EBF 2011 4th Open Symposium

- Less is More -

Barcelona, Spain

Introducing The Japan Bioanalysis Forum

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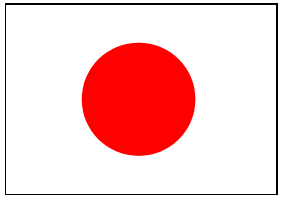
Shimadzu Techno-Research, Inc.

Regulatory Organization & Discussion groups



- Ministry of Health, Labour and Welfare（MHLW）
- Pharmaceuticals and Medical Devices Agency（PMDA）
- National Institute of Health Sciences （NIHS）
- Japan Pharmaceutical Manufacturers Association (JPMA）
- Japan Bioanalysis Forum (JBF, 2011 Aug.)

- EMA：European Medicines Agency
- CHMP：Committee for Medicinal Products for Human Use
- European Federation of Pharmaceutical Industries Associations (efpia)
- European Bioanalysis Forum (EBF, since 2006)

Japanese Regulatory Organization & Responsibilities

Ministry of Health, Labour and Welfare [MHLW]

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

e.g.

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

Pharmaceuticals and Medical Devices Agency [PMDA]

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

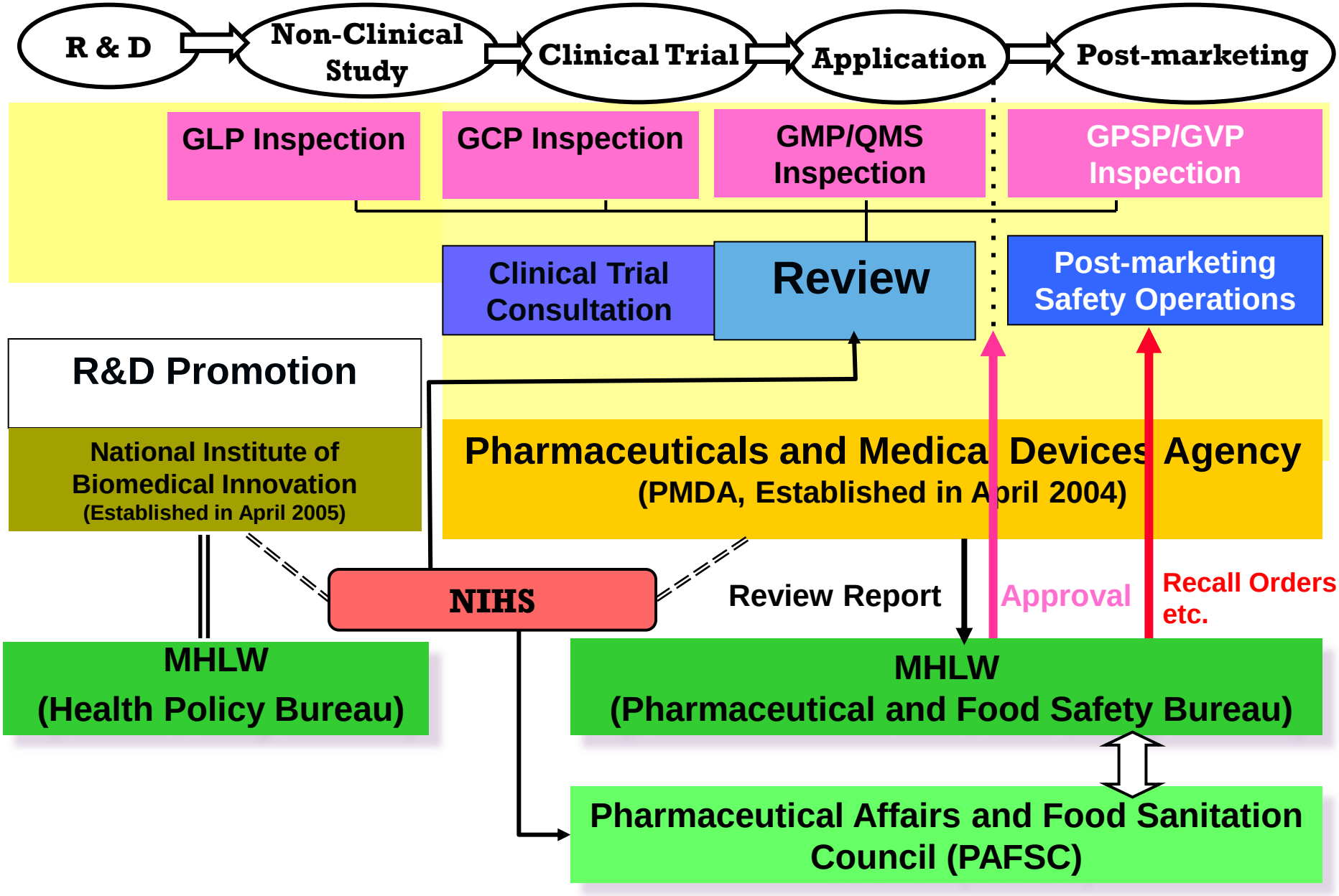
e.g.

- **Review of pharmaceuticals, GMP/GLP/GCP inspections, clinical trial consultations**
- **Acquisition, examination, analysis, assessment and provision of ADR information**

National Institute of Health Sciences [NIHS]

- **testing, research, and studies toward the proper evaluation of the quality, safety, and efficacy of pharmaceutical products, foods, and the numerous chemicals that are closely related to people's lives.**

Work Flow of Drug / Device Development



Bioanalysis related Guidelines, Ordinances and other Documents in Japan, EU & US.

Year		
~ 1995	The Guideline for Toxicology Test (1989) The Guideline for Pharmacokinetic Test (1991)	EU: International Reid Bioanalytical forum Initiated (1975) US: •GLP for Nonclinical Lab. Studies 21 CFR Part 58 •BA & BE requirements. CFR Part 320, Sec. 320.29 Analytical methods for an in vivo bioavailability or bioequivalence study •1st AAPS/FDA Bioanalytical workshop (1990) "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies" Conference report published. Shah et al. Pharm. Res. 9, 588-592 (1992)
1996 - 1998	Japan Pharmaceutical Manufacturers Association（JPMA）TK, Method Validation guidance document for TK studies (1995) The Guidance for Toxicokinetics (ICH S3A Step4, 1996)	
	The Guidance for Analytical Validation (ICH Q2A,B, 1997)	OECD principle of GLP (1997, revised)
	Non clinical test practice standard for drug safety (GLP Ordinance of MHW, 21th, 1997 Mar)	US: FDA Draft guidance "Guidance for industry: Bioanalytical method validation for human studies" (Dec)
	Guideline for Bioequivalence Studies of Generic Products (Q&A, 1998)	
	General Considerations for Clinical Trials (ICH E8, 1998) GCP	
	The Guideline for Non clinical Pharmacokinetic test (1998) June	

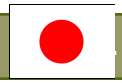
Bioanalysis related Guidelines, Ordinances and other Documents in Japan, EU & US.

