

State of GLP in Japan and Statistical Considerations in the Bioanalytical Guidance

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Topics

- 1. The actual status of GLP in Japan.**
- 2. The history of GLP and Analytical Method Validation in Japan.**
- 3. Relationship between Japan and Other Countries.**
- 4. Statistical considerations for Bioanalytical Guidance.**



The actual status of GLP in Japan



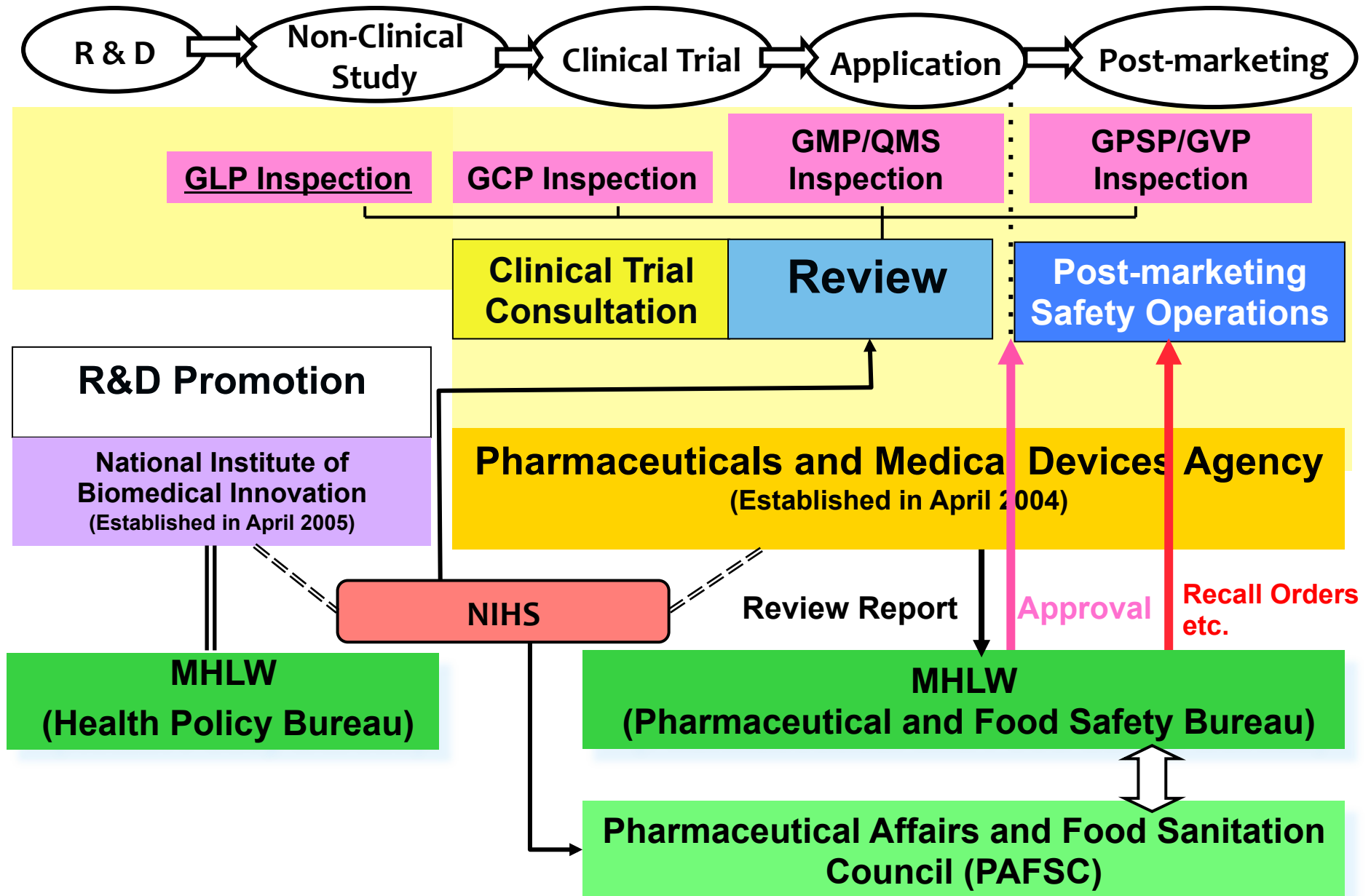
The Pharmaceutical Affairs Law (Law No. 145)

Article 43 of Enforcement Regulations of the Pharmaceutical Affairs Law

“The data pursuant to the provisions of the last part of Article 14, Paragraph 3 of the Law shall be collected and complied as specified in the **MHW Ordinance on Implementation Standards for Non-Clinical Studies on Safety of Drugs (MHW Ordinance No.21, 1997)** , , **MHLW Ordinance on Implementation Standards for Non-Clinical Studies on Safety of Medical Devices (MHLW Ordinance No.36, 2005)**”

* MHW became MHLW in 2001.

