

# Chinese regulations on IVDs and traceability requirements

*Hongmei Li*  
*CMD/NRCCRM*  
*NIM China*

**NOV 30,2015 at BIPM**

# Outline

*1. IVD In China*

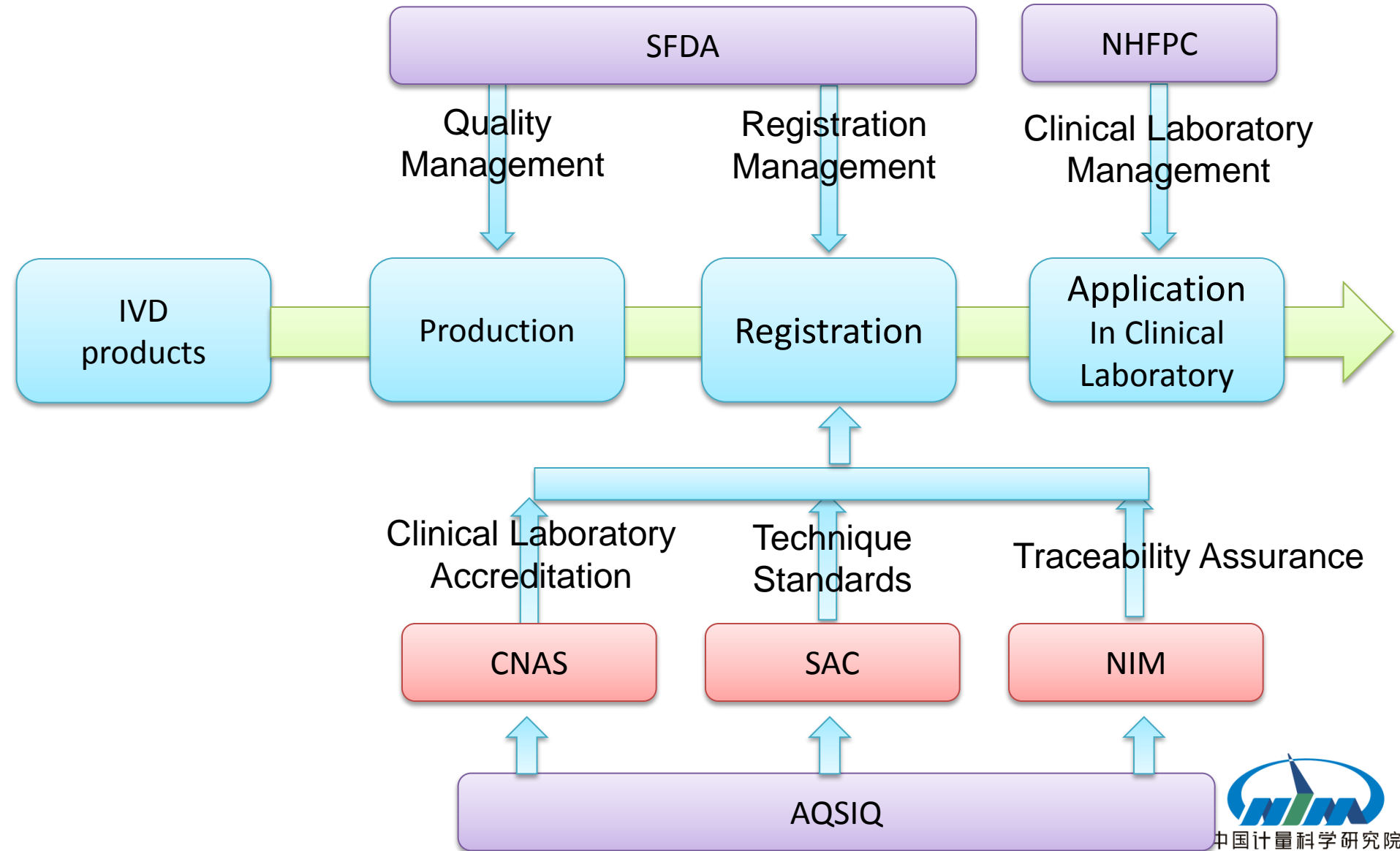
*2. China's Efforts on IVD traceability*