Year		 
2000 - 2001	**Clinical Pharmacokinetics of Pharmaceuticals (MHLW iyakushin#796, background information for ICH E8)**	**2000** **US:** **■The 2nd AAPS/FDA bioanalytical workshop "Bioanalytical Method Validation, A revisit with decade of progress" Pharm Res. 2000; 17: 1551-1557 (Jan,)** **■AAPS Workshop on"Bioanalytical Methods Validation for Macromolecules" (Mar)** **▪ Sep, Krys J. Miller, Ronald R. Bowsher, et al., "Workshop on Bioanalytical Methods Validation for Macromolecules: Summary Report" *Pharm Res*. 2001; 18: 1373-1383** **■FDA, Guidance for Industry (May) - Bioanalytical method validation -**
Post FDA Guidance 2002 -		**2003** **US: AAPS Workshop on"Bioanalytical Methods Validation for Macromolecules in Support of Pharmacokinetic Studies" (May)** **▪ DeSilva B, Smith W, Weiner R, et al., "Recommendations for the bioanalytical method Validation of ligand-binding assays to support pharmacokinetic assessments of macromolecules" *Pharm Res*. 2003; 20: 1885-1900 (Nov)** **2005** **US: "Draft Guidance for Industry: Safety Testing of Drug Metabolites" MIST (June)**

Bioanalysis related Guidelines, Ordinances and other Documents in Japan, EU & US.

Year		
2006 - 2008	**2008: Symposium for the AAPS/FDA White Papers (MASS2008, Tsukuba, Japan), Dr. Viswanathan was invited on Regulatory update ISR.** **Non clinical test practice standard for drug safety (Ordinance of MHLW, 114th , revised, 2008) GLP** **General procedure of audit for GLPs of pharmaceuticals and medical devices (Ordinance of PMDA, #0815008, 2008)**	**2006** **US: The 3rd AAPS/FDA bioanalytical workshop "Bioanalytical Method Validation, A revisit with decade of progress" (May) Focused on Incurred sample reanalysis Tired approach for determination of metabolites during drug development** **AAPS/FDA White Paper (2007 -)** **EU: European Bioanalysis Forum established** **2007** **US: FDA & AAPS discussion and issued White paper on BMV introducing ISR concept.** **Workshop/conference report published, The AAPS Journal; 9(1) article 4 (2007)** **2008** **US: AAPS/FDA ISR workshop on current topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples – Implications of Crystal City Recommendations (Feb).** **Workshop Report and Follow-Up published, *The AAPS Journal*; 11 (2) 238-241 (2009)** **US: Guidance for Industry: Safety Testing of Drug Metabolites "MIST Guidance" (Feb)** ▪ **"Regulatory Update Incurred Sample Reanalysis" Dr. C.T. Viswanathan (DSI/CDER/FDA)** ▪ **"Incurred Sample Reproducibility: Examples of Scientific and Operational Considerations" Dr. Richard M. Lelacheur (Taylor Technology, Inc., US)**

Bioanalysis related Guidelines, Ordinances and other Documents in Japan, EU & US.

Year		 
2009		**2009** **EU:** **• ISR white paper "Incurred sample reproducibility: view & recommendations by EBF"** **• Nov. Draft Guideline on Validation of Bioanalytical Methods. EMEA/CHMP/EWP/192217/2009 (2009)** **•Dec. 2nd Annual Open Symposium "The Broadening Scope of Validation"** Conference report "The Broadening scope of validation: Towards best practices in the world of bioanalysis **EU: 1st Annual Open Symposium "Burning Issues in bioanalysis" Dec. 2009** **US: FDA & AAPS discussion and ISR White paper issued.** **Workshop report and follow-up, published,TheAPPSJournal;11(2)238-241(2009)**
2010 - 2011	**•Japan Bioanalysis Forum established (2011 Mar)** **•1st JBA symposium, *ca.*200 Scientists gathers (2011 Aug)** **•BMV Working Group established (2011 Oct)** **•JBF was asked by BMV Working Group to draft out the guidelines which should not be largely different form FDA and EMA guidance**	**EU:** **2011 Aug.: Guideline on bioanalytical method validation (EMEA/CHMP/EWP)**

Japan Bioanalysis Forum

- Establishment circumstances -

Bioanalysis method validation (BMV):

has been a subject for longer than a decade.

Its importance has widely been recognized.

not a growing tendency to establish it
(Regrettable!!)

In practice, BMVs have been carried out in accordance mostly with FDA guideline.

Guideline for Bioequivalence Studies of Generic Products (Q&A, 1998)

By References

Analytical validation: V.P. Shah et al., Analytical methods validation: Bioavailability, bioequivalence and pharmacokinetic studies. J. Pharm. Sci., 81, 309 (1992).

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

Voices

summarized by Dr. Katori, N (NIHS)

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?***

Questions from JBF

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?***

Japan Bioanalysis Forum

- Establishment circumstances -

Early 2010 Japan Regulatory & administration Agencies received a request for attending

"The First Asia Pacific Conference on Recent Issues in Regulated Bioanalysis (Shanghai, China)"

Late 2010 The Pharmaceutical Society of Japan was requested for a candidate to join the steering committee of GBC .

Several Pharmaceutical companies received an invitation to participating in GBC.

2011 Jan. **The First Asia Pacific Conference on Recent Issues in Regulated Bioanalysis (Shanghai, China)**

Session 1 : Hot topics & Scientific challenges in small molecules bioanalysis Metabolite Quantification

"Our approach for Quantitative Metabolite Assessments according to MIST Guidance" Kobayashi, Nobuhiro (Dai-Ichi Sankyo Pharm.)