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**



PMDA

Review Departments

GLP team
Inspections

Information sharing

GCP team
Inspections

TK

PK, BE

Document Based Conformity Inspection team
Investigations of submitted application dossiers

**Office of
Conformity
Audit**

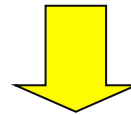
GPSP team
Inspections

BMV

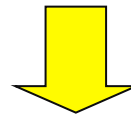
Reporting GLP Inspection Results (PMDA)

Inspectors' Findings

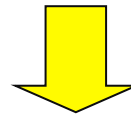
Agreed by both the inspection team and the test facility
at the closing meeting



Inspection Report



The GLP Evaluating Committee (Consisting of External Experts)



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

Areas of Expertise (GLP)

For Pharmaceuticals

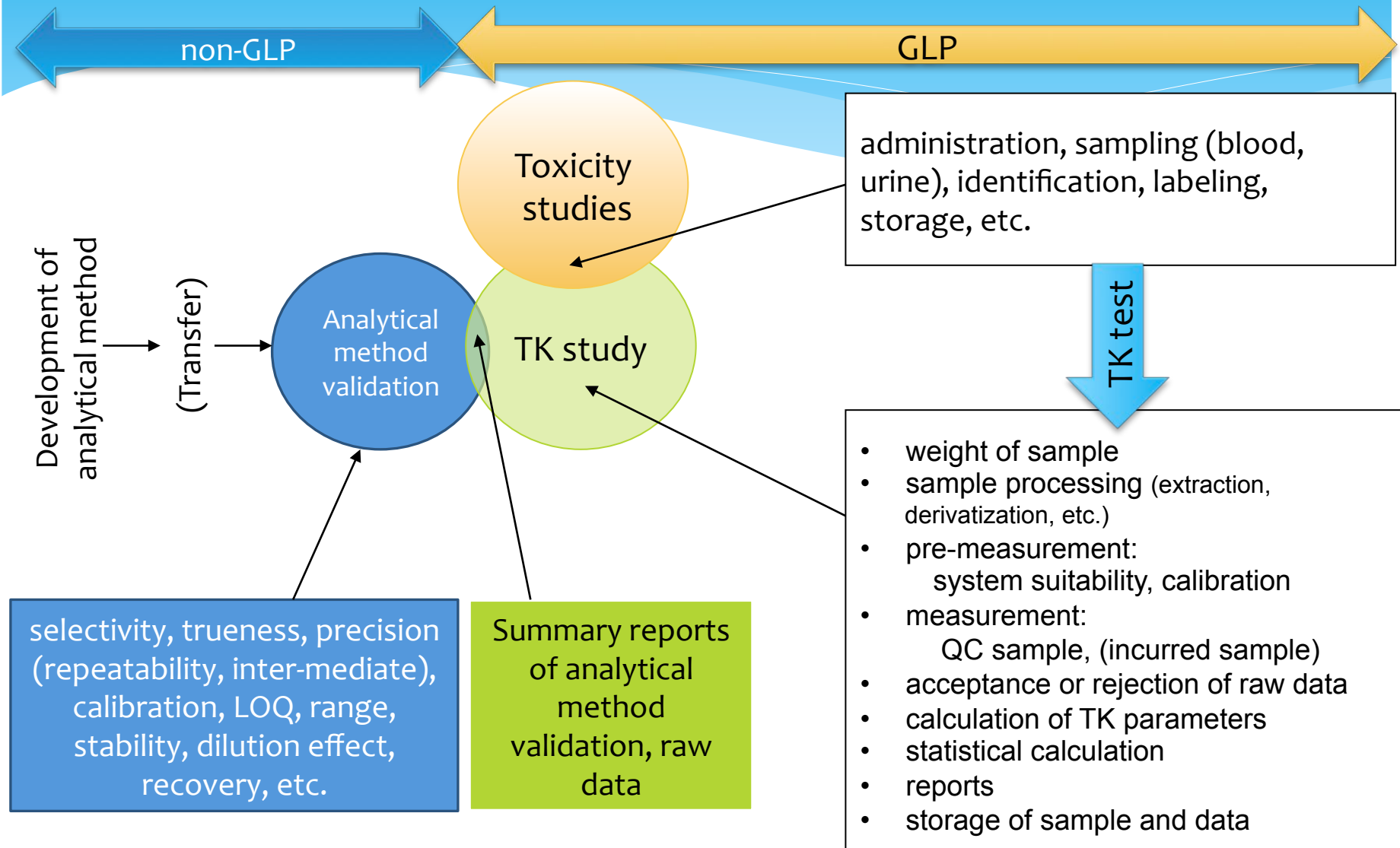
- Single Dose toxicity study
- Repeated Dose toxicity study
- Reproduction toxicity study
- Carcinogenicity study
- Genotoxicity study
- Local tolerance study
- Immunotoxicity study
- Sensitization study
- Antigenicity study
- Dependence study
- Safety Pharmacology
- Toxicokinetics