*3. Future Demands and Tendency*



# 1. IVD Regulations In China

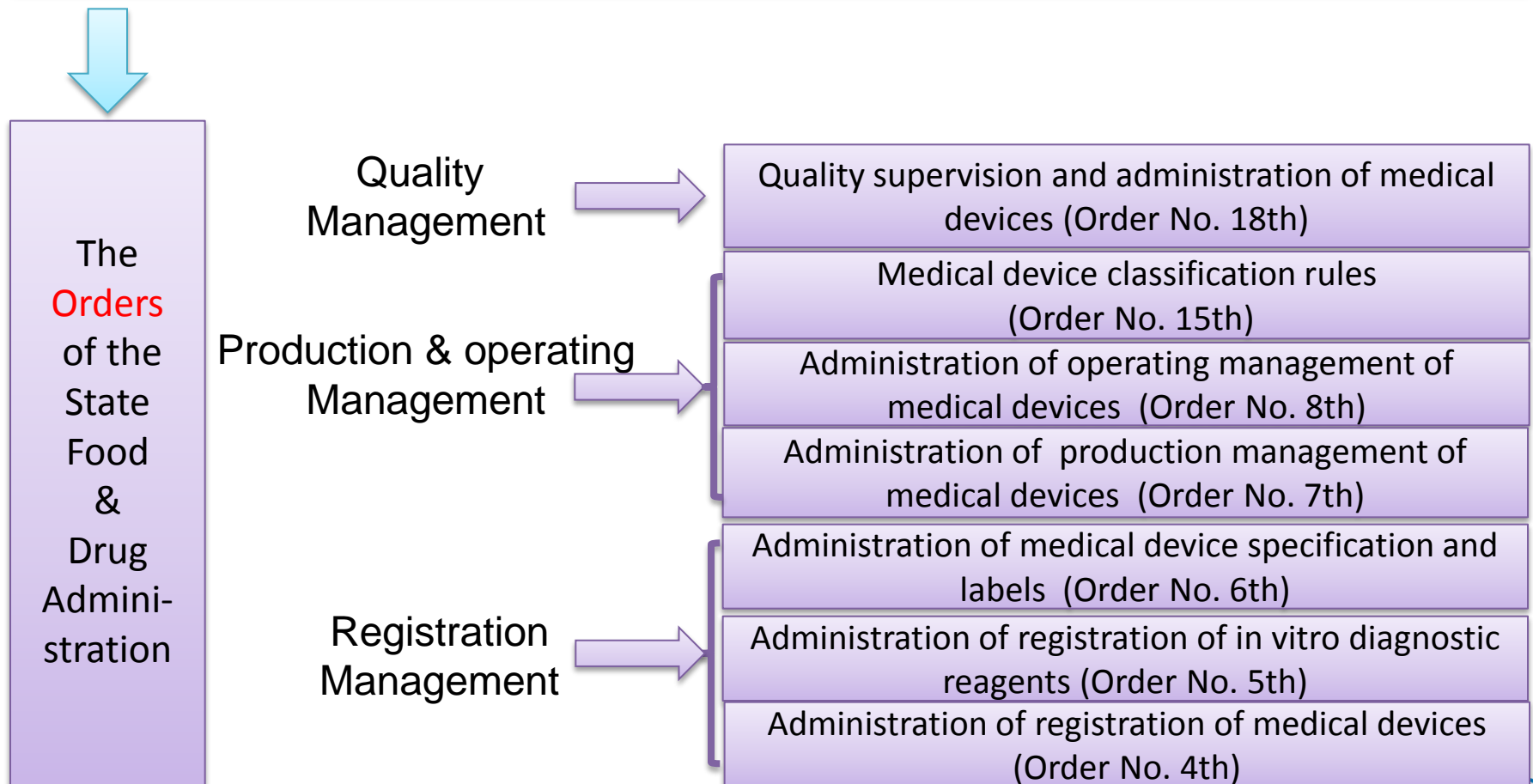
## IVD Management in China



# 1. IVD Regulations In China

## IVD Management in China - SFDA

**Regulations** on the supervision and administration of medical