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

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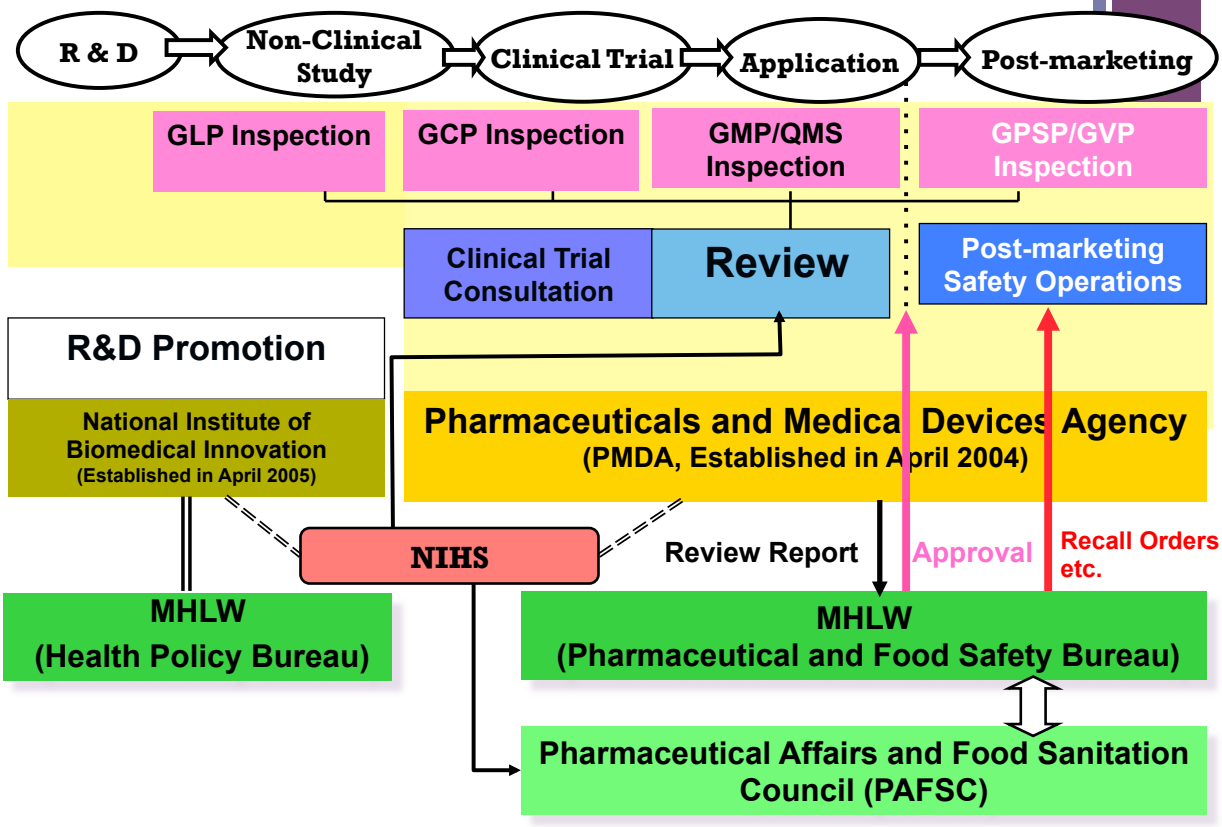
Topics

- 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



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

ex.