Session 4 : Regulatory Agencies & Hearth Authority Updates

"State of GLP in Japan and Statistical Considerations in the Bioanalytical Guidance" Katori, Noriko（NIHS）

- **As Japanese participants were overwhelmed by the active discussions, The Consolidation of Japanese bioanalysts was voluntary initiated.**

2011 Feb. BMV studying society (provisional) organized

Prof. T.Kurokawa was officially recommended by PSJ for GBC-Steering committee upon the request from GBC

2011 Mar. 10 A meeting was held with Dr. Garofolo and the BMV studying society delegates.

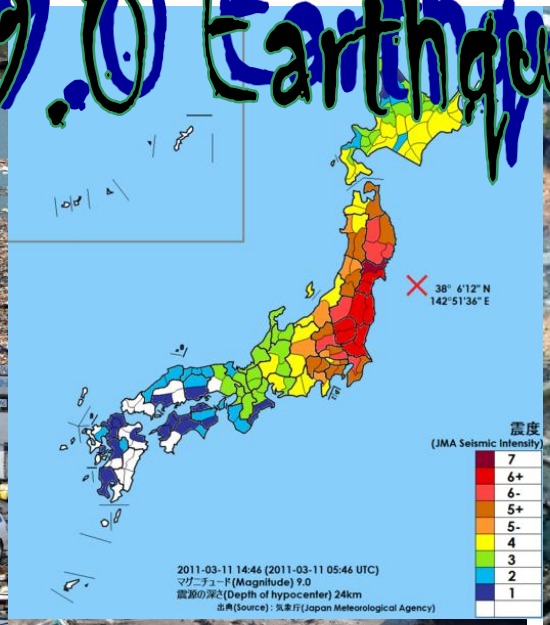
NEXT DAY:

Japan Bioanalysis Forum

- Establishment circumstances -

14:46:18 JST Mar 11, 2011

M9.0 Earthquake Disaster



Japan Bioanalysis Forum
- Establishment circumstances -

Mar. 30 Japan Bioanalysis Forum (JBF) was named at the 1st Founders meeting held in Osaka

Apr. JBF establishment was officially announced by Dr. Katori, Noriko at the 5th Montreal Bioanalysis Workshop

June 1st JBF symposium was decided to be held in August 10 at 2nd Founders meeting

Aug 10, 1st JBF, - Kick-off -, symposium in Funabori, Tokyo

- >200 participants; mainly from Pharmaceutical companies, CROs

Characteristics of JBF

1. **bioanalysis experts from Industry, Academy and Regulatory Agency**
2. **All member of GBC-HT are from JBF with consensus & supports**

JBF Committee member 22 as of Oct end

Industry

Pharma

- Hara, Hisanori (Novartis Pharma AG, Switzerland) **HT-A8**
- Kobayashi, Nobuhiro, (Daiichi Sankyo)
- Mabuchi, Masanori (Mitsubishi Tanabe Pharma) **HT-A3**
- Matsumaru, Takehisa (Nippon Boehringer Ingelheim)
- Nakayaka, Akira (Ajinomoto Pharmaceuticals)
- Ohtsu, Yoshiaki, (Astellas Pharma) **HT-A6**
- Osumi, Takahiko (Otsuka Pharmaceutical) **HT-A4**
- Tachiki, Hidenao (Towa Pharmaceutical) **HT-A9**
- Yahata, Kenji (Sanofi-Aventis)
- Yoneyama, Tomoki, (Takeda Pharmaceutical) **HT-A2**
- Igarashi, Harue (GlaxoSmithkline Japan) **HT-A5**
- Imazato, Mami (Novartis Pharma, Japan) **HT-L4**
- Yamamoto, Katsuhiko (Kyowa-Kirin) **HT-L1**

CRO

- Inoue, Noriko (JCL Bioassay) **HT-S1**
- Togashi, Kazutaka (Sumika Chem Anal Servic) **HT-S2**
- Nakai, Keiko (Mitsubishi Medience) **HT-A10**
- Minamide, Yoshiyuki (Shimadzu Techno Res) **HT-L2**
- Kudoh, Shinobu (Shimadzu Techno Research) **GBC-SC**

Academy

- Kurokawa, Tatsuo (Prof., Keio Univ.) **JBF Leader**
- Haginaka, Jun (Prof., Mukogawa Women's Univ.)
- Masujima, Tsutomu (Prof., Hiroshima Univ.)

Government Agency

- Katori, Noriko (National Institute of Health Sci)

+ HT supporters

Japan Bioanalysis Forum
Mission & Logotype

Decided in October 2011

(Personal understanding)

- **Facilitating science driven discussions on bioanalysis**
- **Helping setting in Japan BMV by Providing scientific rationale and consensus amongst Japanese bioanalysts**
- **To Be A Partner representing Japanese bioanalytical community for Global Harmonization**
- Voice for other APO countries?, Korea, Taiwan, Singapore, (Australia, New Zealand)

Symbolizing;

- **Shape & Colour: One team of Japan**
- **Tricolored: Industrial-Academic-Government Cooperation**
- **Red: Strong will**
- **White: Uprightness in science**
- **Brown: Fertile ground in Bioanalysis**
- **Word lining: Free from ill-precedents**

Are we similar?
Is it easy?

Japanese lesson 1
Difficulty in communication

- I'm writing this letter slowly because you can not read English fast. But I'll rush to a post at the supermarket.
- 私はこの**手紙**をゆっくり書いています．何故って貴方は英語を速く読めないからね．でも，スーパーマーケットにある郵便ポストへは急いで行きます
- Chinese characters (>3000)
- Hiragana characters (51)
- Katakana characters (51)
- 手 (palm/hand)
- 紙 (paper)
- **手紙 (?)**

Do Japanese scientists/bioanalysts communicate

in Chinese, Korean or English ?

Japan Bioanalysis Forum
- Establishment circumstances -

Oct 6, Working group for preparation of the guidelines for the quantitation method drugs in biological samples. (Leader: Yasuo Ohno, Director General, National Institute of Health Sciences.)

- **Regulatory Agencies**
  - NIHS: Okuda, Kawasaki, Katori
  - MHLW Pharmaceutical and Food Safety Bureau Evaluation & Licensing Div. : Mitsuoka
  - Pharmaceuticals and Medical Devices Agency (PMDA): 2
- **Japan Pharmaceutical Manufacturers Association: 2 (1/2)**
- **Japan Association of Contract Laboratories for Safety Evaluation: 2**
- **Japan Generic Medicines Association: 1**

red: JBF

2011 Oct 31: JBF was requested as a scientific experts on bioanalysis.

- Scope: Primarily, Low molecular drugs including metabolites, for TK & PK in Non-clinical, Clinical and BE studies.
- LC-MS, LC-MS/MS
- With no remarkable disagreements with those by EMA and FDA
- Time line Due date: item listing, Dec 7 2011,
- Draft, Feb end, 2012 for small molecular drugs
- Large molecular drugs and biomarkers For others, not yet decided

Japan Bioanalysis Forum in a short range

Running-in topics

- **Consolidation of JBF organization**
- **Regulations of the society**
- **Operational expenses**

2011 Aug — 11 1st JBF Symposium, **Done**
>200 Industries, Academies, Regulatory bodies.

Sept — **WG for J-BMV Guideline**, consolidated
(MHLW/PMDA/NIHS/JPMA/JACL)

