Regulated bioanalysis status in Japan and notable points of the draft Japanese guideline

EBF 5th Open Meeting
“Old Battles, New Horizons”,
November, 16, 2012, Barcelona

Noriko Katori, PhD
National Institute of Health Sciences, Japan
Contents

1. Activity of JBF and Recent History of regulatory bioanalysis in Japan

2. Draft of BMV guideline (JBF version)

3. Make up process of Japanese guides
Regulatory Bioanalysis – Global Movement


2001 FDA; Guidance for Industry (Bioanalytical method validation),

2006 EBF was founded at the initiative of 12 pharmaceutical companies,

2007 FDA/AAPS White paper, (Introduction of ISR),

2009 EMA; Draft Guideline on Validation of Bioanalytical Methods,

2010 GBC was established,

2011 EMA; Guideline on Validation of Bioanalytical Methods.

How about Japan?
The recent history of BMV in Japan

- **2008**
  - GBC approached Japanese organizations

- **2009**
  - First workshop for ISR in Japan (Tsukuba)
  - Discussions about BMV were held by pharmaceuticals and CROs in Japan.
  - 3.11 Earthquake!

- **2010**
  - The 5th Workshop on Recent Issues in Bioanalysis (Montreal)

- **2011**
  - GBC discussion started
  - The First Asia Pacific Conference on BMV (Shanghai)

- **2012**
  - Aug/10: Kick-off meeting of the BMV Study Group for Japanese BMV guideline
  - Oct/6: EBF 2011 4th Open Symposium (Barcelona)
  - Dec/7: J-BMV Guideline items were listed-up by JBF
  - Mar/8: The 1st JBF Symposium (Tokyo)
  - Mar/31: The 2nd JBF Symposium (Tokyo)
  - Mar: Preliminary draft of BMV guideline by JBF (for small molecule)

- **Now!**
  - Aug/8: The 3rd JBF Symposium (Tokyo)
JBF Scope and mission

Scope
- Small molecule bioanalysis
- Large molecule bioanalysis
- (Possibly biomarker measurement)

Mission
- Facilitating a discussion on regulated bioanalysis in Japan
- Interact with Japanese regulators in the field of bioanalysis
- Represent Japan in worldwide bioanalysis community
### Japan Bioanalysis Forum (JBF) - Foundation Members -

<table>
<thead>
<tr>
<th><strong>Representative</strong></th>
<th><strong>Tatsuo Kurokawa</strong> (Prof., Keio Univ.)</th>
</tr>
</thead>
</table>
| **Academia**       | **Jun Haginaka** (Prof., Mukogawa Women's Univ.)  
                      **Tsutomu Masujima** (Prof., Hiroshima Univ.) |
| **Regulatory**     | **Noriko Katori** (National Institute of Health Sciences) |
| **Pharmaceutical** | **Akira Nakayama** (Ajinomoto Pharmaceuticals Co., Ltd.)  
                      **Fumihiro Jinno** (Takeda Pharmaceutical Company Ltd.)  
                      **Hidehisa Tachiki** (Towa Pharmaceutical Co., Ltd.)  
                      **Hisanori Hara** (Novartis Pharma AG, Switzerland)  
                      **Kenji Yahata** (Sanofi-Aventis)  
                      **Masanari Mabuchi** (Mitsubishi Tanabe Pharma Co.)  
                      **Nobuhiro Kobayashi** (Daiichi Sankyo Co., Ltd.)  
                      **Takahiko Osumi** (Otsuka Pharmaceutical Co., Ltd.)  
                      **Takahiro Kondo** (Takeda Pharmaceutical Company Ltd.)  
                      **Takehisa Matsumaru** (Nippon Boehringer Ingelheim Co., Ltd)  
                      **Tomoki Yoneyama** (Takeda Pharmaceutical Company Ltd.)  
                      **Yoshiaki Ohtsu** (Astellas Pharma Inc.) |
| **CRO**            | **Masahiro Taniguchi** (SCAS-BTT Bioanalysis C0., Ltd.)  
                      **Noriko Inoue** (JCL Bioassay Co., Ltd.) |
Current whole picture of JBF