devices  
(the State Council Order No. 650th)

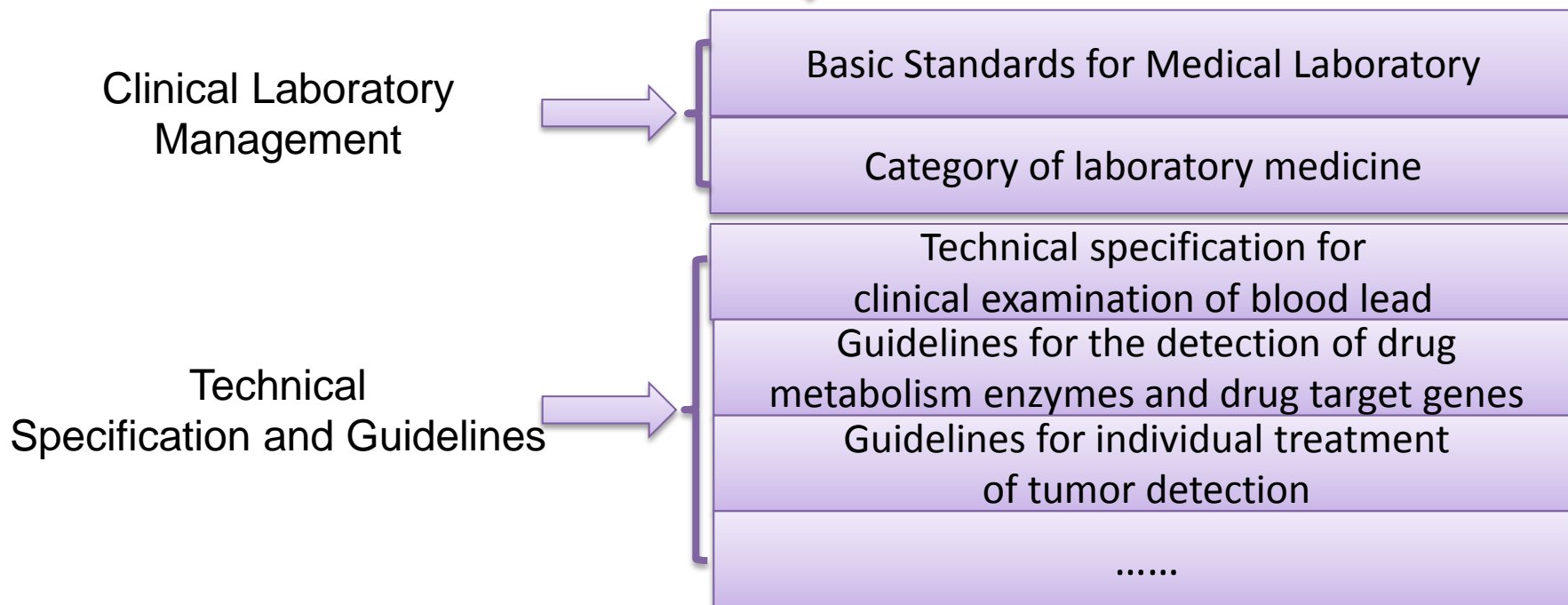


# 1. IVD Regulations In China

## IVD Management in China - NHFPC

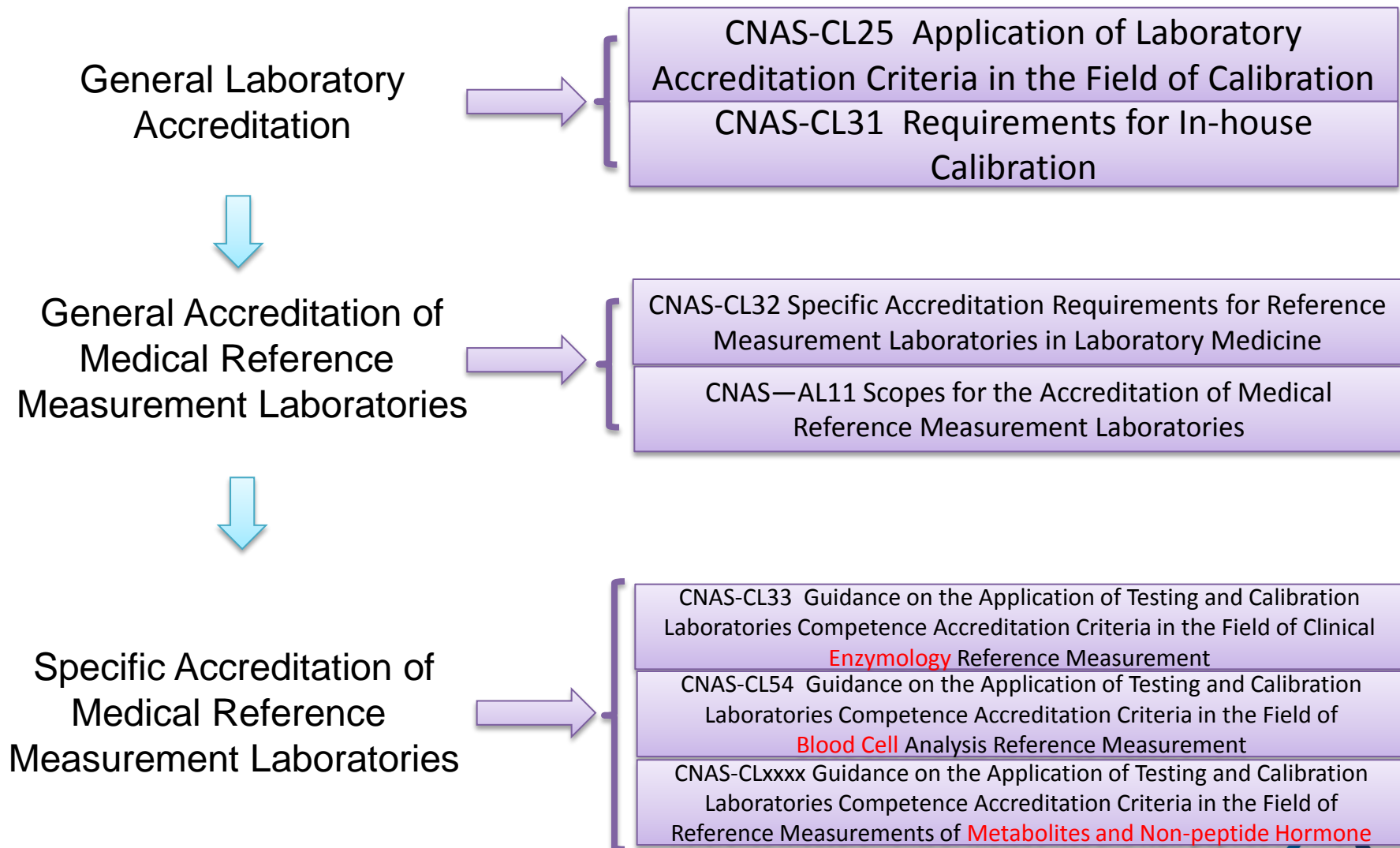
National Health and Family Planning Commission of the PRC  
(NHPFC)