Oct — BMV WG Requested JBF for drafting J-BMV guideline

Nov — **Now: EBF, Building a Good relationship**

Dec — Dec 7: J-BMV Guideline items list-up

2012 Jan — **J-BMV Guideline Draft-out for small molecular drugs**

Feb

Mar — **8,9: 2nd JBF Symposium**

GBC-HT Supporters Enrollment On-going till Nov end


JBF
Thank EBF
for this opportunity
2011/08/10
大津義明
中山聡
来山智城
富樫一天
立木秀尚
工藤忍
香取典子

Gracias / Thank / Obrigado/ Grazie/
Merci/ Tanke/ Dankeschön/ Tack/
Kiitoksia/ Dêkuji/ Dziękuję/
Köszönöm/ Sas efharisto/
Spasibo/Sagolun/Dyakooyu

EBF

for

Helping & Supporting Japan

for

Rehabilitation

from

Monstrous Earthquake Disaster

Back Up

Japan (Practical procedures at many laboratories)	
Aspects of Validations	
Full validation	There is no guidance of bioanalytical method validation (BMV) in Japan. It has been done by aligning mostly with the FDA guidance*1). White paper in 2007*2) and EMA guideline *3) have also been refered in conjunction with the one of FDA. *1) Guidance for Industry on Bioanalytical Method Validation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2001. *2) Workshop/Conference Report-Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays, 2007(White Paper). *3) Guideline on bioanalytical method validation, European Medicines Agency, EMEA/CHMP/EWP/192217/2011.
Partial validation	The partial validation is performed in case of minor changes in an analytical method are required. The minor changes means varied but usually the change in analyst/lab, part of method, anticoagulant, matrix, stabiliser, animal, ethnic group, sample treatment process, concomitant medication, etc. This is done by conducting one full analytical run to ensure the intra-day precision and accuracy on multiple numbers of fortified samples at a few concentration levels with newly established calibration curve(s)
Cross-validation	The cross validation is performed when different methods or a method largely modified are applied to the same series of study. Change in analysis site may be subjected to this. Cross-validation is conducted after completion of partial or full-validation and often conducted in a blinded manners.
Reference Standard	Practically, it is kept under the conditions and used up within its expiry date stated in C of A or an equivalent document.
Robustness testing	There is no firmly confirmed practices in terms of testing items and severity for it, depending on the companies or labs' philosophy.
Selectivity	Blank samples and the lower limit of quantitation (LLOQ) samples prepared with the same biological matrix from six individuals (male: 3, female: 3) are processed and analysed with the method established. Specificity is visually assessed and determined by peak integration or quantitation results obtained. The peak areas or determination results of blank samples should not exceed those for analytes by 20% and IS by 5% in LLOQ samples.
Specificity	Ditto
Interferences	Ditto

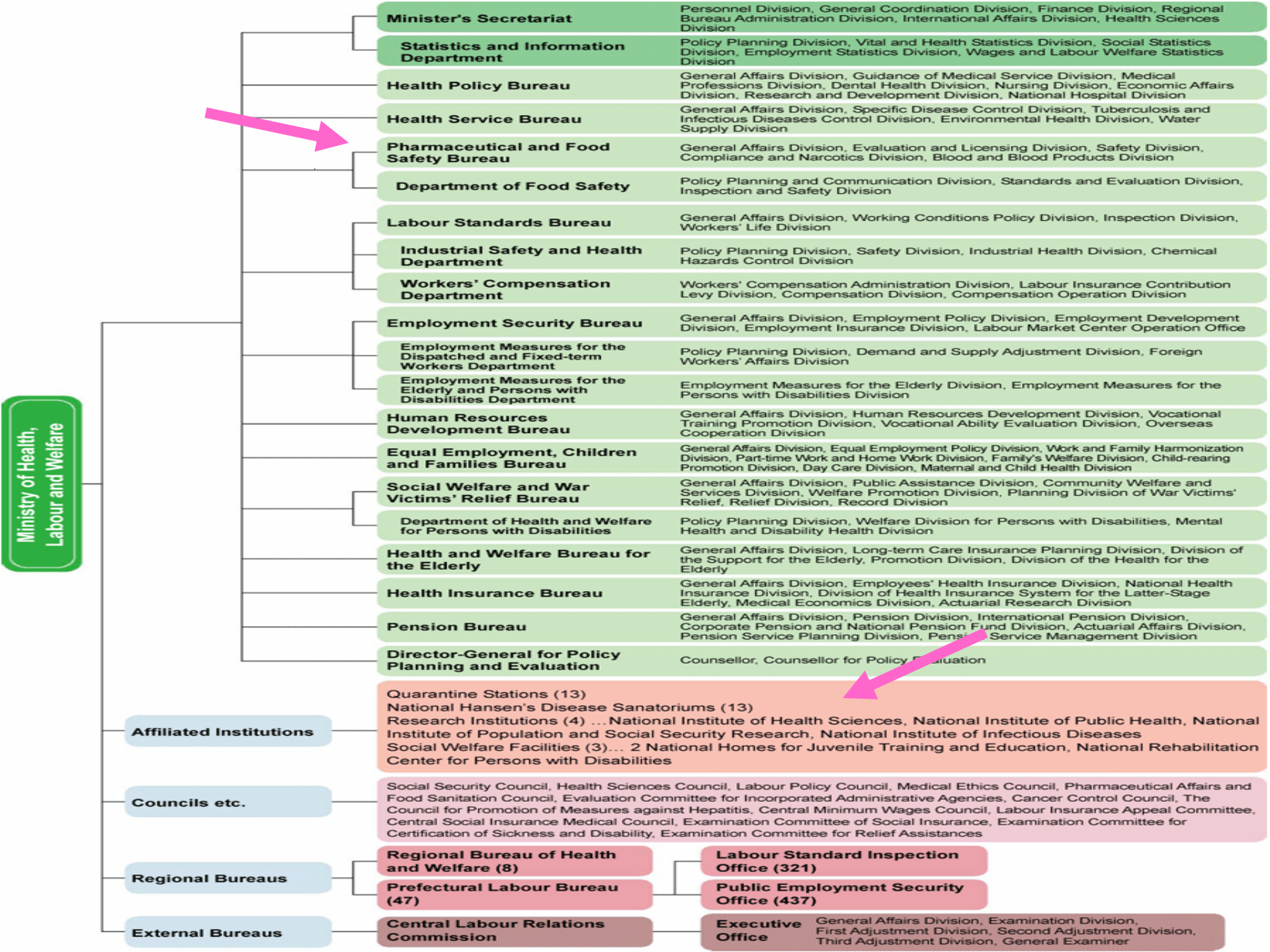
Japan (Practical procedures at many laboratories)	
Aspects of Validations	
Recovery	Recovery samples are prepared at 2 or 3 concentration levels of analyte(s) in triplicate (n=3) for the each concentration level and are processed through the entire determination process. Blank matrix samples are also processed in the same manner right before the subjecting to the determination process (e.g. before sample injection to HPLC). Processed blank matrix samples are fortified with the analyte and IS at the same levels in concentrations for the recovery samples and subjected to the determination process. The peak area ratios of analyte/IS in the recovery samples are compared with those in blank matrix sample at the same concentration as 100% recovery reference.
Matrix Effects	This is assessed generally in the same manner as the procedures described for the recovery test. Standard compounds fortified in e.g. triplicate to processed individual or pooled blank matrix samples and to non-matrix contained samples such as water at typically lower and higher concentration levels in calibration range are compared.
Calibration curve	This is done in accordance with FDA guideline as described in Canadian column.
Regression model	The standard curve should be determined using an appropriate algorithm with a least weight model.
Calibration curve acceptance criteria	The correlation of coefficient (r) or determination (r2) must be 0.9900 or higher. The accuracy of the back-calculated concentrations of the calibration curve must be within ±20.0% at the LLOQ and within ±15.0% at the ULOQ and at a minimum of 4 out of 6 other concentration points. Two concentration points or less (except for the LLOQ and ULOQ) can be omitted to reconstruct a better calibration curve. In case of small molecules, linear regression is preferable.
QC samples requirements and criteria	The QC samples in duplicate at three concentration levels (one near the LOQ (i.e., ≦3 x LOQ), one in midrange, and one close to the high end of the range) should be incorporated in each assay run. The results of the QC samples provide the basis of accepting or rejecting the run. At least four of the six QC samples should be within ±15% of their respective nominal value. Two of the six QC samples may be outside the ±15% of their respective nominal value, but not both at the same concentration.
Accuracy	Accuracy is determined by 5 (minimum) replicate analysis of samples containing known amounts of the analyte at 3 or more concentration levels which well represent the calibration ranges and expecting core concentration range. The mean value should be within 15% of the actual value except at LLOQ, where it should not deviate by more than 20%. The deviation of the mean from the true value serves as the measure of accuracy.