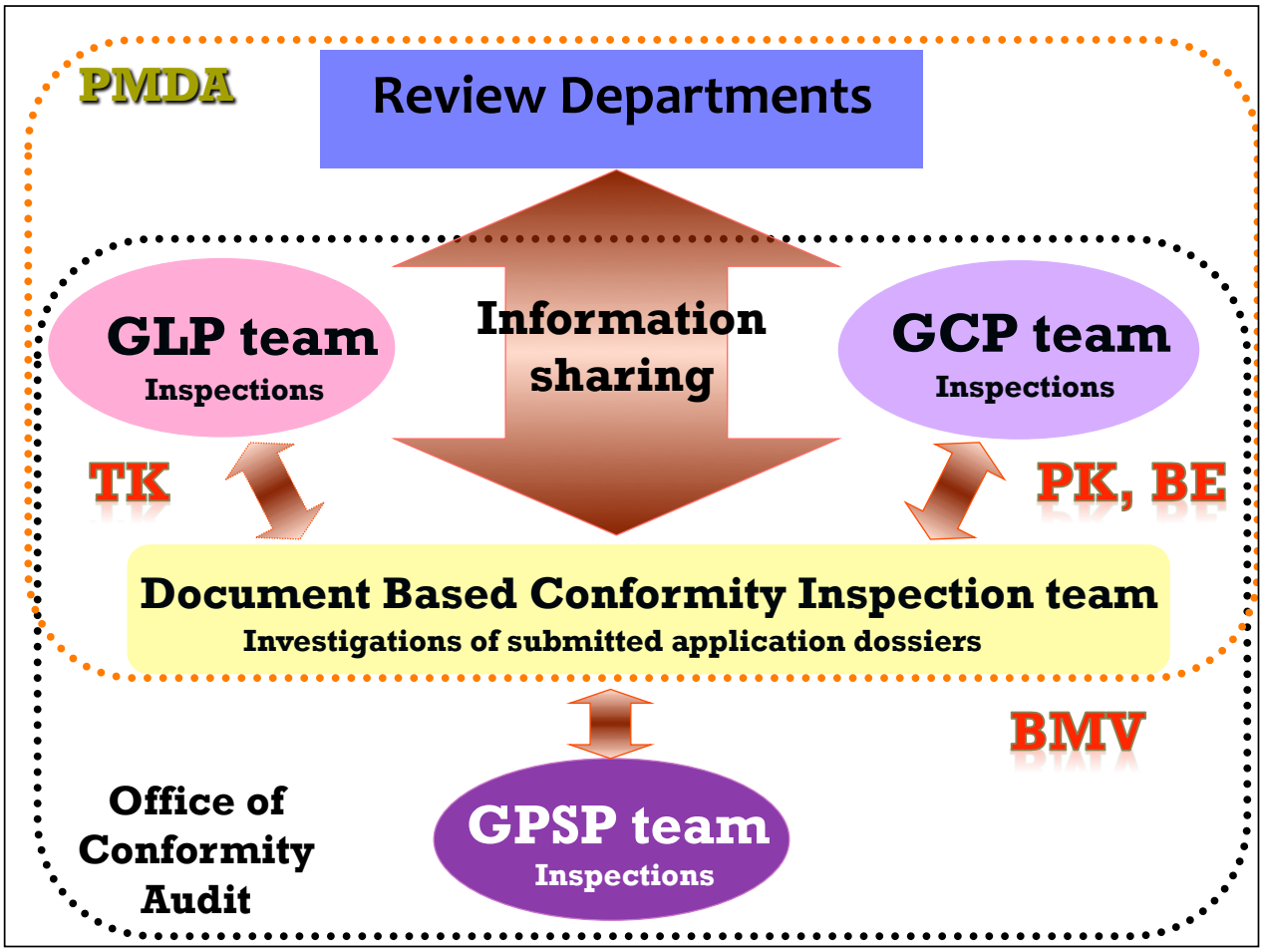
- **Making decision on approval.**
- **Conducting withdrawal and directions of releasing emergent safety information.**
- **Adopting emergent safety measures in significant cases**

[PMDA]

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

ex.

- **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

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Inspection Report

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The GLP Evaluating Committee
(Consisting of External Experts)