Department of Medical Affairs Administration



# 1. IVD Regulations In China

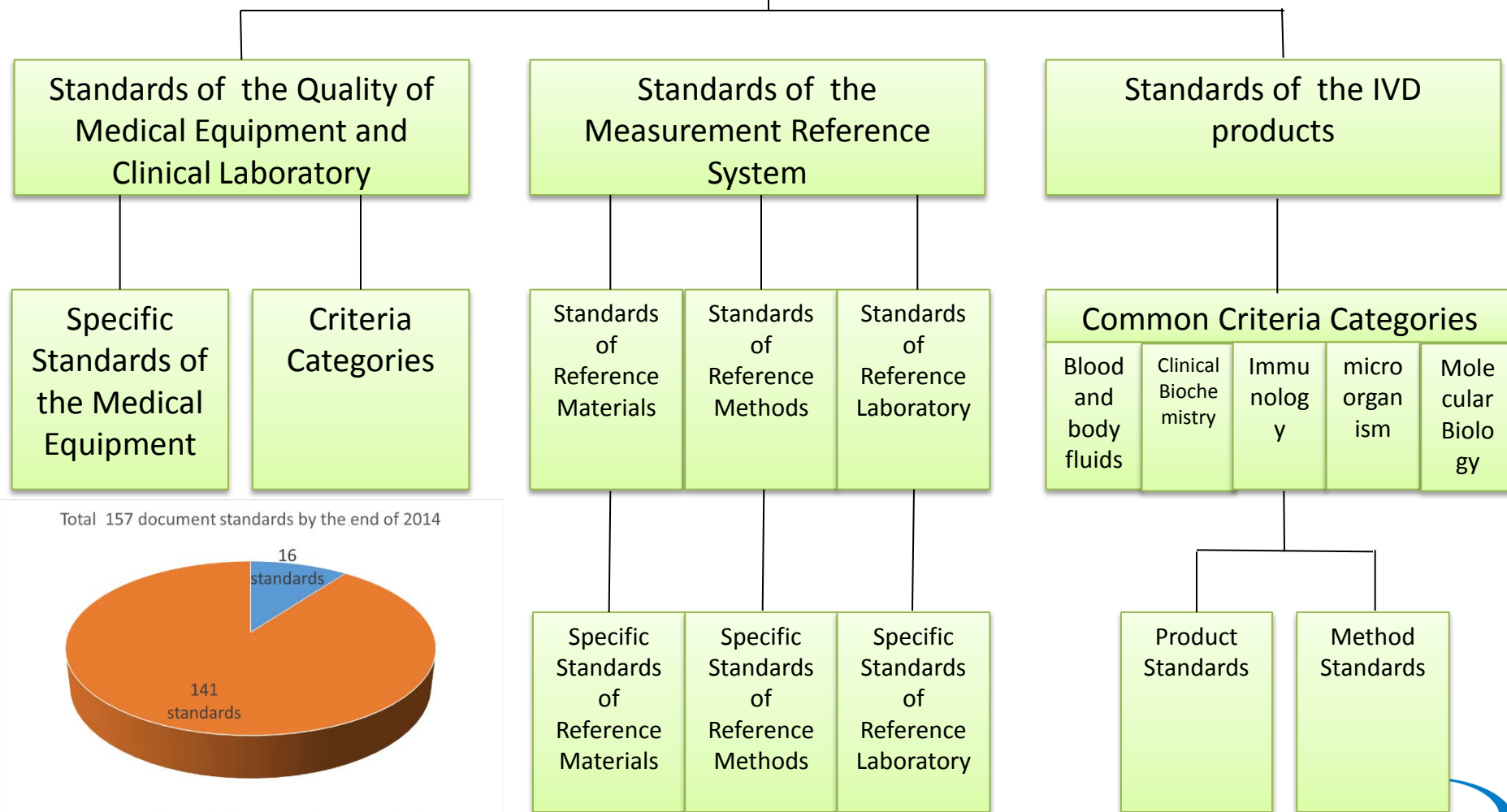
## IVD Management in China - CNAS



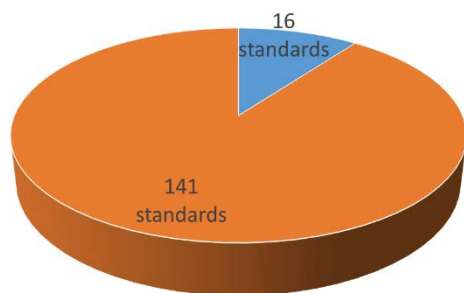
# 1. IVD Regulations In China

## IVD Management in China – SAC

### General Standards of Clinical Laboratory and IVD



Total 157 document standards by the end of 2014



■ National standards ■ Industry standard

SAC/TC136 National medical clinical laboratory and in vitro diagnostic system

# 1. IVD Regulations In China

## IVD Management in China – NIM

Traceability



JJGs “Verification Scheme of Measurement Instruments” and “Value traceability chart”



Traceability and Quality Assurance



Reference  
Measurement  
Procedure



JJF xxx The values of enzymatic activity concentrations assigned for the clinical enzymatic reference materials and the expression of measurement uncertainty

JJF xxx Reference Measurement Procedure of Hemoglobin A1c in Whole Blood ( HPLC/CE )

JJF xxx Reference Measurement Procedure of Bilirubin

JJF xxx Reference Measurement Procedure of Total Serum Protein

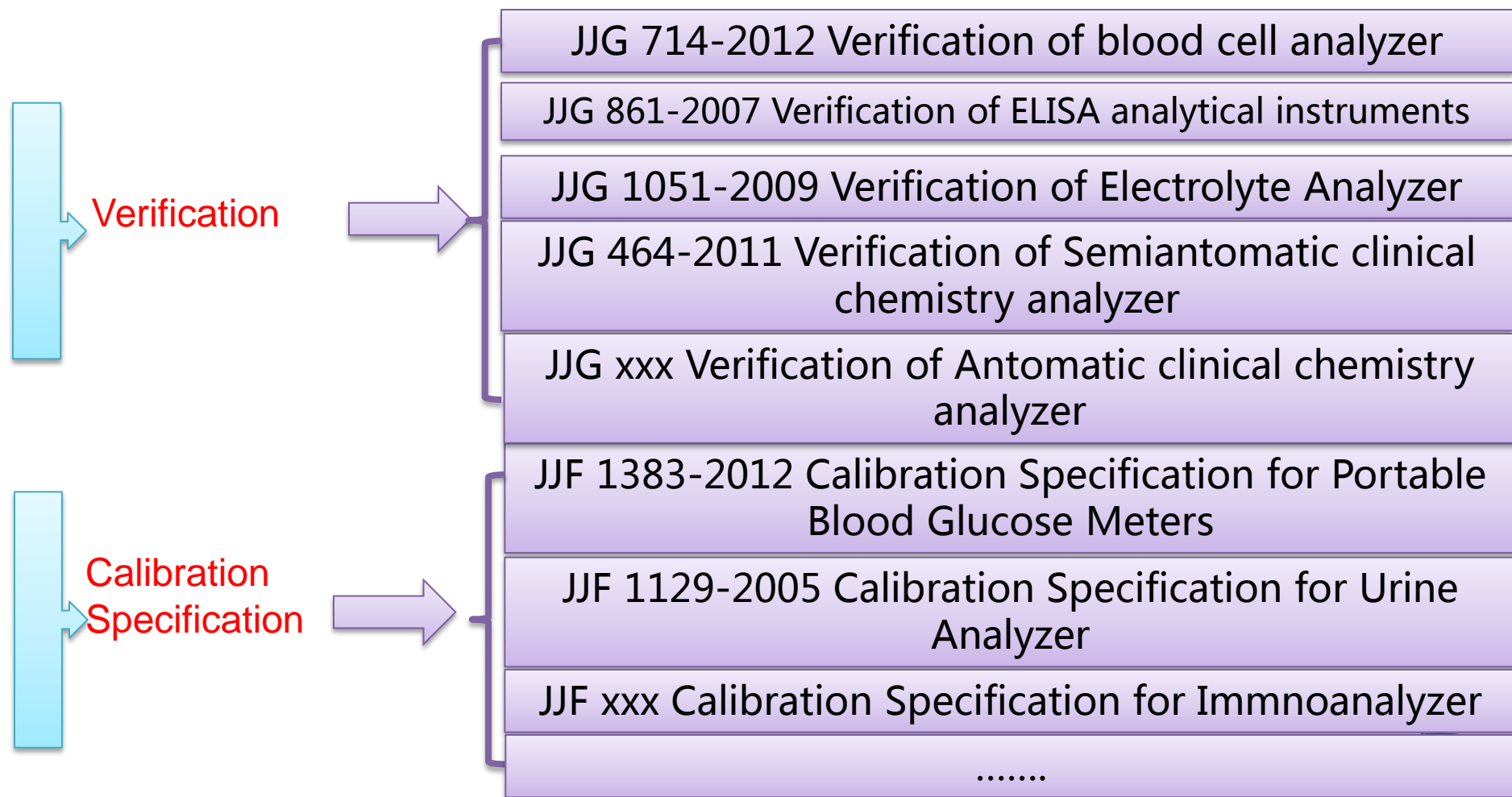
.....