Japan (Practical procedures at many laboratories)	
Aspects of Validations	
Precision	Precision should be measured using a minimum of five determinations per concentration. A minimum of three concentrations in the range of expected concentrations is recommended. The precision determined at each concentration level should not exceed 15% of the coefficient of variation (CV) except for the LLOQ, where it should not exceed 20% of the CV. Precision is further subdivided into within-run, intra-batch precision, which assesses precision during a single analytical run, and between-run, inter-batch precision or repeatability, which measures precision with time, and may involve different analysts, equipment, reagents, and laboratories.
Sensitivity	The lower limit of quantitation (LLOQ) is the lowest amount of analyte in a sample which can be quantified reliably, with an acceptable accuracy and precision. The precision must not be more than 20.0% and the accuracy must be within ±20.0%.
Carryover and Contamination Evaluation	The blank samples are prepared in triplicate (n=3) . These samples will be analyzed right after injection of ULOQ sample that is consecutively done in some labs. The measurement is typically conducted in the following order: calibration standard sample, blank-1, blank-2 and blank-3. This procedure is sometimes performed on 3 different days along with 3-day validation samples. The peak areas of carryover peaks at the retention times of each analyte at the blank samples must be 20.0% or less of those of each analyte on the chromatograms of the respective LLOQ . (Personally, ULOQ is considered as not adequately high enough as it dose not secure the determination for the samples analysed right after the sample exceeding the calibration range, which happed occasionally and dilution sample criteria is set)
Determination of Metabolites during Drug Development	Not available
Stock Solution	Not available
Stability (general)	
Freeze-Thaw Stability	The samples at 2 concentrations (e.g., QC low and high level) are stored at -20° C and -80° C in freezers and thawed at ambient room temperature or in a lukewarm water bath. The freeze/thaw cycle is repeated 3 to 5 times in triplicate. The samples are frozen for longer than 24 hours on the first cycle and for longer than 12 hours on the second and afterward.