JBF SC (27)
- Pharma (15)
- CRO (7)
- University (3)
- Regulatory agency (2)

HT member/supporter community (43)
- Support Japanese scientists in GBC
- Have scientific discussion

Representative
Deputy representative
Advisor
Committees
Task forces
JBF Committees and Task Forces

● Committees
  * F&A committee
  * Financial auditors committee
  * Website administration committee
  * Membership committee
  * Event execution committee
  * Public relations committee
  * International affairs committee
  * EBF window persons
  * Documentation committee

● Task forces
  * Membership system startup
  * GBC HT support
  * Small molecule (chromatography) BA method guideline
  * LBA BA method guideline

Website http://bioanalysisforum.jp/en
Relationship between JBF and other organizations

EBF 5th Open Meeting “Old Battles, New Horizons” N. Katori

Nov. 16, 2012, Barcelona
BMV Related Organization & Scientific Groups in Japan

Companies
* Japan Pharmaceutical Manufacturers Association (JPMA)
* Japan Generic Medicines Association (JGA)
* Japan Association of Contract Laboratories for Safety Evaluation (JACL)

Scientific Group
* Pharmaceutical sciences Japan (PSJ)
* Mass Spectrometry society of Japan (MSSJ)

Authorities
* National Institute of Health Sciences (NIHS)
* Ministry of Health, Labour and Welfare (MHLW)
* Pharmaceuticals and Medical Devices Agency (PMDA)
Asia-Pacific bioanalysis community (ABC) - current status -

* JBF SC initiated communication with Daniel Tang (CBF, China Bioanalysis Forum) in August 2012, exploring opportunities for APAC community.
* The internal discussion on external relationship has been ongoing in JBF SC alongside.
* Not ready for proposing APAC countries to form ‘ABC’ now.

However, if you are from APAC and interested in ABC, please do not hesitate to contact CBF or JBF.
2. Draft of BMV guideline (JBF version)
Preliminary Japanese BMV guideline
- Policy -

* Applied to the bioanalytical methods generating quantitative concentration data in toxicokinetics and clinical studies.

* Small molecule (LC-MS, LC-MS/MS) guideline is prepared first
  Large molecule guideline (LBA) will be prepared following that of small molecule.

* Analysis of metabolite can be considered

* Terminology; conform to ICH Q2a, b

* Not to be largely different from FDA/EMA guides.

* Q&A for the guideline should be prepared
# Preliminary Japanese BMV guideline

- Contents (JBF draft) -

| 1. | Introduction |
| 2. | Scope |
| 3. | Reference Standard |
| 4. | Method Validation |
| 4-1. | Full Validation |
| 1. | Selectivity |
| 2. | LLOQ |
| 3. | Calibration Curve |
| 4. | Accuracy and Precision |
| 5. | Matrix Effect |
| 6. | Recovery |
| 7. | Carry Over |
| 8. | Dilution Integrity |
| 9. | Stability |
| 4-2. | Partial Validation |
| 4-3. | Cross Validation |
| 5. | Analysis of Study Samples |
| 5-1. | Validity of the Method |
| 1. | Calibration Curve |
| 2. | QC Samples |
| 3. | Carry Over |
| 4. | ISR |
| 5-2. | Notice |
| 1. | Calibration Range |
| 2. | Re-analysis |
| 3. | Integration |
| 6. | Documentation |
| 6-1. | Validation Reports |
| 6-2. | Analytical Reports |
| 6-3. | Data Management |
| 7. | Supplemental Definitions |
7. Supplemental

* Tiered approach → move to addendum part
devolution stage, metabolites, etc.,

* Rare matrix → move to 4.1 Full validation
tissue, cerebral fluid, bile, etc.,

* Endogenous materials → move to Q&A
alternative matrix, stable isotope,

* System suitability → move to 5.2 Notice
not essential.
<table>
<thead>
<tr>
<th>Item</th>
<th>JBF Draft</th>
<th>AAPS/FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>• TK and clinical trial (without animal PK)</td>
<td>—</td>
<td>• TK and clinical trial (without animal PK)</td>
</tr>
<tr>
<td></td>
<td>• small molecule (LC, GC)</td>
<td></td>
<td>• small and large molecule (LC, GC, LBA)</td>
</tr>
<tr>
<td>Rules</td>
<td>• GLP principle</td>
<td>—</td>
<td>• GLP/GCP principle</td>
</tr>
</tbody>
</table>

