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

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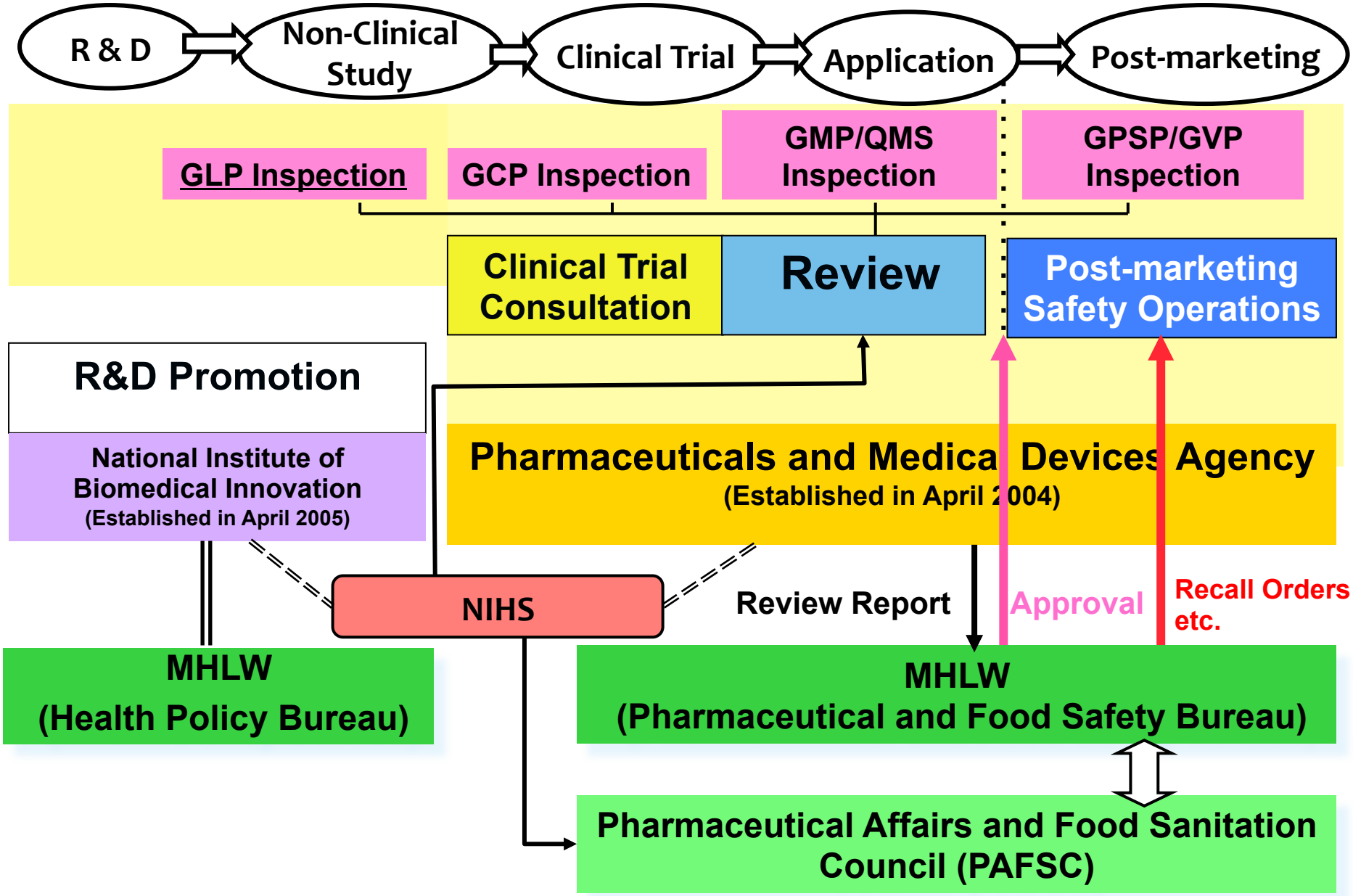
The Pharmaceutical Affairs Law
(Law No. 145)