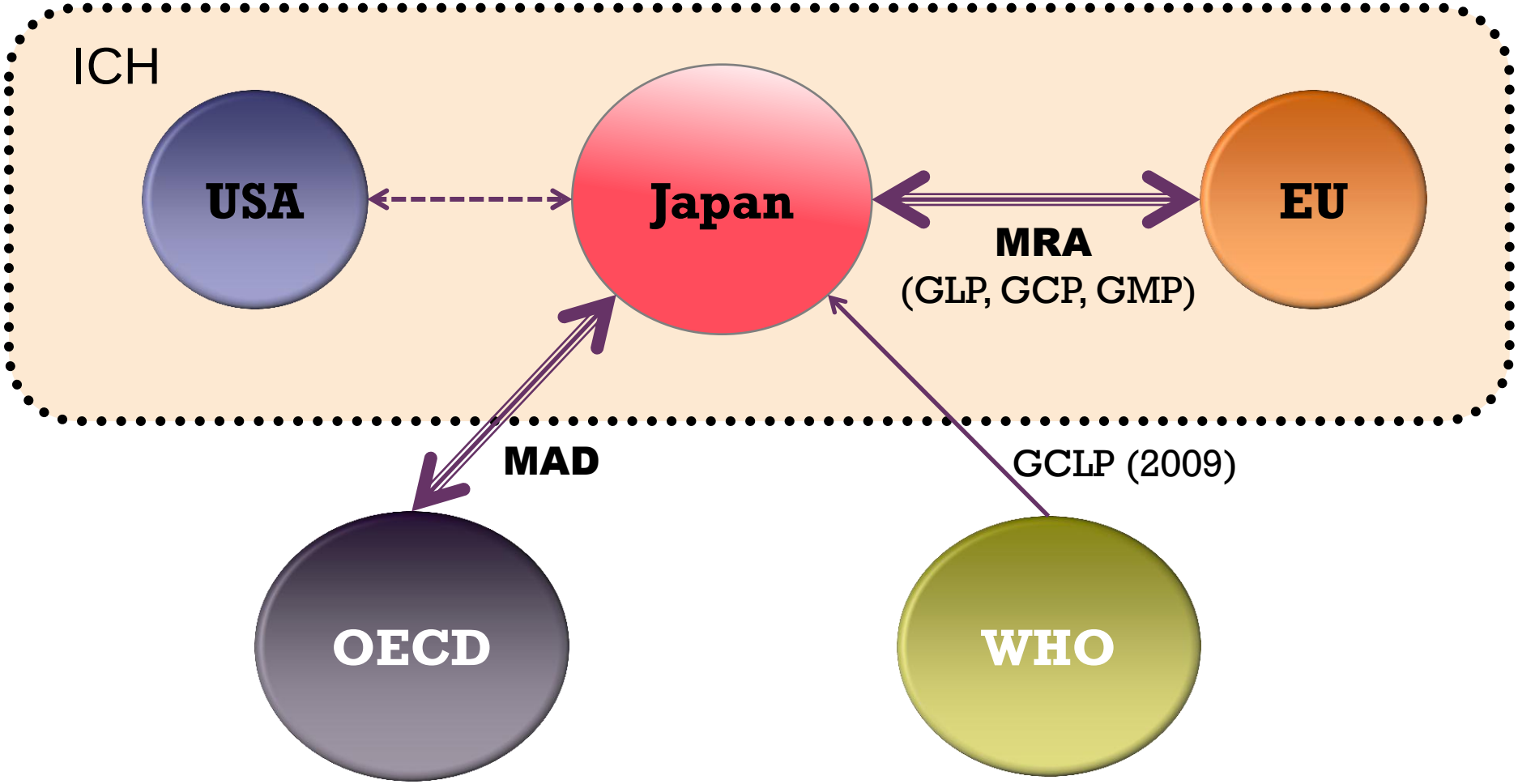
Japan (Practical procedures at many laboratories)	
Aspects of Validations	
Short term Stability	at 2 concentrations (e.g., QC low and high level) are stored at -20dC and -80dC in triplicate.
Post-Prep (two types comparison against self upon reanalysis vs against fresh curve)	Not available
Long-term Stability	(same as short-term stability)
Stock Stability	The stability of stock solutions of analyte and the internal standard should be evaluated at room temperature and storage conditions (-20˚ C or -80˚ C, refrigerated). After completion of the storage, the stability should be evaluated by comparing the freshly prepared solutions. Deuterium-labelled IS stock solution, in particular is subjected to MS spectrometry to ensure labelled condition.
System Suitability	It is a common practice that a sensitivity confirmation sample (e.g., LLOQ) is injected before each assay run to ensure analytical conditions.
Dilution Integrity & *Sample Dilutions*	The samples with the same matrix prepared by fortifying with standard compounds at some concentration(s) exceeding the ULOQ. They are diluted with the same matrix (or alternate matrix) to be in the aiming calibration range before subjection to sample pretreatment processes and determination. The determined dilution process and magnitude are applied to the authentic samples when they exceed the calibration range validated.
Matrix Requirements	The same biological matrix obtained with the same anticoagulant as the matrix in the intended samples must be used for validation purposes. Substitution can be considered for availability of matrix such as limited cells, tissues and some body fluids. Sample dilution may be done with an alternative matrix if appropriately validated.
Sample Analysis	
ISR - Since this is primarily for sample analysis, we should only consider times when incurred samples are used in validations (e.g., cross validations)	It is not applicable to Japanese practice. Personally, I understand that cross validation should be done with authentic samples although practically difficult. But many of us including me are hardly convinced whether it is scientifically relevant because the original method is anyway validated with spiked samples. Also, there are still discussions if ISR itself is truly meaningful and the way conducting it on a different day is better than the way of duplicate assays on selected number of samples.

Japan (Practical procedures at many laboratories)	
Aspects of Validations	
Documentation Maintained at the Lab	
Reporting	
General	The listed below are typical reporting items - Title of study - Name and Address of Sponsor - Study Initiation Date and Study Completion Date - Name and Address of Testing Facility - Name of Staff and Work Assigned - Name of Study Director - Signature of Study Director and Date Signed - Summary - Objective - Compliance Ordinances - Materials and Methods - Results and Discussions - Conclusions - References - Unforeseeable Circumstances That May Have Ill Effects on the Reliability of the Study and the Deviations from the Protocol - Archive Storage - Tables - Figures
Reference Standard Certificate of Analysis (COA)	It should be provided certificate of analysis in the raw data.
Reanalysis	The adopted concentration will be specified in result table. Description in context: sample ID, reason for reanalysis, decision for adopted concentration
Calibration curves	Result of calibration curve in every run (correlation coefficient, slope, intercept, accuracy)
SOPs	Not specified
Reintegrated chromatograms	Not specified

	Japan (Practical procedures at many laboratories)
Aspects of Validations	
Topics with no US consensus	
Cross-Validation Of Bioanalytical Methods When Using Different Anticoagulant Counter-Ions	Not available In some cases, a partial validation is performed as an intra-day assay.
Cross-Validation Required When Using Different Strains or Sexes of a Species	Not available In some cases, a partial validation is performed as an intra-day assay.
Cross-Validation Required When Moving a Method Between LC-MS/MS Instruments	A partial validation is performed as an intra-day assay.
Specific Criteria for Cross-Validation	The same criteria as for the intra-day validation is applied.
Separate Stability Experiments Required At –70° C if Stability Shown at –20° C	Stability is usually assessed at the both storage conditions from the beginning. Additional stability at lower temperature should be required for macromolecules and may also be performed for small molecules as needed. (*2)
Stability Criteria for Stock Solution Stability	After completion of the storage, the stability should be evaluated by comparing the freshly prepared solutions. The variation is to be within ±15.0%.
Acceptance Criteria for Internal Standards	Not available. It is common that the day-to-day IS peak areas are traced. More importantly, especially for Deutilated IS, MS spectrum should be confirmed in an appropriate occasion.
Stability for co-formulated drugs in matrix	No difference as for the single drug in matrix.