# 1. IVD Regulations In China

## IVD Management in China – NIM

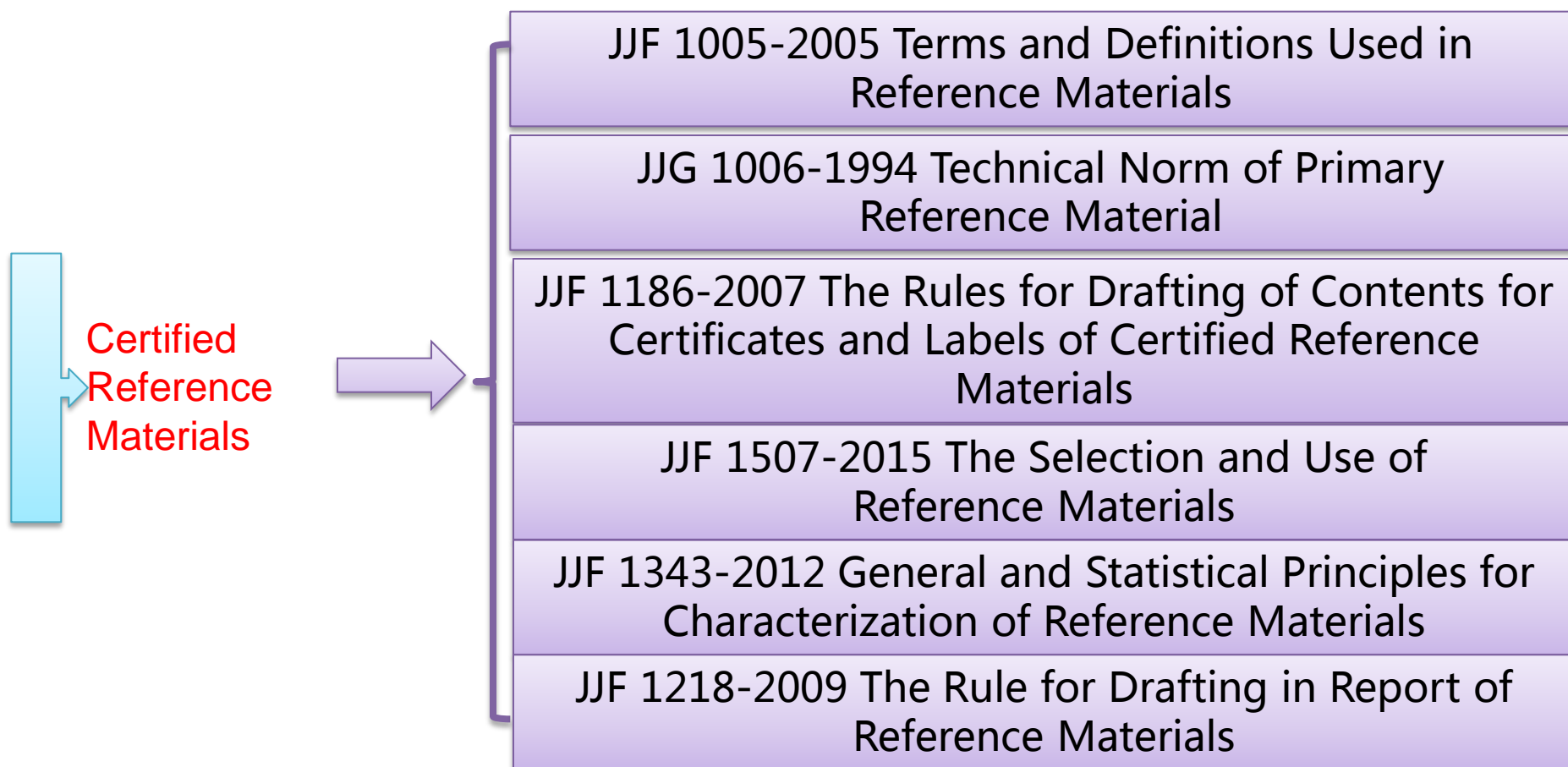
### Traceability and Quality Assurance - cont.



# 1. IVD Regulations In China

## IVD Management in China – NIM

### Traceability and Quality Assurance - cont.



# 1. IVD Regulations In China

## IVD Management in China – NIM

**NIM CHEMISTRY DEPARTMENT**  
Coordination of International Chemical Standard Activities

**CCQM OAWG**

Organic purity  
CRMs



**CJCTLM**

**Founded in 2007**

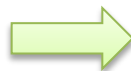
- ◆ CCQM Comparison in Laboratory Medicine
- ◆ Reference Measurement Systems
- ◆ Proficiency Test



# 1. IVD Regulations In China

## IVD Management in China – NIM

### Mission of the Committee



Drafting metrology technical specification in clinical

Evaluating reference materials, reference methods and reference laboratories

Organizing intercomparisons for reference laboratories

Providing support for Clinical Laboratory and Reference Laboratories preparing for accreditation

Participating in the activities of JCTLM

Organizing proficiency testing for clinical laboratories

Transporting knowledge in metrology and training

### Contains:

- 31 members
- 2 Consultants

CJCTLM Chair: Wu Fangdi (NIM), Vice Chair: Li Hongmei (NIM)

CJCTLM Executive Secretary: Xu Bei (NIM)

**CJCTLM developed to help IVD industry meet metrological traceability requirements of the CHINA IVD Directive**



# 1. IVD Regulations In China

## IVD Management in China – NIM

Reference Measurement Procedures Coordinated by CJCTLM

<b>JJF 1383-2012</b>	<b>Calibration Specification for Portable Blood Glucose Meters</b>
<b>JJG1051-2009</b>	<b>Calibration Specification for Electrolytes Analyzers</b>
<b>JJG714</b>	<b>Verification Regulation of Blood CELL analyzer</b>
<b>JJF 1353-2012</b>	<b>Calibration Specification for Hemodialysis Equipment</b>
<b>Finished in 2015</b>	<b>Reference method for total bilirubin in serum</b>
	<b>Reference method for total biliprotein in serum</b>
	<b>Reference method for glucose in serum(UV Spectrometer)</b>
	<b>Reference method for Catalytic activity of alkaline phosphatase in serum</b>
<b>To be finished in 2016</b>	<b>Reference method for Glycosylated hemoglobin concentration in whole blood</b>
	<b>Reference method for uric acid in serum</b>
	<b>Terminology for clinical medical metrology</b>