Medical Devices specific

- Cytotoxicity study
- Implanted toxicity study
- Blood compatibility study
- Pyrogenicity study
- Biodegradability study



Toxicokinetic Study in non-clinical tests and GLP



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)	OECD principle of GLP (1997, revised)
	The Guidance for Analytical Validation (ICH Q2A,B, 1997)	
	Non clinical test practice standard for drug safety (Ordinance of MHW, 21 th , 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, 114 th , 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)

ICH Guideline topics and the progress

Step	Quality			Safety			Efficacy			Multidisciplinary		
	Code	Priority number	Discussion Title	Code	Priority number	Discussion Title	Code	Priority number	Discussion Title	Code	Priority number	Discussion Title
Step 5	Q1A(R2)	Q1A	Stability Testing of New Drug Substances and Products	Q1B		Test for Chromatographic Similarity of Pharmaceuticals	Q1		The Impact of Population Exposure to Suboptimal Quality of Drugs Submitted for Long-Term Treatment of Non-Life-Threatening Conditions	NE (2004/004)		Medical Devices for Regulatory Activities
	Q1B		Stability Testing - Reliability Testing of New Drug Substances and Products	Q1C		Testing for Chromatographic Similarity of Pharmaceuticals	Q1A		Pharmacovigilance Data Management: Definition and Standards for Expedited Reporting	ME-QA(19)		Electronic Standards for the Transfer of Regulatory Information
	Q1C		Stability Testing for New Drugs Form	Q1C(R2)	Q1C-R2	Drug Selection for Chromatographic Similarity of Pharmaceuticals	Q1C(R2)	Q1C(R2)	Multicenter or Multiple Site Clinical Trials: Management Including Data Elements for Transmission of Individual Case Safety Reports	ME-QC(19)		Electronic Common Technical Document (eCTD)
	Q1D		Stability and Marketing Integrities for Stability Testing of New Drug Substances and Products	Q1D		Guidance on Specific Aspects of Regulatory Chemistry Test for Pharmaceuticals	Q1D(R2)	Q1D-R2	Clinical Safety Data Management: Standard Safety Update Report for Marketed Drugs	ME(R2)	ME(R2)	Guidance on Statistical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals
	Q1E		Evaluation of Stability Data	Q1E		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1E		Pharmacovigilance Data Management: Definition and Standards for Expedited Reporting	ME(R2)		The Common Technical Document
	Q1E(R1)	Q1E, Q1E	Evaluation of Stability Procedures for New Drug Substances	Q1E		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1E		Pharmacovigilance Planning	ME(R2)		
	Q1A(R2)		Impurities in New Drug Substances	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1		Structure and Content of Clinical Study Reports			
	Q1B(R2)		Impurities in New Drug Products	Q1	Q1, 31A, 31A	Evaluation of Chemical Safety Testing in Animal, Human and Non-Human Primate Studies	Q1		New Regions Submitted to Support Drug Registration			
	Q1C(R2)	Q1C, Q1C	Impurities: Guidance for Biotech Products	Q1C(R2)	Q1C, 31B	Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1C(R2)		Other Factors in the Acceptability of Foreign Clinical Trials			
	Q1D		Evaluation and Reconciliation of Pharmaceutical Tests for Use in the ICH Region	Q1		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1 (Q1A-Q1E)		Guidance on Approval: Safety Factors in the Acceptability of Foreign Clinical Trials			
	Q1D Annex 1(B)		Guidance on Impurities/Residual Solvent/General Chapter	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D(R2)	Q1	Good Clinical Practice			
	Q1D Annex 2(B)		Guidance on Impurities/Residual Solvent/General Chapter	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance to Support of Special Populations: Overview			
	Q1D Annex 3(B)		Guidance on Impurities/Residual Solvent/General Chapter	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		General Considerations for Clinical Trials			
	Q1D Annex 4(B)		Guidance on Impurities/Residual Solvent/General Chapter	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Statistical Principles for Clinical Trials			