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

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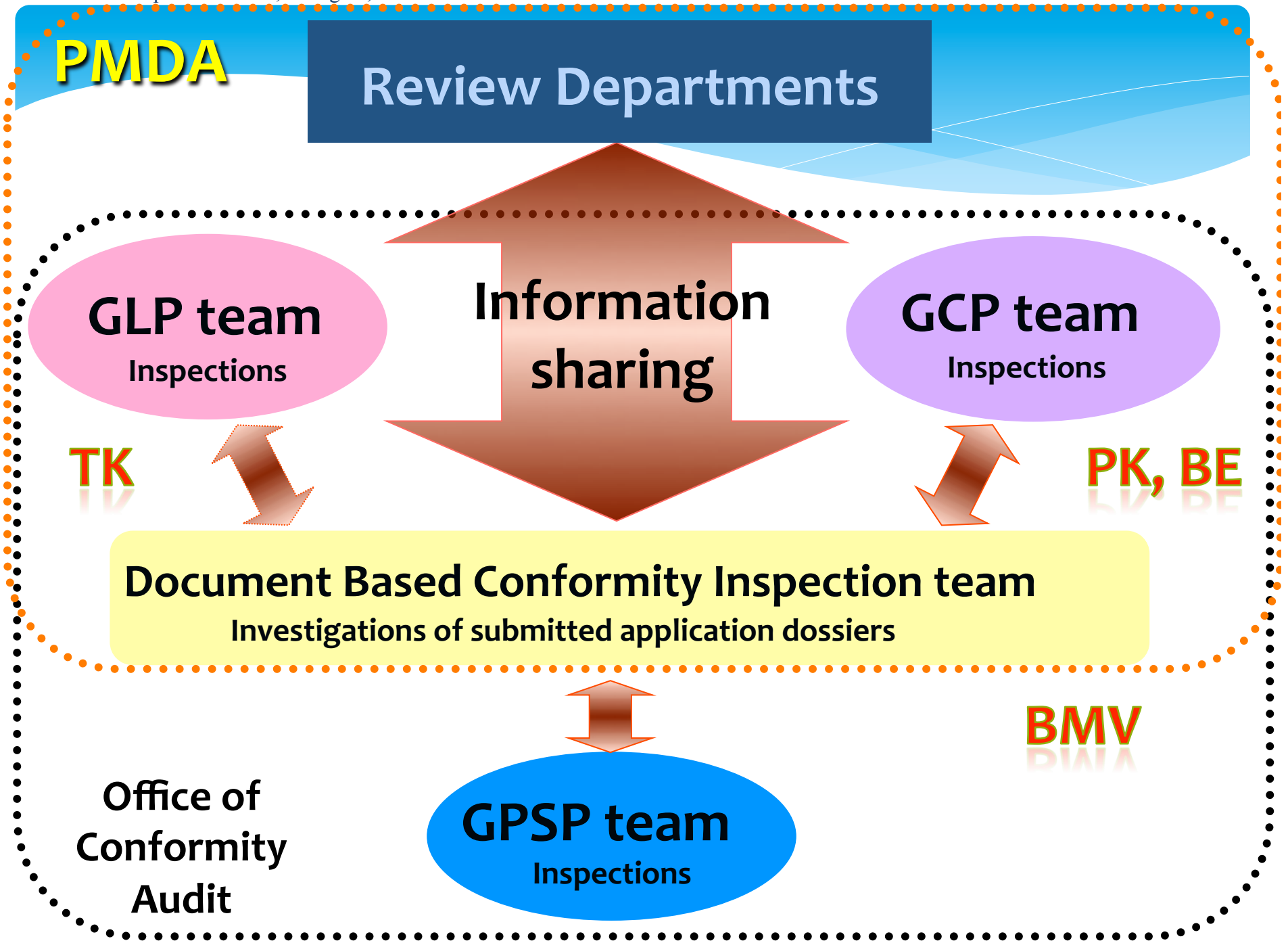
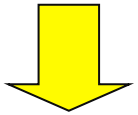

PMDA
Review Departments
GLP team
Inspections
Information sharing
GCP team
Inspections
TK
PK, BE
Document Based Conformity Inspection team
Investigations of submitted application dossiers
BMV
Office of Conformity Audit
GPSP team
Inspections

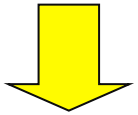
Reporting GLP Inspection Results (PMDA)