# Hierarchy of Laboratories

---

**National Metrology Institutes**

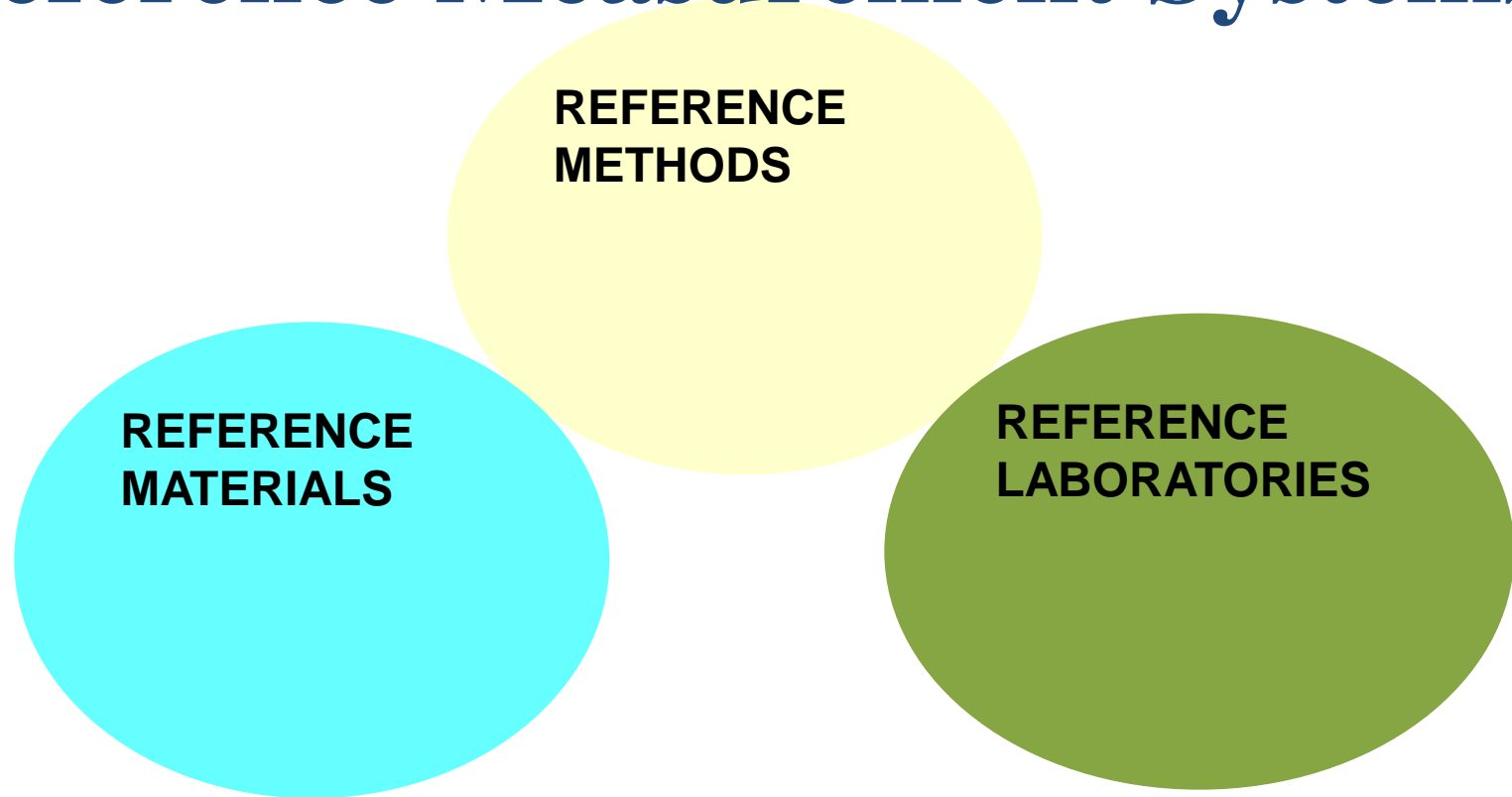


**Accredited Reference Laboratories**



**Routine (Testing) Laboratories**

# Reference Measurement Systems

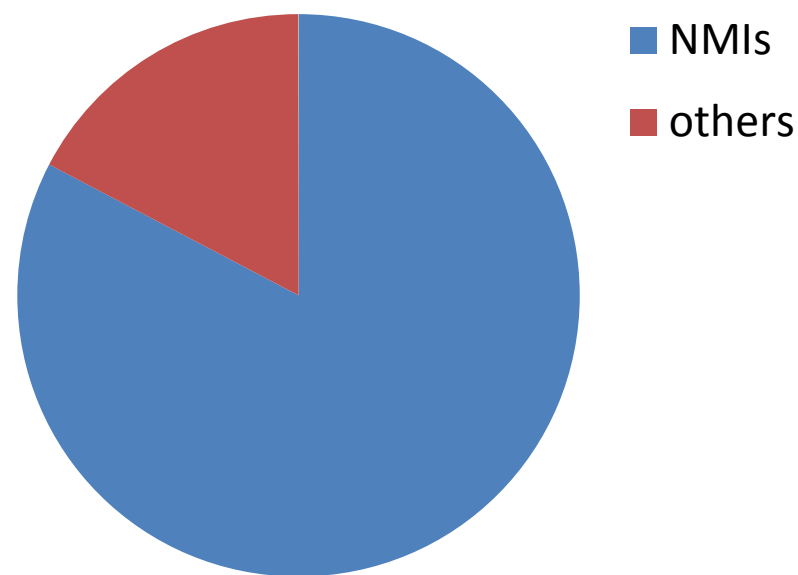


**A technical process to reach conformity of measurement procedures by applying highest scientific standards**

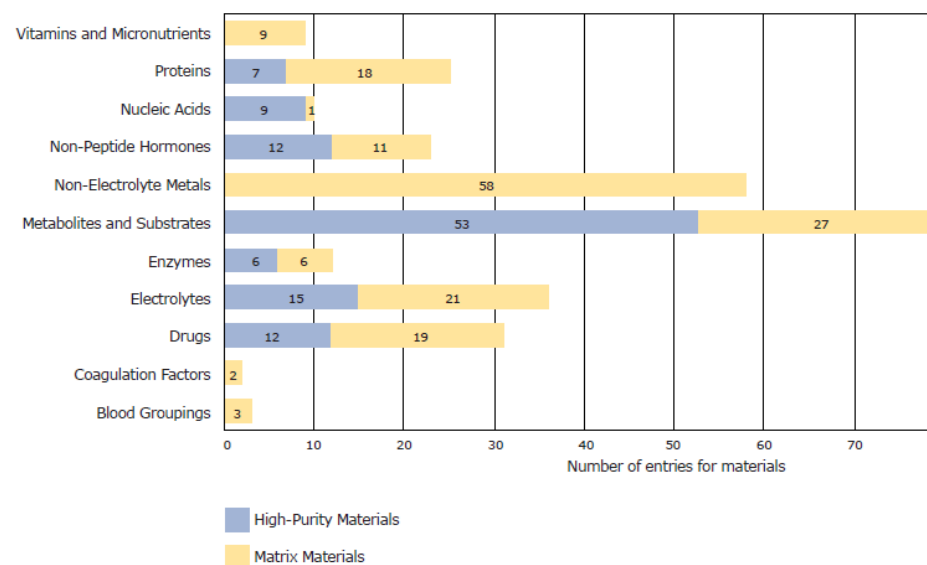
## 2. China's Efforts on IVD traceability