	Q1D Annex 5(B)		Guidance on Impurities/Residual Solvent/General Chapter	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Phases of Clinical Trials and Related Issues in ICH Region			
	Q1D Annex 6(B)		Guidance on Impurities/Residual Solvent/General Chapter	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Other Considerations of Multiple Products in the Same Region			
	Q1A(R2)	Q1A	Stability Evaluation of Biotechnology Products: General Aspects of Tests of Human or Animal Origin	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D	Q1D	Guidance for Clinical Evaluation of New Anticancerous Drugs			
	Q1B		Guidance on the Impurities Content in Cells Used for Production of a DNA Derived Protein Product	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		The Clinical Evaluation of Anticancerous Drugs: Pharmacovigilance and Post-marketing Potential for New Anticancerous Drugs			
	Q1C		Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs			
	Q1D		Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs			
Q1E		Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs				
Q1A		Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs				
Q1B		Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs				
Q1C	Q1A	Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs				
Q1D		Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs				
Q1E		Stability Testing of Biotechnology of Biological Products	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals	Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs				
Step 4	Q1D Annex 7(B)		Guidance on Impurities/Residual Solvent/General Chapter				Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs			
	Q1D Annex 8(B)		Guidance on Impurities/Residual Solvent/General Chapter				Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs			
	Q1D Annex 9(B)		Guidance on Impurities/Residual Solvent/General Chapter				Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs			
	Q1D Annex 10(B)		Guidance on Impurities/Residual Solvent/General Chapter				Q1D		Guidance on Clinical Evaluation of New Anticancerous Drugs			
Step 3	Q1C(R2)		Impurities: Guidance for Biotech Products	Q1C(R2)		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals			Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports			
	Q1D Annex 6(B)		Guidance on Impurities/Residual Solvent/General Chapter	Q1D		Guidance on Chemical Safety for Toxicology Testing for Pharmaceuticals				ME		Guidance on Standards and Standards for Drug Evaluation
	Q1D Annex 10		Guidance on Impurities/Residual Solvent/General Chapter									
Step 2	Q1D Annex 10		Guidance on Impurities/Residual Solvent/General Chapter									
	Q1D		Development and Manufacture of Drug Substances	Q1D		Pharmaceutical Evaluation of Pharmaceuticals						
Step 1	Q1D		Impurities: Guidance for Biotech Products							ME		Guidance on Standards and Standards for Drug Evaluation
	Q1D		Impurities: Guidance for Biotech Products							ME		Guidance on Standards and Standards for Drug Evaluation

ICH guideline topic and the progress (Safety)

Safety

Status	Code	Previously coded	Document Title
Step 5	S1A		Need for Carcinogenicity Studies of Pharmaceuticals
	S1B		Testing for Carcinogenicity of Pharmaceuticals
	S1C(R2)	S1C, S1C(R)	Dose Selection for Carcinogenicity Studies of Pharmaceuticals
	S2A		Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals
	S2B		Genotoxicity: A Standard Battery for Genotoxicity Testing for Pharmaceuticals
	S3A		Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
	S3B		Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
	S4	S4, S4A	Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)
	S5(R2)	S5A, S5B	Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility
	S6		Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
	S7A		Safety Pharmacology Studies for Human Pharmaceuticals
	S7B		The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
	S8		Immunotoxicity Studies for Human Pharmaceuticals
S9		Nonclinical Evaluation for Anticancer Pharmaceuticals	
Step 4			
Step 3	S2(R1)		Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
	S6(R1)		Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
Step 2			
Step 1	S10		Photosafety Evaluation of Pharmaceuticals

