Symposium on Traceability in Laboratory Medicine

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IVD Regulations in Japan

- Innovation Towards Global Harmonization -

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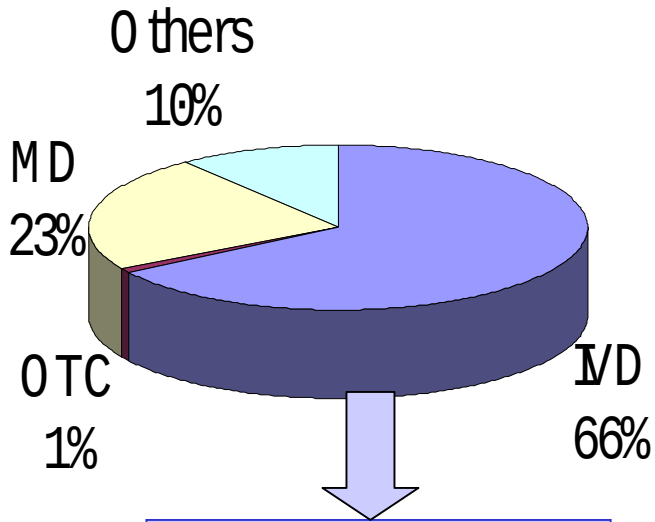
Background of the speaker(TK)

- Japanese Ministry of Health, Labour and Welfare
  - Vice-chair, In Vitro Diagnostic Devices Section, Pharmaceuticals and Foods Affairs Council
  - Chair, IVD Standardization Study Group(1996~2002)
- International Organization for Standardization
  - Chair, ISO/TC212, National Committee, Japan
- NCCLS
  - Member, Board of Directors
- Professor Emeritus, Laboratory Medicine, Jichi Medical School; FASCP(Hon.), MDGLM(Hon.)

IVD-MD Market in Japan, 2002

- Total Medical Cost 8% of GDP
- Total IVD-MD Sold 3.5% of Pharceuticals ca. 30 billions US$
  - Domestic Products 64%
  - Imported Products 36%



Immunology 39%
Chemistry 32%
Microbiology 8%
Hematology 7%
Urine, etc. 7%

IVD-MD Regulatory Agency in Japan

- Ministry of Health, Labour and Welfare (MHLW)
  - Pharmaceutical and Food Safety Bureau,
    Evaluation and Licensing Division
    - Measures for securing the efficacy and safety of drugs/quasi-drugs, cosmetics and medical devices
- National Institute of Health Sciences (NIHS)
  - 12 Research Divisions
  - Biological Safety Research Center
  - Pharmaceuticals and Medical Devices Evaluation Center

Pharmaceuticals and Medical Devices Evaluation Center (PMDEC)

- Established on July 1st, 1997 to strengthen the government's evaluation capacity
- Evaluation of quality, efficacy and safety of each In vitro diagnostics and medical devices,

Evaluation Division IV

- Director & Evaluation Manager
- Evaluation Teams
- External experts, visiting or advisory

Why PMDEC has been established

- Social backgrounds
  - HIV infections through blood products
  - International Conferences on Pharmaceutical Regulations Harmonization Issues among Japan-USA-EU
- 1994~5 : MHLW Committee to discuss measures to assure safety of pharmaceuticals
- 1996: Amendment of the Pharmaceuticals Law
  - Pharmaceuticals Bureau → P & Medical Safety Bureau
  - Evaluation: Ministry → PMD Evaluation Center

In Vitro Diagnostics Premarket Approval Process applied for both medical and public uses

- Premarket application(PMA)
  - accepted to the Minister for MHLW, Pharmaceutical and Food Safety Bureau, Evaluation and Licensing Division
- Evaluation of each in vitro diagnostic device at the Evaluation Center
  - New devices with a new clinical utility or measuring principle: a full evaluation process by the evaluation team including a group of experts in its specific field, ca. 600/ year
  - Devices similar to the other legally marketed: evaluation for equivalent performance to the other legally marketed , ca. 400/year

Factors Influencing to Modernization and Global Harmonization in IVD Regulations

- GHTF (Global Harmonization Task Forces in Medical Devices)
- ISO/TC212, Clinical laboratory testing and in vitro diagnostic test systems, 1996~
- MHLW Research Group on Development of Performance Standards for IVD Evaluation (1994~6)
- MHLW Study Group on In Vitro Diagnostics Standardization (1996~2001)

MHLW Research Group on Development of Performance Standards for IVD Evaluation

(1994~6, chaired by A Tanaka)