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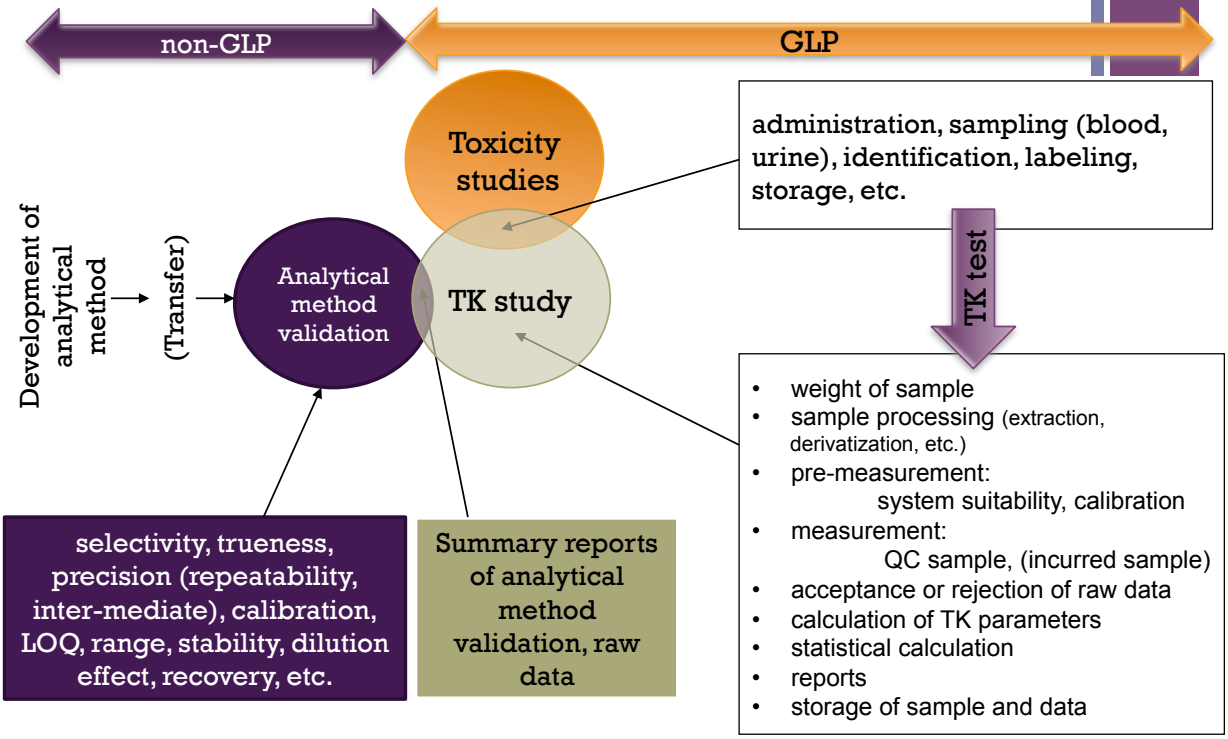
Inspection Result Notification to the Test Facility
(by PMDA Chief Executive)

Toxicokinetic Study in non-clinical tests and GLP



New Drug Application in Japan

The History of GLP and Analytical Method Validation in Japan

The History of Guidelines in Japan (GLP / PK/ TK / BE)

Year	Japan	Other Countries
1989-1992	The Guideline for Toxicology Test (1989) The Guideline for Pharmacokinetic Test (1991)	Shah et al. "Analytical Methods Validation: ..." Pharm. Res. 9, 588-592 (1992)
1996-1998	The Guidance for Toxicokinetics (ICH S3A, 1996)	
	The Guidance for Analytical Validation (ICH Q2A,B, 1997)	OECD principle of GLP (1997, revised)
	Non clinical test practice standard for drug safety (Ordinance of MHW, 21th, 1997) GLP	
	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)	
2001	Clinical Pharmacokinetics of Pharmaceuticals (iyakushin#796, background information for ICH E8)	FDA, Guidance for Industry (Bioanalytical method validation)
2007-2009	Symposium for the AAPS/FDA White Papers (MASS2008, Tsukuba, Japan), Dr. Viswanathan was invited.	AAPS/FDA White Paper (2007 -)
	Non clinical test practice standard for drug safety (Ordinance of MHLW, 114th , revised, 2008) GLP	Draft Guideline on Validation of Bioanalytical Methods. EMEA/CHMP/EWP/192217/2009 (2009)
	General procedure of audit for GLPs of pharmaceuticals and medical devices (Ordinance of PMDA, #0815008, 2008)	WHO GCLP (2009, Japanese version, introduced by JQA)