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

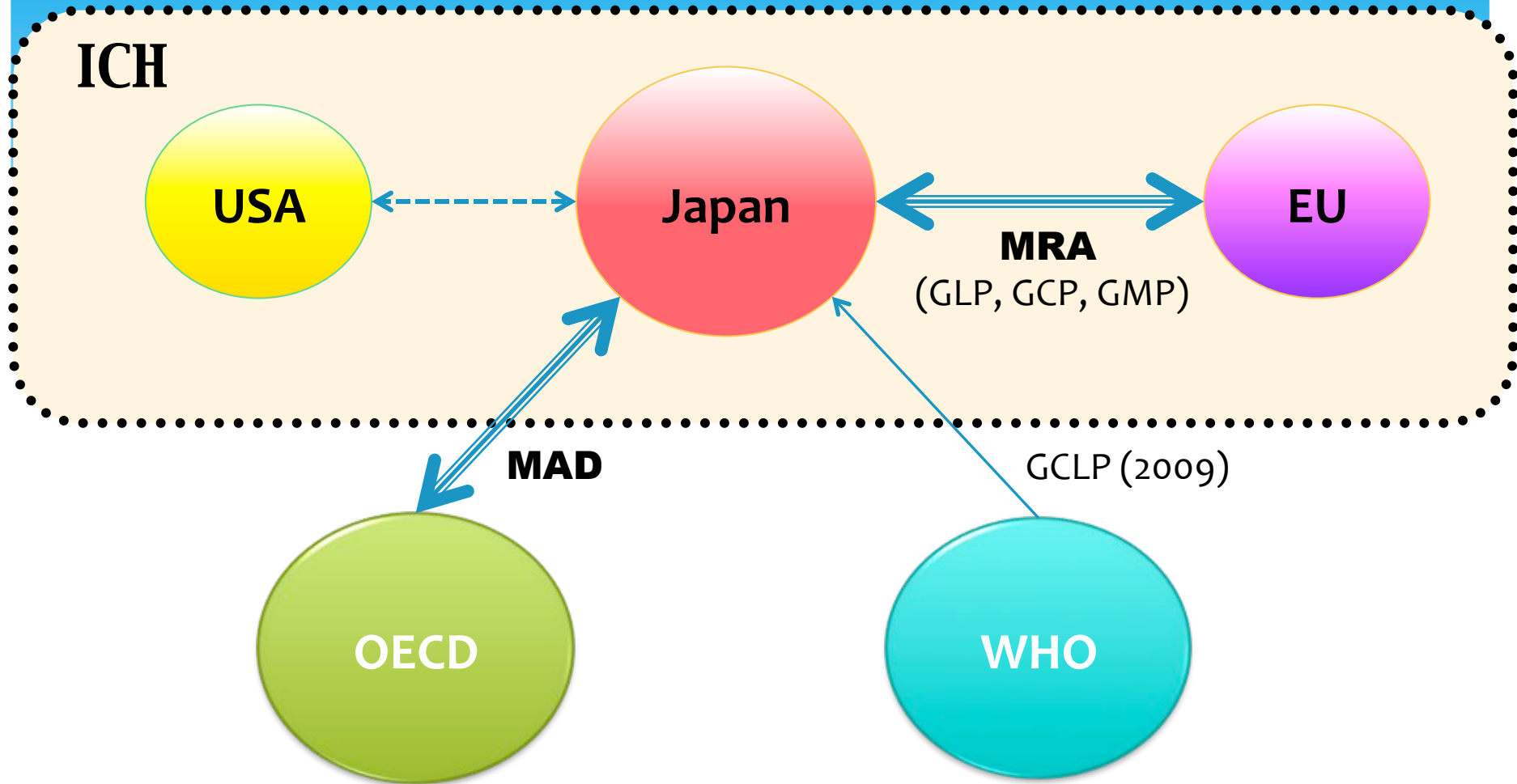
- * ISO 5725-6 Accuracy (trueness and precision) of measurement methods and results - part 6: Use in practice of accuracy values
- * JIS z 8402