- Selected 37 analytes with reliable reference materials or reference methods available
- Questionnaire study among representative clinical laboratories in Japan, as to current state-of-art analytical performance, inter-laboratory variability, reference intervals
- Recommended the target analytical performance on 37 analytes

MHLW Study Group on IVD Standardization

(1996~2001, chaired by T Kawai)

- 1996 - Studies on comparison between national and international IVD regulations and standardization
- 1997 - Studies on national and international measures of assuring analytical performance and of certifying IVDs
- 1998-1999 - Studies on requirements for de-regulating IVD approval process

MHLW Study Group on IVD Standardization

(1996~2001, chaired by T Kawai)

- 2000
  - Studies on measures of introducing and improving the quality system and GMP in IVD manufacturers
  - Studies on measures of postmarket monitoring and regulations
- 2001
  - Studies on developing and providing IVD reference materials and calibrators in Japan and US-EU

Steps Towards Global Harmonization in IVD Regulations

- 1997.8.28. P &F Safety Bureau Report ,

  simplifying the approval process on 31 analytes, provided that the IVD's analytical performance be assured by the corresponding reputable certified reference materials. ⟹ Next slide

- 2002 Amendment of the Pharmaceuticals Law
  - Discussed in the Diet, currently, and expected to be approved by the end of the current Diet session
  - Implemented stepwise within 3 years

31 Blood Analytes, applicable

AST, ALT, GGT, LD, ALP, CK; TP, CRP, ALB, IgG, IgA, IgM; TC, TG, HDL-C; Na, K, Cl, Ca, Fe, Mg; UN, UA, Cr; TB, Glu, HbA1c; IRI, E2, CS, GH

Reputable Certified Reference Materials, available from;

JCCLS(Japanese Committee for Clinical Laboratory Standards)
HECTEF(Healthcare Technology Foundation), Japan
JDS(Japanese Diabetes Society),
NIHS(National Institute of Health Sciences), Japan
NIID(National Institute of Infectious Diseases), Japan
IRMM(Institute of Reference Materials and Measurements),EU
NIST(National Institute of Standards and Technology), USA, etc.

Amendment of the Pharmaceuticals Law 2002

Regulation on In Vitro Diagnostics

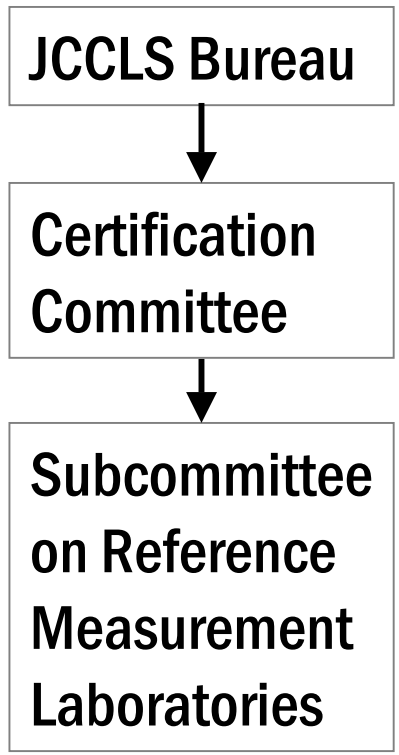
- Implementation of GMP based on Quality System, required in IVD manufacturers
- IVD for Medical Use, Classified by "risk"
  - High risk group: Approval by the Minister
  - Group with reputable reference materials: No approval needed
  - Other groups: Certification by the Third-Party Certifying Bodies
- IVD for Public Use
  - Certification by the Third-Party Certifying Bodies

Amendment of the Pharmaceuticals Law 2002
Postmarket Regulation

- Subject to:
  - Manufacturing processes (quality system requirement) to ensure that manufacturers consistently make well-designed devices, according to appropriate specifications
  - Reporting requirements for adverse outcomes related to device failures to identify problems
- "High risk" IVDs: HIV, HBV, HCV, blood typing, gene testing, etc.
  - To be evaluated by National Institutions, if necessary
- Monitoring analytical performance through nationwide EQAS/PT

JCCLS Japanese Committee for Clinical Laboratory Standards

- Established in 1985, represented by professional, industrial and governmental constituencies
- JCCLS Certification Committee, started in April, 1997
- Certified RMs, provided
  - Ion electrodes RM
  - IRMM/JCCLS CRM470
  - JCERM (6 enzymes, assigned by JSCC recommended methods)