Preliminary draft (by JBF)/FDA/EMA Comparison 1
<table>
<thead>
<tr>
<th>Item</th>
<th>JBF Draft</th>
<th>AAPS/FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix effect (concentrations)</td>
<td>—</td>
<td>—</td>
<td>2 levels (near LLOQ/ULOQ)</td>
</tr>
<tr>
<td>Rare matrix (MF)</td>
<td>—</td>
<td>—</td>
<td>Should be evaluate</td>
</tr>
<tr>
<td>Stability</td>
<td>within ±15% of the nominal concentration</td>
<td>—</td>
<td>within ±15% of the nominal concentration</td>
</tr>
<tr>
<td>Std. stability</td>
<td>Stock solution, Working solutions (analyte)</td>
<td>Stock solution</td>
<td>Stock solution, Working solutions (analyte and IS)</td>
</tr>
<tr>
<td>Cross-Validation</td>
<td>QC sample : within ±20% of mean study sample : within ±20% of mean (≥ 2/3)</td>
<td>—</td>
<td>QC sample : within ±15% of mean, or wider study sample : within ±20% of mean (≥ 67%)</td>
</tr>
<tr>
<td>Item</td>
<td>JBF Draft</td>
<td>AAPS/FDA</td>
<td>EMA</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Validation level (species, anticoaigrant)</td>
<td>Full Validation (species, matrix change) same anticoaigrant is preferable</td>
<td>Partial Validation/Cross-Validation (Full Validation, 2007)</td>
<td>Full Validation (species, matrix change) same anticoaigrant is preferable</td>
</tr>
<tr>
<td>interfering components (definition)</td>
<td>analyte : ≥20% of LLOQ IS : ≥ 5% of IS (≥20% of LLOQ, 2007)</td>
<td></td>
<td>analyze : ≥20% of LLOQ IS : ≥ 5% of IS</td>
</tr>
<tr>
<td>Calibration curves</td>
<td>At least 75% of the calibration standards within ±15% (±20% at LLOQ).</td>
<td>At least 4/6 of the calibration standards within ±15% (±20% at LLOQ).</td>
<td>At least 75% of the calibration standards within ±15% (±20% at LLOQ).</td>
</tr>
<tr>
<td>Recovery</td>
<td>Need not be 100%, but should be consistent, precise, and reproducible.</td>
<td>Need not be 100%, but should be consistent, precise, and reproducible.</td>
<td>—</td>
</tr>
</tbody>
</table>
Regulatory Bioanalysis
Development Stage and Bioanalysis

Screening  Pre-clinical  Clinical Phase I II III  Post Approval

IND  NDA

PK Study for Animal (ADME, DDI)  PK Study for Human (GCP)

Non-GLP TK  GLP TK

High-throughput Method  Bioanalysis  Validated Method

Japanese BMV Guideline  : in the scope  : out of the scope
GLP regulations

GCP regulations

Clinical Research

PK, PK/PD
Clinical Pharmacokinetics of Pharmaceuticals
(2001.6.1, PMSB/ELD Notification No. 796)

BA/BE, DDI

Non clinical PK (animal)
The Guideline for Non clinical Pharmacokinetic test
(1998.6.26, PMSB/ELD Notification No. 496)

TK
Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (ICH S3A)

The Scope of BMV Guideline

Nov. 16, 2012, Barcelona
Draft Guideline on Bioanalytical Method Validation in Japan
by Japan Bioanalysis Forum

Tomoki YONEYAMA*1, *2, Noriko INOUE*1, *3, Hidehisa TACHIKA*1, *4, Kazutaka TOGASHI*1, *5, Akira NAKAYAMA*1, *6, Takashi KUDO*2, Hisao SHIMIZU*2 and Noriko KATORI*1, *7
3. Make up process of Japanese guides
Relationship between the JBF and the BMV Study Group