Relationship between Japan and Other Countries



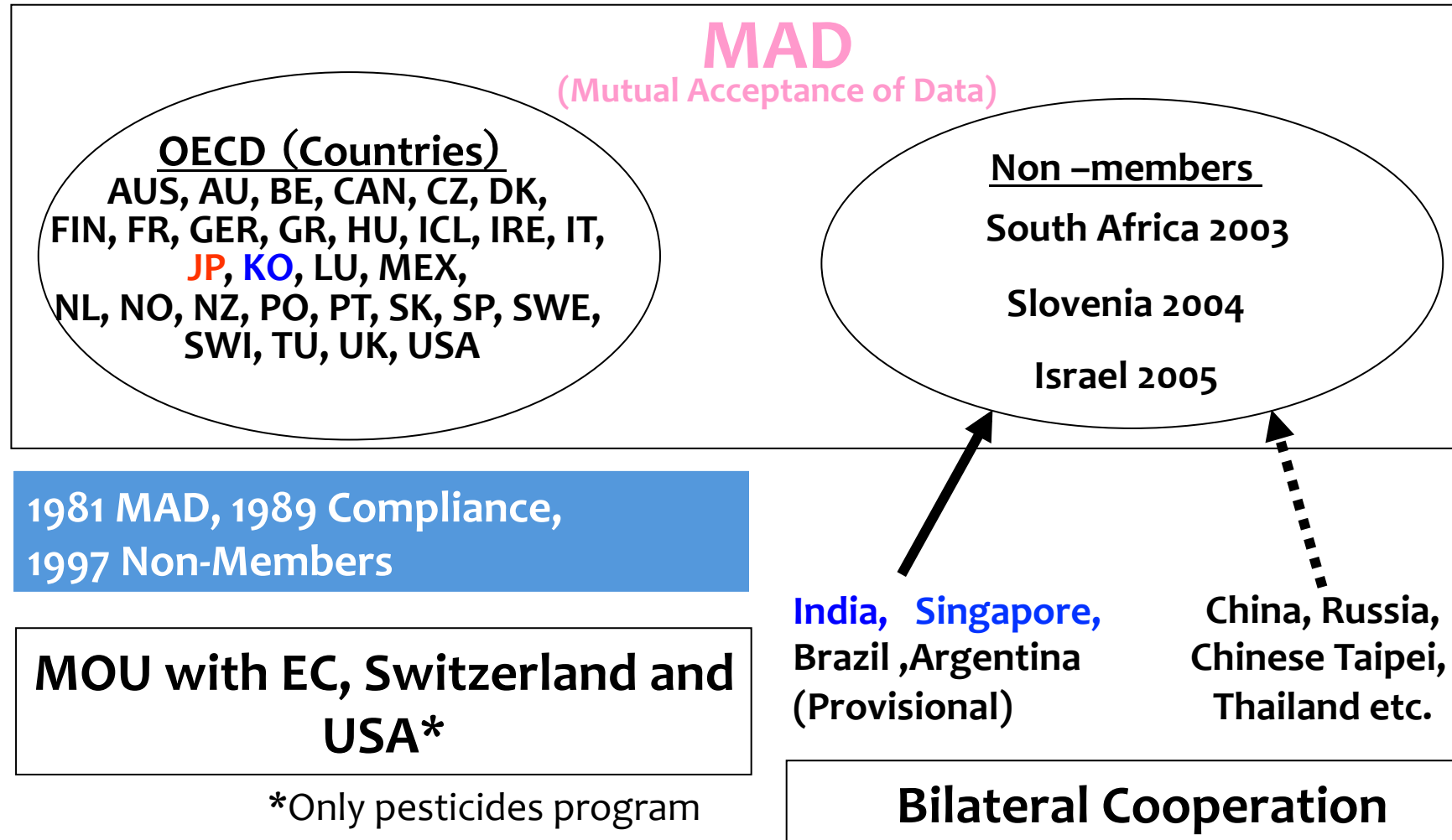
Relationship between Japan and Other Countries 1



