evaluation?
6. Differences in slopes of the calibration curves on different LC-MS/MSs:
   - Is there any impact on the data?
7. Chromatograms integration:
   - When is manual integration accepted?
8. Systems cross-validation:
   - Is it needed and if yes in which cases?
9. Variability of the internal standard (IS) in analytical and abnormal IS:
   - Do we need to establish acceptance criteria for IS?
   - Is Internal Standard trend analysis recommended by the Agency to evaluate method reliability?
10. Re-injection vs. re-analysis vs. non-reportable values:
    - What are the Agency’s recommendations?
11. Stability issues in bioanalytical methods validation and the definition of “fresh”:
    - Is it necessary to use fresh QCs for stability assessments (not just calibrators)?
12. Matrix stability for co-formulated drugs and co-administered drugs:
    - What are the Agency’s recommendations?
13. Hemolysis:
    - What if the method is not insensitive to hemolysis?
    - Can we still assign samples as “Not Reportable” or do we have to redevelop a “hemolysis-insensitive” method?
14. “fit-for-purpose” validations:
    - Clarification and definition?
15. Method Development data:
    - Can these data be integral part of an inspection/audit?
16. Regarding method transfer validation between laboratories, what would be minimum recommended parameters to be tested?
17. Are there any recommended parameters for system suitability test (SST) to be performed before each batch analysis?
1. Alternate detectors (AMS, High Resolution MS, ICPMS)

- Which guidance to follow for method validation and sample analysis?

- No guidance is available for these detectors.

2. It seems that different auditors interpret the guideline in different ways:

- Is it possible to create consistency amongst inspectors?

- “The GLP Evaluating Committee” can accommodate the inconsistency.
- Supplemental guidance for auditors and/or Q&A documents may improve the consistency.
3. Batch failure:

- What is an acceptable level of batch failure 10%, 20%,... 50%...more?

- Although no criterion is currently employed, a root cause is tried to be identified in case of continuous batch failure.

4. Whole blood stability evaluation:

- What are the Agency’s recommendations for this evaluation?

- No recommendation to evaluate this.
- The difference between before and after a few hours storage on bench top is started to be evaluated in a few companies.
- Usage of spiked blood may need equilibrium time.
5. Effect of counter-ion anticoagulants:

- Is it real or just a matrix effect when we analyze multiple plasma lots?
- What are the Agency’s recommendations for this evaluation?

- A consistent anticoagulant should be used throughout the clinical development.

6. Differences in slopes of the calibration curves on different LC-MS/MSs:

- Is there any impact on the data?

- Stable isotope-labeled internal standards may somehow compensate the difference.
- In case of system change, the linearity of calibration curves and accuracy around LLOQ should be carefully evaluated.
7. Chromatograms integration:

- When is manual integration accepted?

  - Manual integration is basically not preferable.
  - Manual integration is deemed acceptable when original and modified chromatograms are retained with proper reason for change.
  - A SOP should be prepared for manual integration.

8. Systems cross-validation:

- Is it needed and if yes in which cases?

  - The cross-validation is performed in case of major changes in analytical methods, and the partial validation is for minor changes.
    1. Major changes: methodology or laboratory changes etc.
    2. Minor changes: instrument (the same grades) or analyst changes etc.
9. Variability of the internal standard (IS) in analytical and abnormal IS:

- Do we need to establish acceptance criteria for IS?
- Is Internal Standard trend analysis recommended by the Agency to evaluate method reliability?

- IS responses are routinely monitored.
- Some analytical CROs have their own criteria for re-analysis due to anomalous IS response.

10. Re-injection vs. re-analysis vs. non-reportable values:

- What are the Agency’s recommendations?

- Re-injection is done in case of instrument malfunction if re-injection could be performed within acceptable stability period.
- Re-analysis is for failed batches, anomalous values and PK repeats.
- Non-reportable values are the result of large variability through re-analysis or insufficient sample volume. The process should be determined prior to re-analysis.
11. Stability issues in bioanalytical methods validation and the definition of “fresh”:

- Is it necessary to use fresh QC samples for stability assessments (not just calibrators)?

- QC samples for run acceptance are not always fresh while those should be used within established stability period.
- QC samples for run acceptance should be analyzed with stability QC samples.

12. Matrix stability for co-formulated drugs and co-administered drugs:

- What are the Agency’s recommendations?

- No recommendation to evaluate this.
- Matrix stability with co-formulated and co-administered drugs is getting evaluated in a few companies.
13. Hemolysis

- What if the method is not insensitive to hemolysis?
- Can we still assign samples as "Not Reportable" or do we have to redevelop a "hemolysis-insensitive" method?

- Hemolyzed sample is reported as a reference value.
- The impact of hemolysis cannot be fully evaluated during method validation because hemolysis could be caused by variety of reasons, generating various extents of hemolyzed samples.

14. "fit-for-purpose" validations

- Clarification and definition?

- Fit-for-purpose validation is performed case by case depending on the development stage and utility of results.
15. Method Development data

- Can these data be integral part of an inspection/audit?

  The validity of measured values can be ensured by method validation data, and there may be no need for method development data.

16. Questions from Japan Bioanalysis Forum 1

- Regarding method transfer validation between laboratories, what would be minimum recommended parameters to be tested?

  Full-validation is recommended.
17. Questions from Japan Bioanalysis Forum 2

- Are there any recommended parameters for system suitability test (SST) to be performed before each batch analysis?

  - Check of the baselines after injections of mobile phase.
  - Peak response around LLOQ.

Thank You!