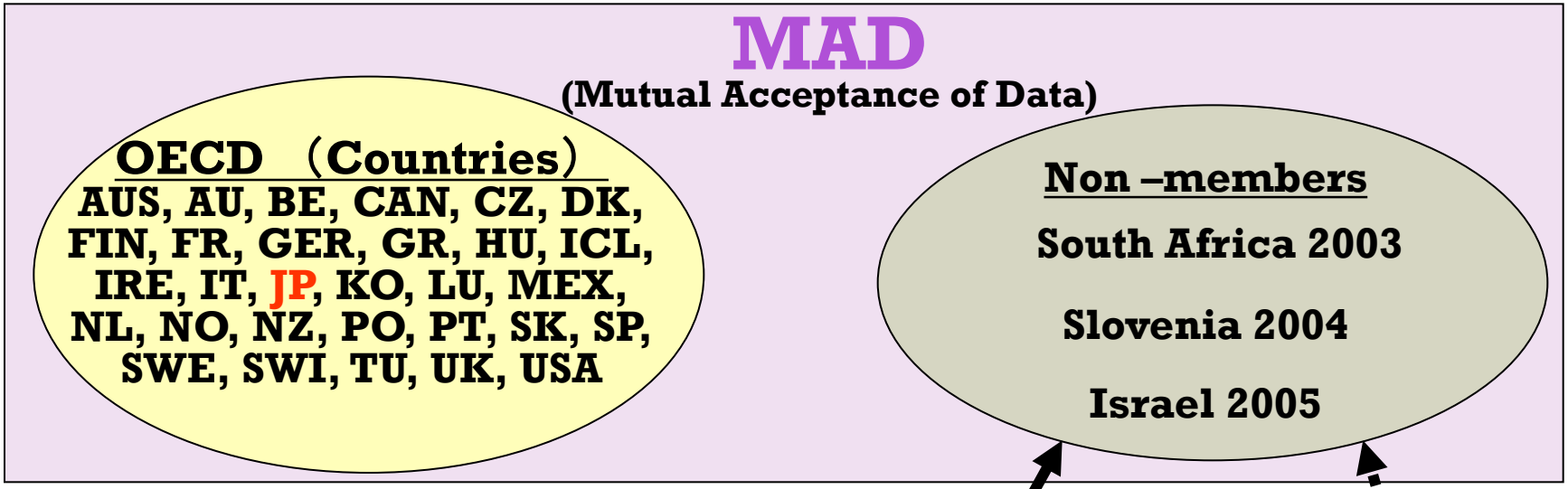

Ministry of Health, Labour and Welfare
Minister's Secretariat
Personnel Division, General Coordination Division, Finance Division, Regional Bureau Administration Division, International Affairs Division, Health Sciences Division
Statistics and Information Department
Policy Planning Division, Vital and Health Statistics Division, Social Statistics Division, Employment Statistics Division, Wages and Labour Welfare Statistics Division
Health Policy Bureau
General Affairs Division, Guidance of Medical Service Division, Medical Professions Division, Dental Health Division, Nursing Division, Economic Affairs Division, Research and Development Division, National Hospital Division
Health Service Bureau
General Affairs Division, Specific Disease Control Division, Tuberculosis and Infectious Diseases Control Division, Environmental Health Division, Water Supply Division
Pharmaceutical and Food Safety Bureau
General Affairs Division, Evaluation and Licensing Division, Safety Division, Compliance and Narcotics Division, Blood and Blood Products Division
Department of Food Safety
Policy Planning and Communication Division, Standards and Evaluation Division, Inspection and Safety Division
Labour Standards Bureau
General Affairs Division, Working Conditions Policy Division, Inspection Division, Workers' Life Division
Industrial Safety and Health Department
Policy Planning Division, Safety Division, Industrial Health Division, Chemical Hazards Control Division
Workers' Compensation Department
Workers' Compensation Administration Division, Labour Insurance Contribution Levy Division, Compensation Division, Compensation Operation Division
Employment Security Bureau
General Affairs Division, Employment Policy Division, Employment Development Division, Employment Insurance Division, Labour Market Center Operation Office
Employment Measures for the Dispatched and Fixed-term Workers Department
Policy Planning Division, Demand and Supply Adjustment Division, Foreign Workers' Affairs Division
Employment Measures for the Elderly and Persons with Disabilities Department
Employment Measures for the Elderly Division, Employment Measures for the Persons with Disabilities Division
Human Resources Development Bureau
General Affairs Division, Human Resources Development Division, Vocational Training Promotion Division, Vocational Ability Evaluation Division, Overseas Cooperation Division
Equal Employment, Children and Families Bureau
General Affairs Division, Equal Employment Policy Division, Work and Family Harmonization Division, Part-time Work and Home Work Division, Family's Welfare Division, Child-rearing Promotion Division, Day Care Division, Maternal and Child Health Division
Social Welfare and War Victims' Relief Bureau
General Affairs Division, Public Assistance Division, Community Welfare and Services Division, Welfare Promotion Division, Planning Division of War Victims' Relief, Relief Division, Record Division
Department of Health and Welfare for Persons with Disabilities
Policy Planning Division, Welfare Division for Persons with Disabilities, Mental Health and Disability Health Division
Health and Welfare Bureau for the Elderly
General Affairs Division, Long-term Care Insurance Planning Division, Division of the Support for the Elderly, Promotion Division, Division of the Health for the Elderly
Health Insurance Bureau
General Affairs Division, Employees' Health Insurance Division, National Health Insurance Division, Division of Health Insurance System for the Latter-Stage Elderly, Medical Economics Division, Actuarial Research Division
Pension Bureau
General Affairs Division, Pension Division, International Pension Division, Corporate Pension and National Pension Fund Division, Actuarial Affairs Division, Pension Service Planning Division, Pens Service Management Division
Director-General for Policy Planning and Evaluation
Counsellor, Counsellor for Policy luation
Affiliated Institutions
Quarantine Stations (13)
National Hansen's Disease Sanatoriums (13)
Research Institutions (4) ...National Institute of Health Sciences, National Institute of Public Health, National Institute of Population and Social Security Research, National Institute of Infectious Diseases
Social Welfare Facilities (3)... 2 National Homes for Juvenile Training and Education, National Rehabilitation Center for Persons with Disabilities
Councils etc.
Social Security Council, Health Sciences Council, Labour Policy Council, Medical Ethics Council, Pharmaceutical Affairs and Food Sanitation Council, Evaluation Committee for Incorporated Administrative Agencies, Cancer Control Council, The Council for Promotion of Measures against Hepatitis, Central Minimum Wages Council, Labour Insurance Appeal Committee, Central Social Insurance Medical Council, Examination Committee of Social Insurance, Examination Committee for Certification of Sickness and Disability, Examination Committee for Relief Assistances
Regional Bureaus
Regional Bureau of Health and Welfare (8)
Prefectural Labour Bureau (47)
Labour Standard Inspection Office (321)
Public Employment Security Office (437)
External Bureaus
Central Labour Relations Commission
Executive Office
General Affairs Division, Examination Division, First Adjustment Division, Second Adjustment Division, Third Adjustment Division, General Examiner

Relationship between Japan and Other Countries (NDA)



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

Relationship between Japan and Other Countries (TK)



1981 MAD, 1989 Compliance,
1997 Non-Members

MOU with EC, Switzerland and USA*

India, Singapore, Brazil ,Argentina (Provisional)