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



Relationship between Japan and Other Countries 2



MOU: Memorandum of Understanding

Statistical Considerations for Bioanalytical Guidance



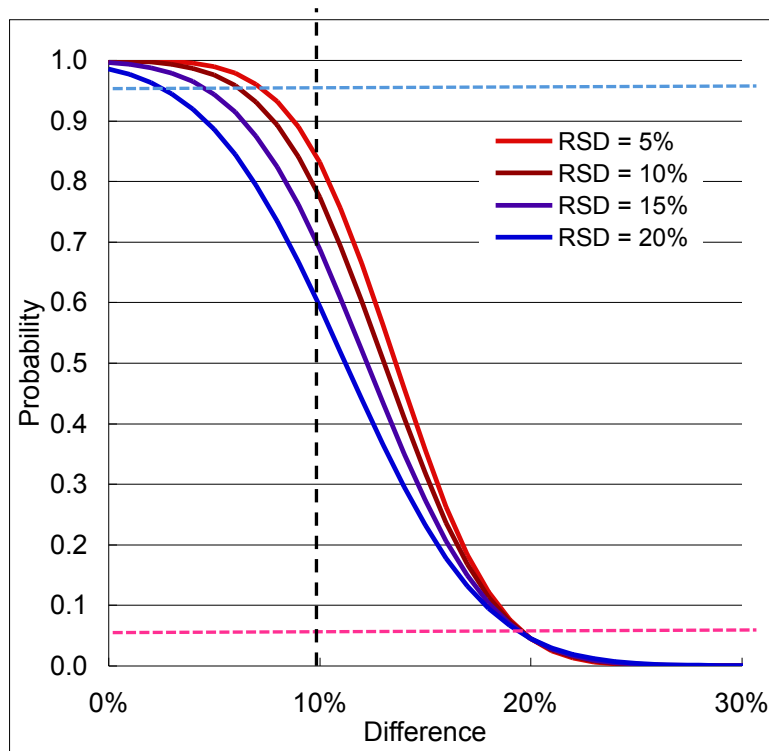
Statistical consideration for bioanalytical guidance

- * Required precision for TK and BE tests.
- * Error showing non-normal distribution and proper risk estimation.
- * Origin of errors.
- * Handling of sudden and unidentified errors.
- * Bias should be corrected ?

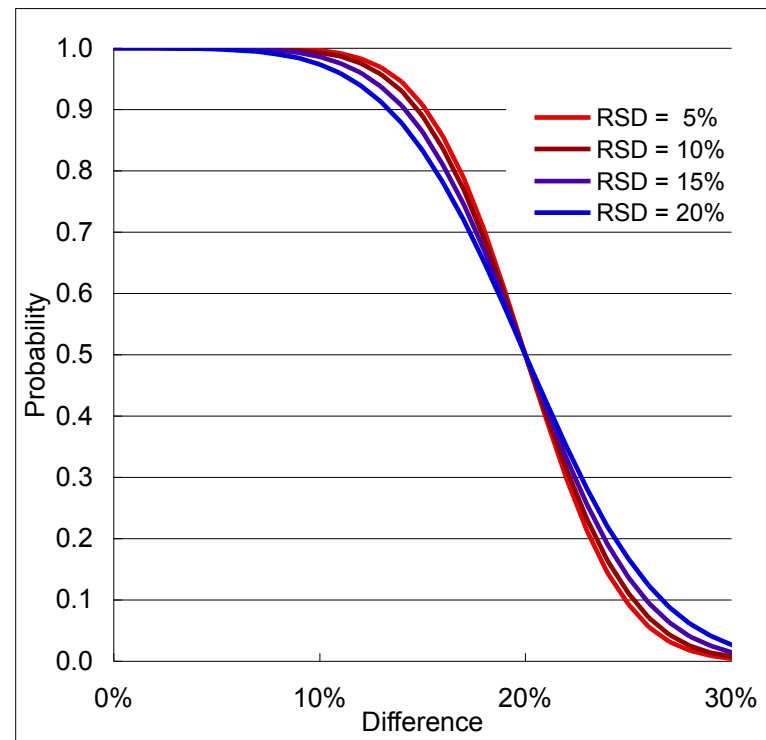


Effect of Analytical Precision on BE Test

A. Confidence Interval $\leq 20\%$ (BE test)



B. Difference $\leq 20\%$ (point estimate)



----- consumer's risk
----- producer's risk

Condition for simulation

- Parameter distributes normally
- Number of subjects = 30
- Inter-individual variation = 20%

謝謝

Thank you