HECTEF/Standard Reference Center

Healthcare Technology Foundation

- Founded in 1994, and started in developing and supplying some reference materials in laboratory medicine in 1995
- Reference materials available from HECTEF:
  - SRS for ion electrodes (Na, K, Cl, Glucose)
  - SRS for electrolytes (Na, K, Cl, tCa, tMg, Ca ion)
  - SRS for iron (Fe)
  - SRS for lipids (TC, TG, HDL-C)
  - SRS for nitrogenous (UN, UA, Cr; Glu)
  - SRS for blood gases (pH, pCO_2, pO_2)
  - SRS for HbA1c

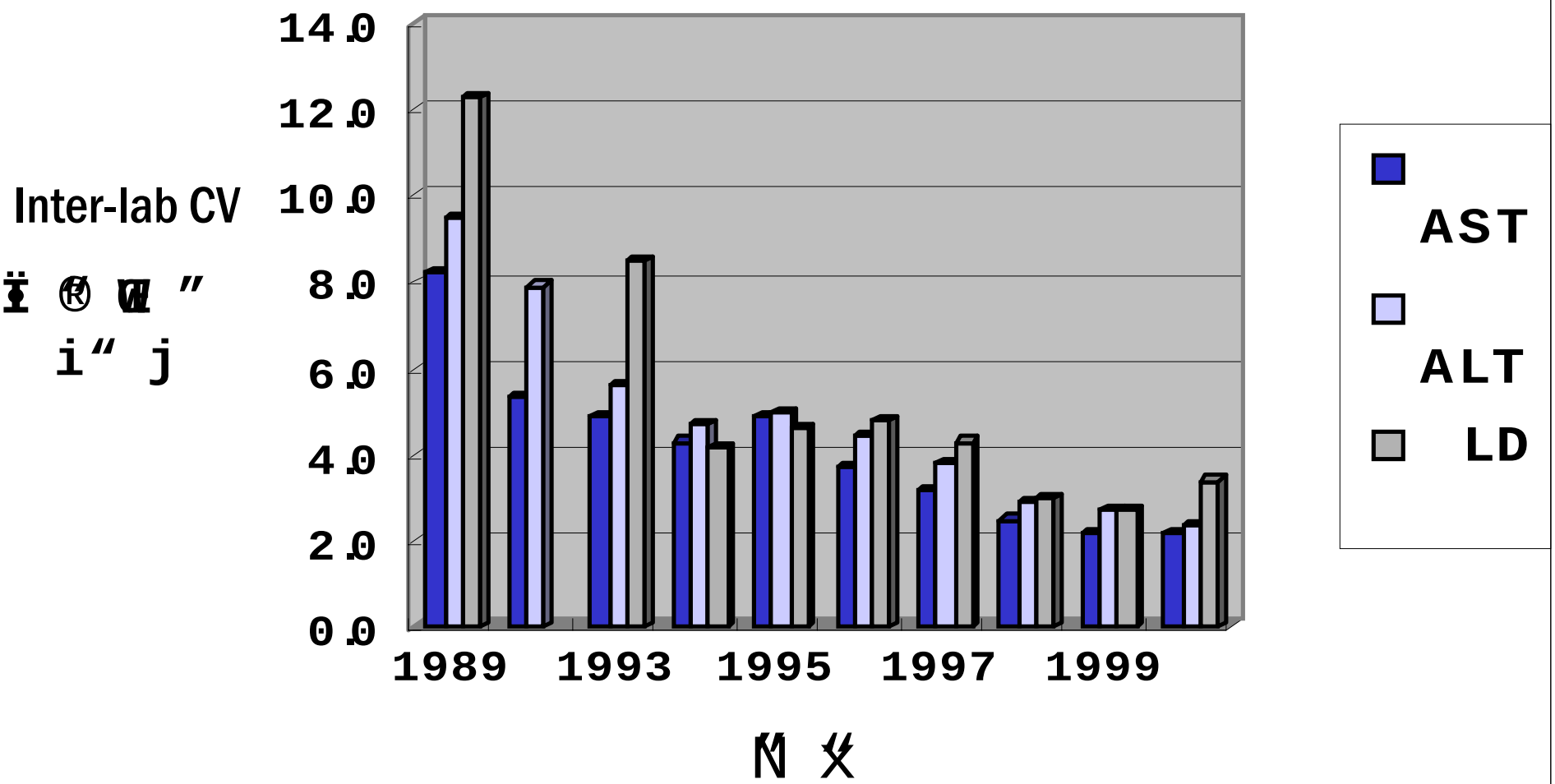
JACR Japan Association of Clinical Reagents Industries