Inspectors' Findings

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

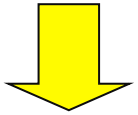


Inspection Report



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

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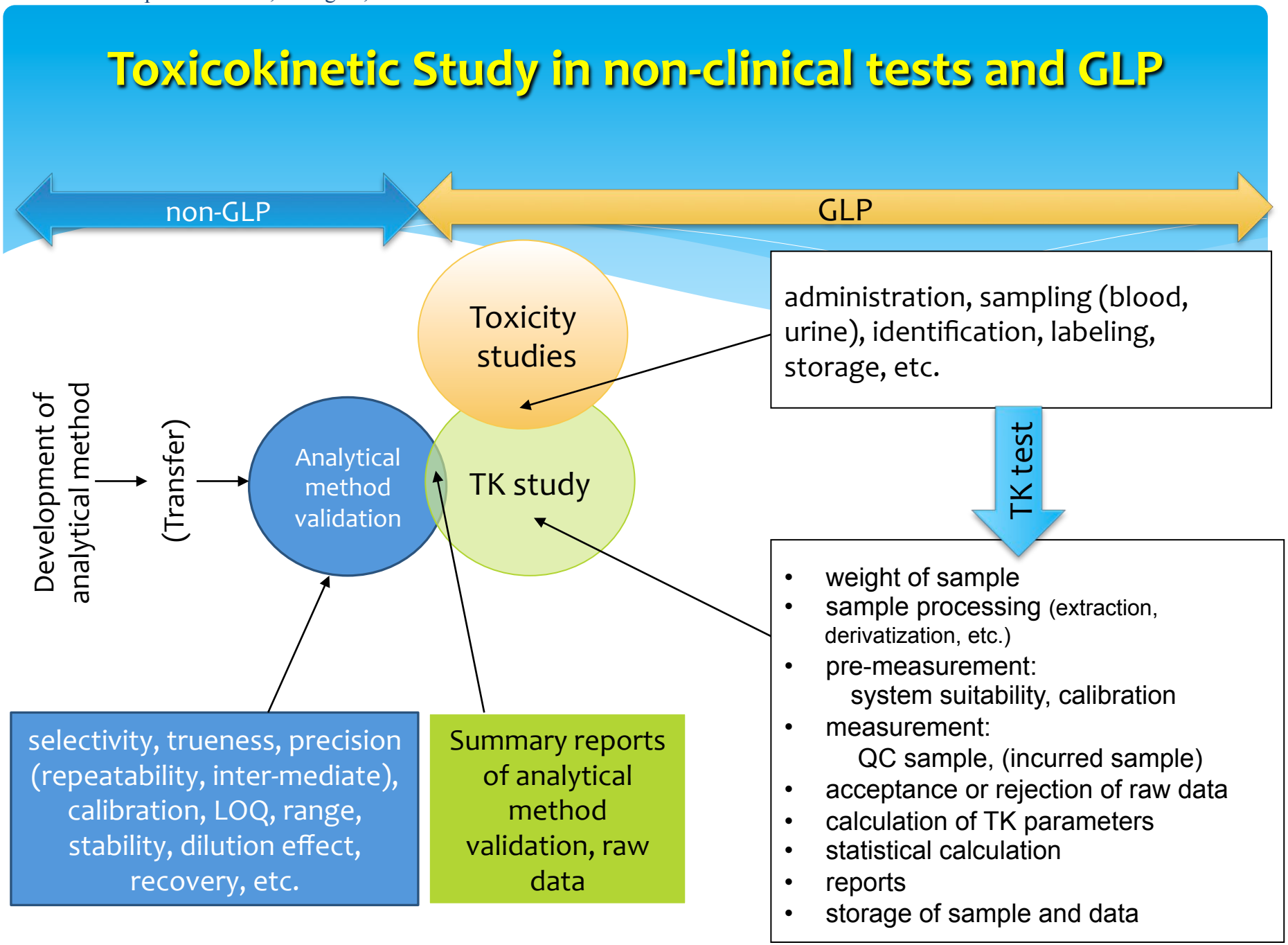
Toxicokinetic Study in non-clinical tests and GLP



The History of GLP and Analytical Method Validation in Japan.