295 **CRMs** in JCTLM Database by NMIs & DIs

### Related CRMs in JCTLM Database



JCTLM Database entries for available certified materials as of February 2015





## 2. China's Efforts on IVD traceability

### Related CRMs in JCTLM Database by NIM CHINA

JCTLM database : Laboratory medicine and *in vitro* diagnostics



Analyte	Matrix/Material	Name of the reference material	Producer	Quantity	Range of certified values in reference material	Range of expanded uncertainties for certified value	Listed in
cholesterol	cholesterol crystalline material	GBW09203b, cholesterol	NIM (National Institute of Metrology), China Phone : +86 10 6422 1811 Fax : +86 10 6421 3149 crmservice@nim.ac.cn	Mass fraction	99.7 %	0.1 % Level of confidence 95 %	List I
uric acid	uric acid crystalline material	GBW09202, uric acid	NIM (National Institute of Metrology), China Phone : +86 10 6422 1811 Fax : +86 10 6421 3149 crmservice@nim.ac.cn	Mass fraction	99.8 %	0.3 % Level of confidence 95 %	List I
urea	urea crystalline material	GBW09201, urea	NIM (National Institute of Metrology), China Phone : +86 10 6422 1811 Fax : +86 10 6421 3149 crmservice@nim.ac.cn	Mass fraction	99.9 %	0.2 % Level of confidence 95 %	List I



## 2. China's Efforts on IVD traceability

### 73 CRMs related to in China (not listed in JCTLM Database)

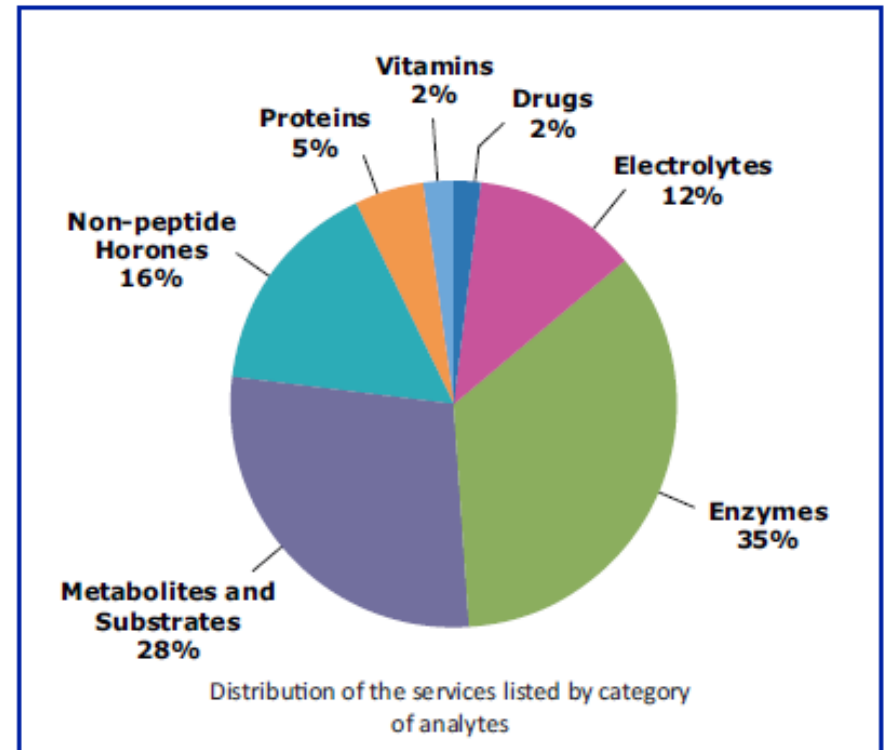
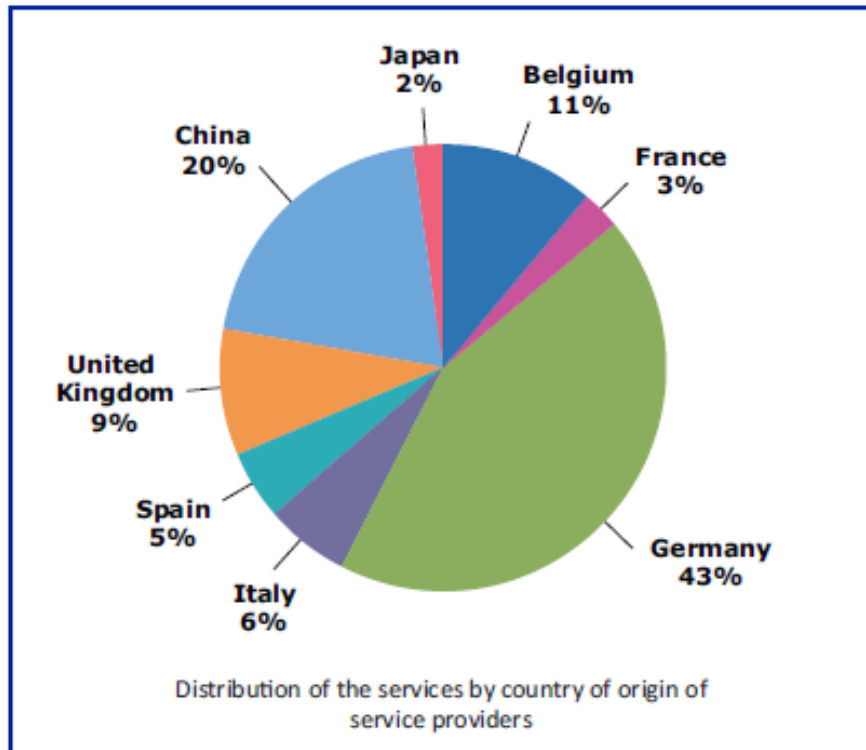
Analyte category	No.	Comments
Blood Cell counting	3	CRMs for cell counting in whole blood
Electrolytes	11	Inorganic spices in urine, serum or hair matrix
Metabolites and substrate	18	UA,CK,UR,GLU,etc. high purity or serum matrix
Non-peptide hormones	10	Anabolic-androgenic steroids (AAS)
Proteins	16	C Peptide,BSA ,Glycated Hemoglobin,etc.
Vitamins	8	Emodin, Rg1,Rb1 ,etc.
others	7	Viscosity CRMs
<b>Total</b>	<b>73</b>	