Organizations (JPMA, JGA, JACL)

BMV Study Group

BMV guideline draft by JBF

request of BMV guideline draft

gathering of comments
The members of the BMV Study Group

❖ Authorities
  ✴ MHLW, 1 (observer)
  ✴ NIHS, 4 (Chief+3)
  ✴ PMDA, 2 (+ many observers)

❖ Companies
  ✴ JPMA, 2 (non-clinical, clinical)
  ✴ JGA, 1
  ✴ JACL, 2

❖ Scientific Group
  ✴ JBF, 2
The members of the LBA Working Group

∗ Authorities
  ∗ MHLW, 1 (observer)
  ∗ NIHS, 5 (Chief+4)

∗ Companies
  ∗ JPMA, 2 (non-clinical, clinical)
  ∗ JACL, 1 - 2 (planned)

∗ Scientific Group
  ∗ JBF, 7 (LBA Guideline Taskforce)
Preliminary Japanese BMV guideline for LBA
- Policy -

* Applied to the bioanalytical methods generating quantitative concentration data in toxicokinetics and clinical studies.

* Guideline for LBA (large and small molecule). LC/MS/MS methods for large molecule are not included.

* Terminology; basically conform to preceding guideline for chromatography (small molecule).

* Not to be largely different from FDA/EMA guides.

* Q&A for the guideline should be prepared next.
Schedule for BMV in Japan and Globe

2012

- Preliminary draft of BMV guideline by JBF (for small molecule)
- Kick-off meeting of the WG for LBA (BMV study group)
- EBF 2012 5th Open Symposium (Barcelona)
- AAPS Annual Meeting (Chicago)
- GBC Global Meeting (US)

2013

- Guideline items will be listed-up by JBF (for LBA)
- Draft of BMV Guideline for small molecule by MHLW

Now!

- FDA BMV guidance (revised)
- FDA/AAPS meeting (Crystal city, USA)
- The 7th Workshop on Recent Issues in Bioanalysis (California)
- The 6th Workshop on Recent Issues in Bioanalysis (San Antonio)
- The 4th JBF Symposium (Tokyo)
- The 7th Workshop on Recent Issues in Bioanalysis (California)

EBF 5th Open Meeting “Old Battles, New Horizons” N. Katori 27 Nov. 16, 2012, Barcelona
3rd JBF Symposium

Conference report will be published in *Bioanalysis*!
Thank you for your attention!
Backups
The recent history of BMV in Japan

- 2008, Symposium for the AAPS/FDA White Papers (MASS2008, Tsukuba, Japan), where Dr. Viswanathan was invited,
- Mar. 30, 2011, The Japan Bioanalysis Forum (JBF) preparatory meeting,
- Aug. 10, 2011, The 1st JBF symposium (Tokyo), The JBF was established formally.
- Oct. 6, 2011, Kick-off meeting of the BMV Study Group for Japanese BMV guideline,
- Nov. 2011, The BMV study group asked to make a preliminary draft of BMV guideline to the JBF.
- Dec. 7, 2011, J-BMV Guideline items were listed-up by JBF.
- Mar. 8, 2012, The 2nd JBF symposium (Tokyo),
- Mar. 31, 2012, Draft BMV guideline by JBF (for small molecule)
Schedule

- **5th EBF Open Symposium (Barcelona)**
  Japanese Guideline will be introduced by Dr. Katori (NIHS)
  14-16 November 2012

- **Items for LBA Guideline** will be listed-up by JBF LBA taskforce by the end of 2012

- **Draft BMV guideline (for public comment, small molecule)**
  early of 2013 (scheduled)

- **Q&A (BMV guideline for small molecule)**
  early of 2013 (scheduled)

- **FDA guidance (BMV, revised)**
  4Q 2012?

- **FDA/AAPS meeting (Crystal city, USA)**
  2013?

- **4rd JBF Symposium (Tokyo)**
  Aug, 2013 (scheduled)