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

Yeare	Japan	Other Countries
1989-1992	The Guideline for ToxicologyTest (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)

ICH Guideline topics and the progress

Status	Quality			Safety			Efficacy			Multidisciplinary		
	Code	[illegible]	Document Title	Code	[illegible]	Document Title	Code	[illegible]	Document Title	Code	[illegible]	Document Title
Step 5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Step 4	[illegible]		[illegible]				[illegible]		[illegible]			
Step 3	[illegible]		[illegible]	[illegible]		[illegible]			[illegible]	[illegible]		[illegible]
Step 2												
Step 1	[illegible]		[illegible]	[illegible]		[illegible]				[illegible]		[illegible]

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

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Relationship between Japan and Other Countries

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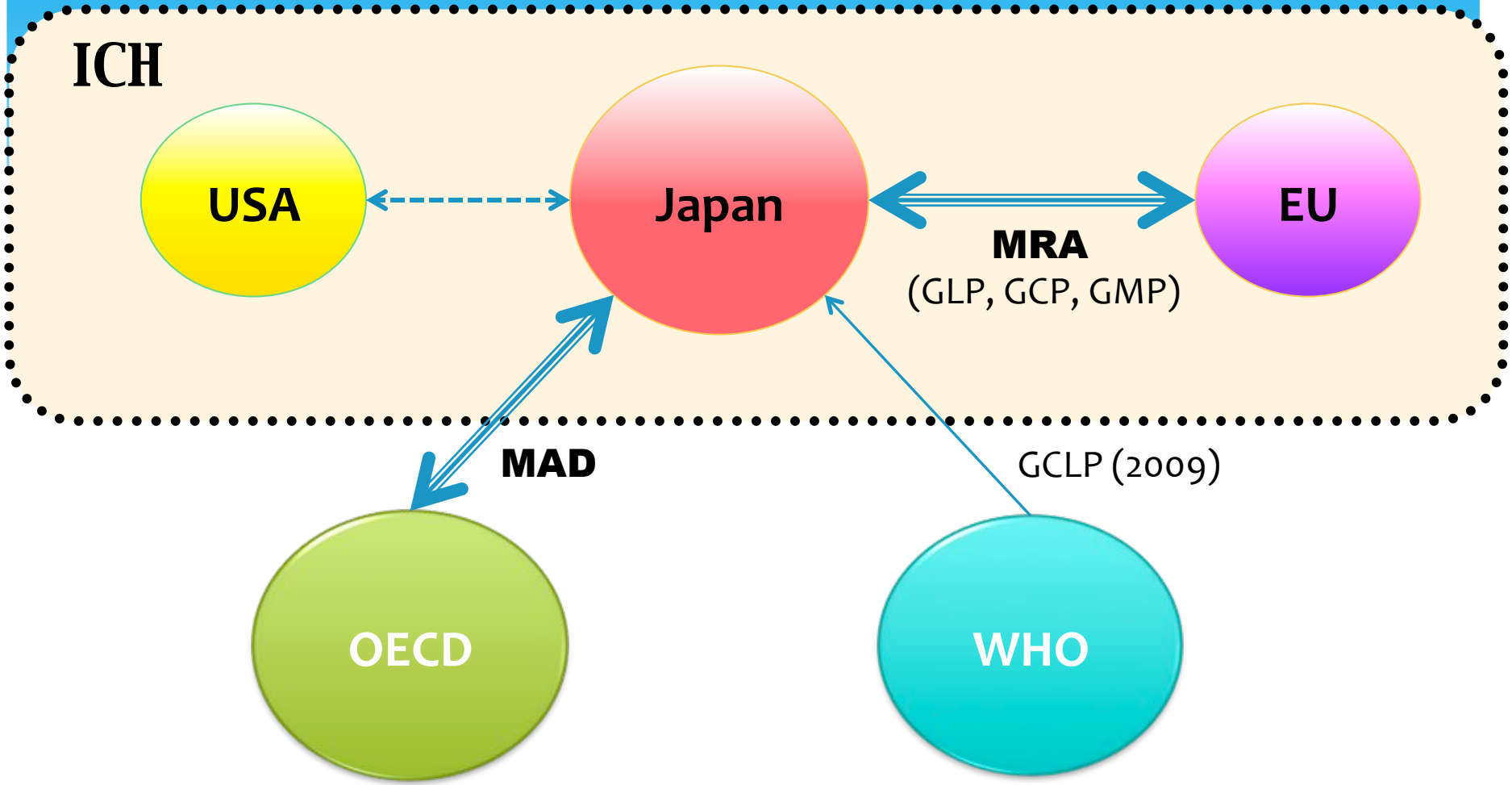
Relationship between Japan and Other Countries 1



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

Relationship between Japan and Other Countries 2

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*

*Only pesticides program

India, Singapore,
Brazil ,Argentina
(Provisional)

China, Russia,
Chinese Taipei,
Thailand etc.