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

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

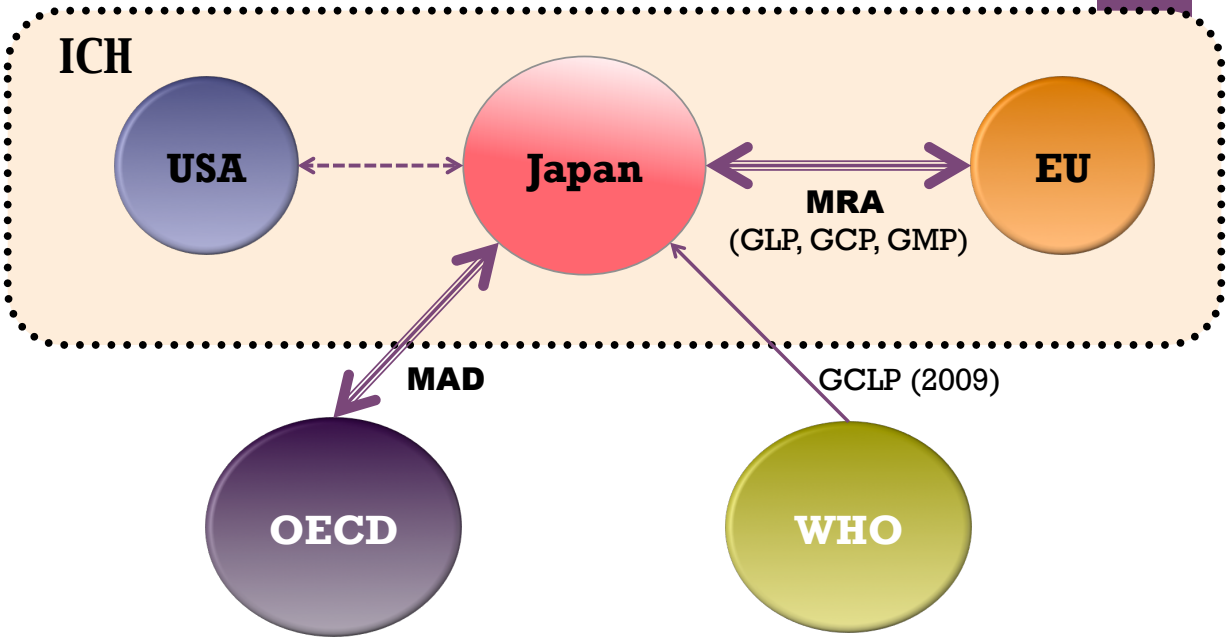
Acceptance criteria for data

- ISO 5725-6 Accuracy (trueness and precision) of measurement methods and results - part 6: Use in practice of accuracy values
- JIS z 8402

New Drug Application in Japan

Relationship between Japan and Other Countries

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)

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

1981 MAD, 1989 Compliance, 1997 Non-Members

MOU with EC, Switzerland and USA*

MOU: Memorandum of Understanding
*Only pesticides program

India, Singapore, China, Russia, Brazil ,Argentina Chinese Taipei, (Provisional) Thailand etc.

Bilateral Cooperation

Japan Bioanalysis Forum (JBF)

Japan Bioanalysis Forum

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.
- Mar. 30, 2011, Kick-off Meeting of JBF (in Osaka).

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

Pharmaceutical
- Hara, Hisanori (Novartis Pharma AG, Switzerland)
- Jinno, Fumihiro (Takeda Pharmaceutical Co., Ltd.)
- Kobayashi, Nobuhiro, (DaiichiSankyo 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?***

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?***

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.***
- ***The effect of counter-ion is deemed minor based on the publication:*** *Bergeron M, Bergeron A, Furtado M and Garofolo F. Impact of plasma and whole-blood anticoagulant counter ion choice on drug stability and matrix effects during bioanalysis. Bioanalysis (2009) 1(3) 537-548*.

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?***

- ***<u>Re-injection</u> is done in case of instrument malfunction if re-injection could be performed within acceptable stability period.***
- ***<u>Re-analysis</u> is for failed batches, anomalous values and PK repeats.***
- ***<u>Non-reportable values</u> 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 QCs 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 !