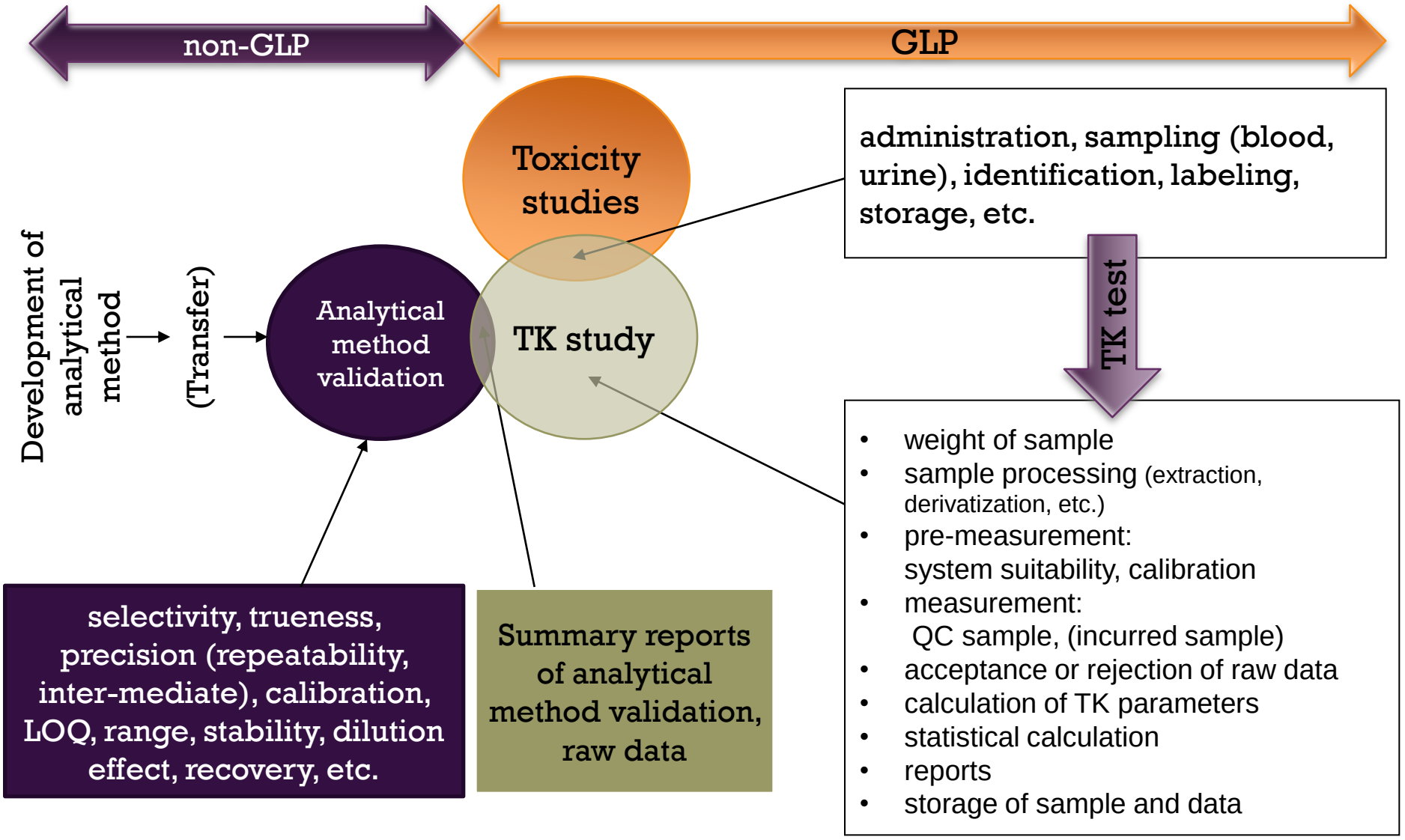
China, Russia, Chinese Taipei, Thailand etc.

Bilateral Cooperation

MOU: Memorandum of Understanding

*Only pesticides program

Toxicokinetic Study in non-clinical tests and GLP



- **Pharmaceutical Affairs and Food Sanitation Council (PAFSC)**薬事・食品衛生審議会
- **Central Pharmaceutical Affairs Council (CPAC)**中央薬事審議会
- **Pharmaceutical Affairs Council (PAC)**薬事分科会
- **Food Sanitation Council (FSC)**食品衛生分科会
- **First Committee on Drugs**医薬品第一部会
- **Second Committee on Drugs**医薬品第二部会
- **Committee on Non-prescription Drugs**一般用医薬品部会

The Pharmaceutical Affairs and Food Sanitation Council (PAFSC; 薬事・食品衛生審議会, formerly the Central Pharmaceutical Affairs Council, 2001 Jan)

- as part of a major ministry/agency reorganization.
- It is an advisory organization for the minister of health that reviews applications for new drugs, as well as data submitted for re-examination and re-evaluation, and presents recommendations to the minister.
- The PAFSC comprises the Pharmaceutical Affairs Council (PAC) and Food Sanitation Council (FSC).
- There are a number of committees and subcommittees under the two councils. Committees under the Pharmaceutical Affairs Council include the First and Second Committees on Drugs (医薬品第一部会, 医薬品第二部会) and the Committee on Non-prescription Drugs (一般用医薬品部会).

- **Japan, China, S. Korea Agree to Draft GL on Joint Clinical Trials(Nov.2.2011)**

- Speaking at the 2011 APEC Multi-Regional Clinical Trials TOKYO Workshop on November 1, Naoyuki Yasuda, General Coordination Division, Health Minister's Secretariat, reported that Japanese, Chinese, and South Korean officials have agreed to hold discussions on drafting guidelines for joint clinical trials in the three countries. Chinese representatives proposed the discussions at the Fourth China-Korea-Japan Director-General Meeting held at the Pharmaceuticals and Medical Devices Agency (PMDA) on the previous day.

  At the workshop, Mr Yasuda reported that the three countries will strengthen their cooperative relationship and further develop study projects in each country. China will play a coordinating role in drafting the guidelines for clinical trials, while Japan will be responsible for studying ethnic differences, and South Korea will act as a coordinator in information sharing in the field of clinical trials between the three countries. Mr Yasuda expressed enthusiasm, saying, "We will link study themes in a coordinated way in order to ensure progress in clinical trials in the three countries."

  At the workshop, Mr Yasuda also reported that an interim report on ethnic differences was presented at the previous day's meeting. According to him, research results obtained to date have shown that single protocols that require standardized external factors such as diet and environment are necessary to study ethnic differences, and that data should be evaluated after clarifying subjects' genetic polymorphisms. "Clinical trials conducted by standardizing not only internal but also external factors might show that what was previously reported as ethnic differences is not," he pointed out.

  At the workshop, representatives from South Korea presented a plan to draw up a table that compares differences between regulatory systems in the three countries. Representatives from China proposed setting up a working team for detailed discussions after drafting a guideline concept paper by the end of the year.