Bilateral Cooperation

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 sadden and unidentified errors.
* Bias should be corrected ?

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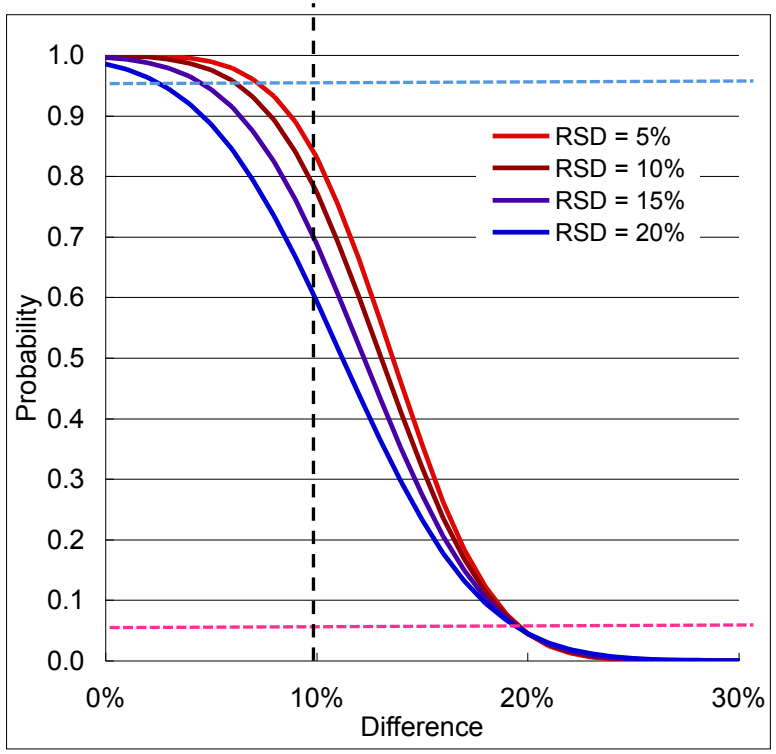
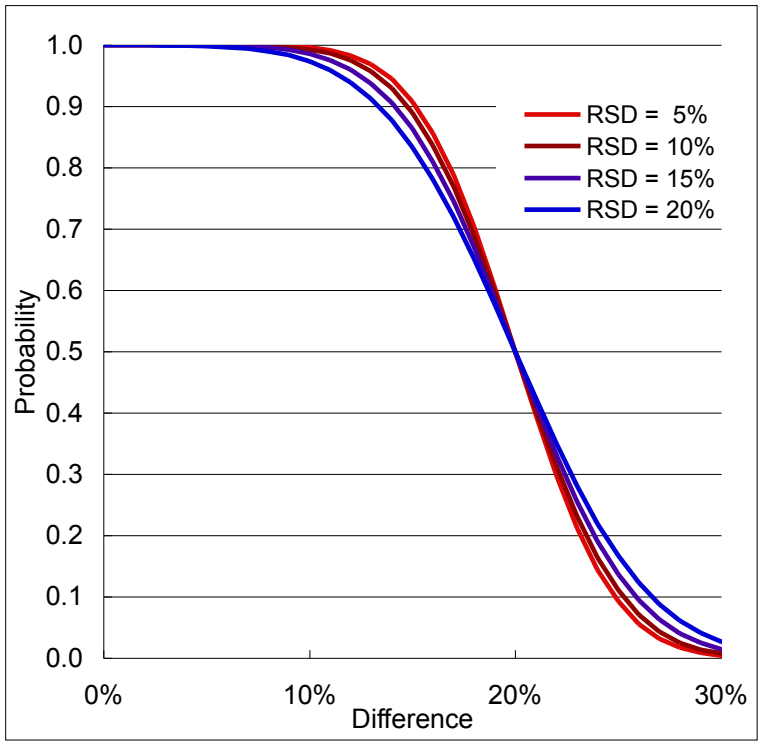
Effect of Analytical Precision on BE Test

A. Confidence Interval ≤ 20% (BE test)



B. Difference ≤ 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

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