Supporting IVD Standardization Activity

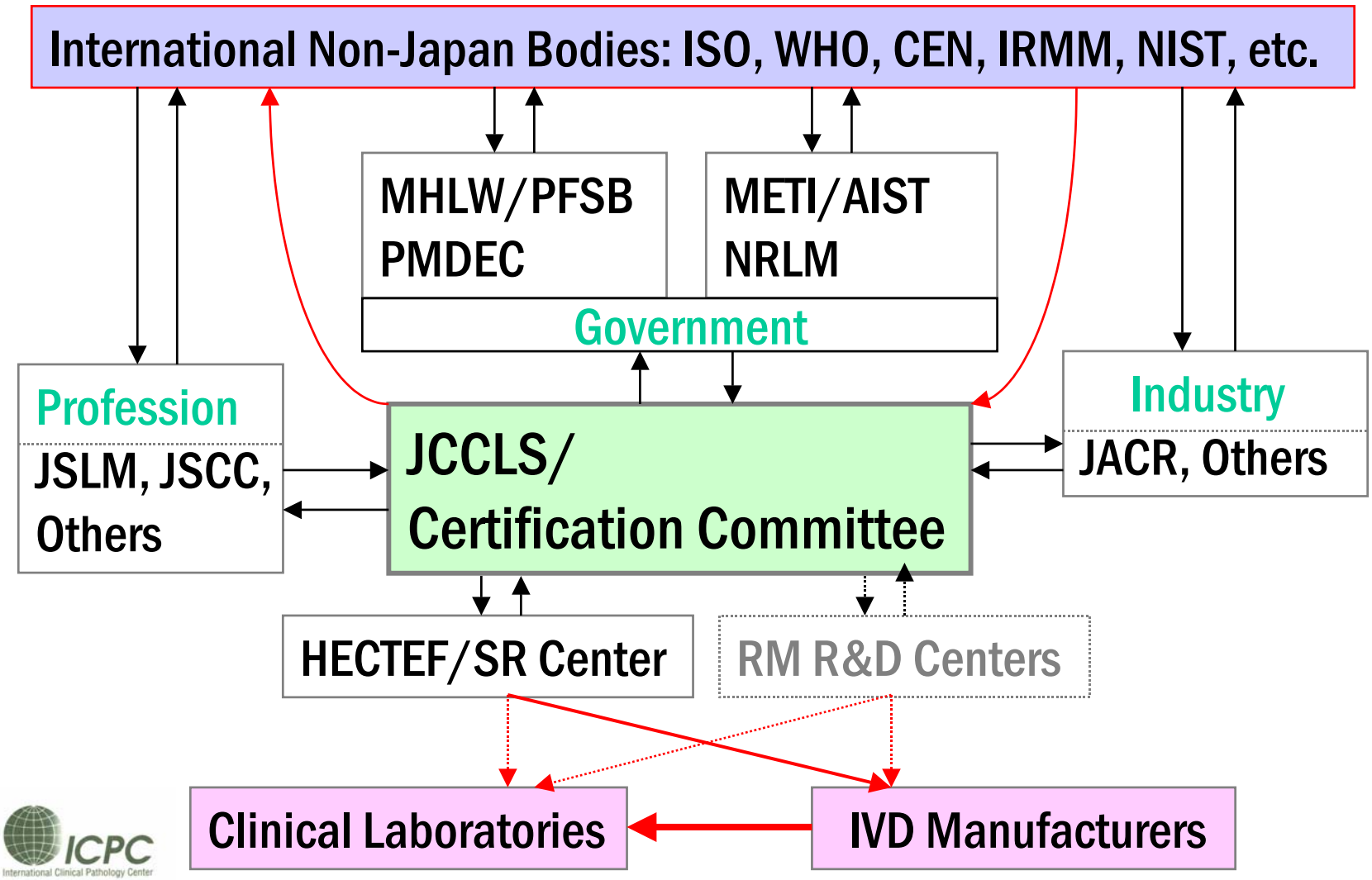
- JACR/Technical Committee is responsible to draft any policy related to standardization in manufacturing IVD-MD
- JACR has been actively participating and supporting the JCCLS/ISO activities ; one of the major contributions is to produce and distribute the JCERM with 6 assigned enzyme activities, resulting in marked improvement of inter-laboratory variability among clinical laboratories in Japan
- JACR hopes JCTLM will contribute significantly to global harmonization of IVD-MD for improving accuracy and/or trueness in laboratory investigation

AST,ALT,LDÌ ï ® Ì M Ÿ „ Ó

Improvement of Inter-lab variability in AMA Proficiency Testing



Proposed System of Developing and Providing RMs in Japan



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Thank you for your attention !

ご静聴有難うございました！