## 2. China's Efforts on IVD traceability

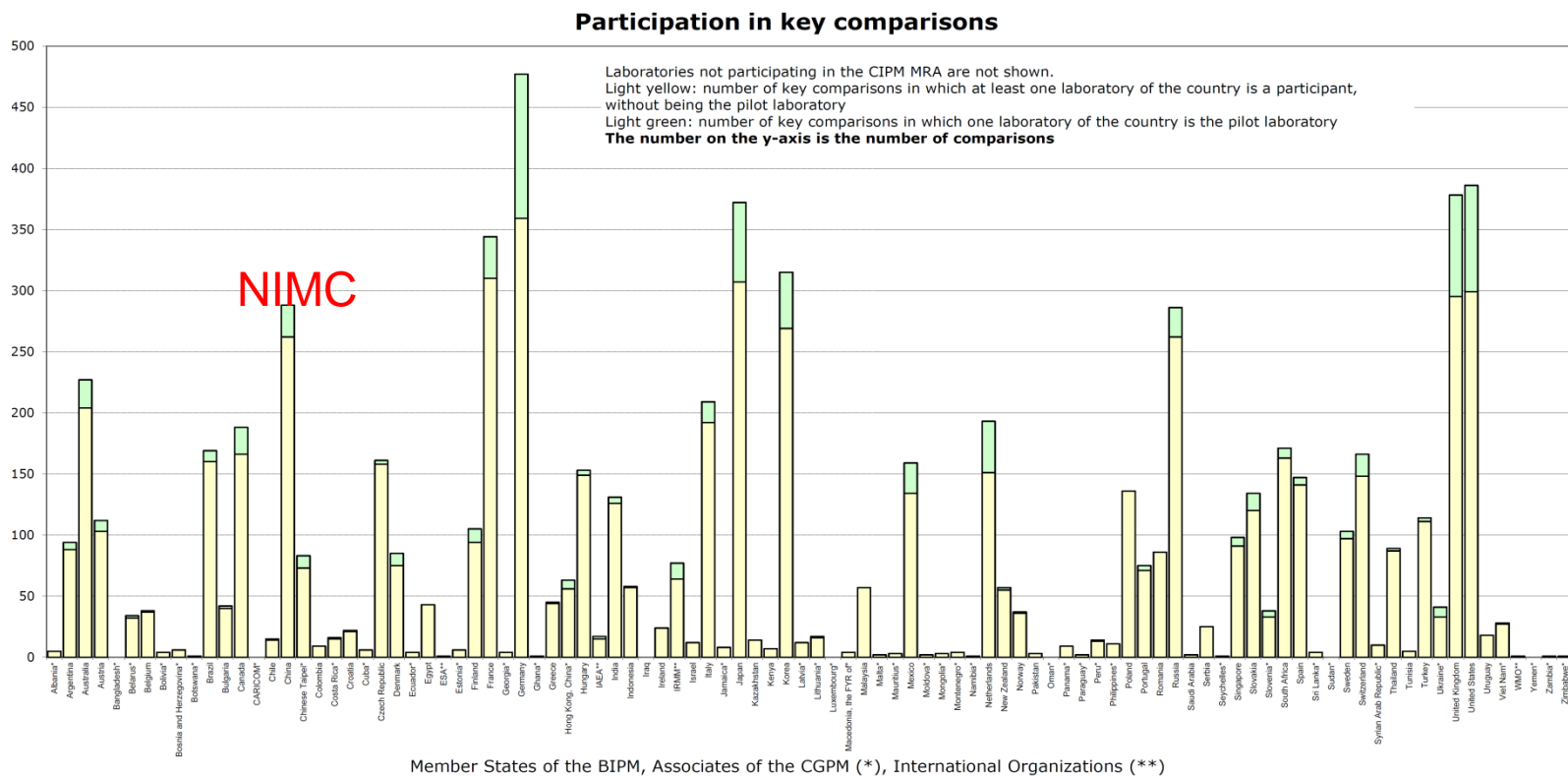
### Reference Laboratories

JCTLM Database entries for reference measurement services provided by reference laboratories worldwide as of February 2015



# 2. China's Efforts on IVD traceability

CCQM Key Comparisons , <http://kcdb.bipm.org/>



## 2. China's Efforts on IVD traceability

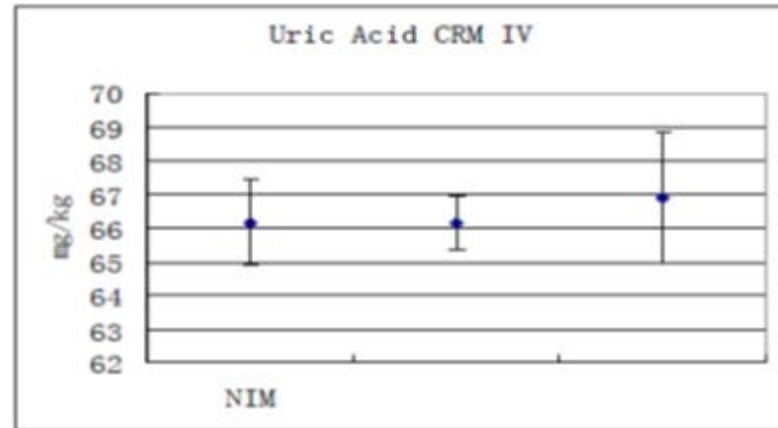
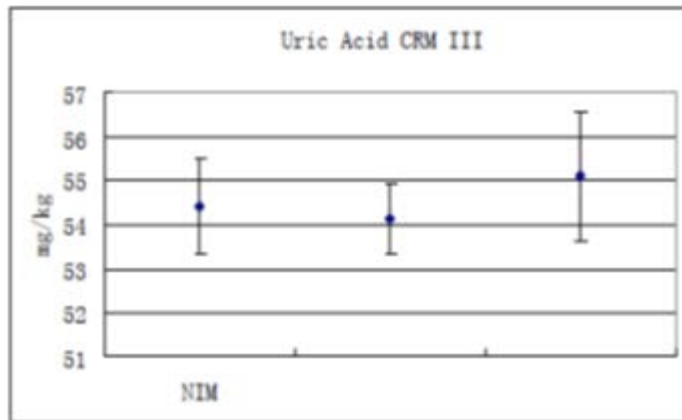
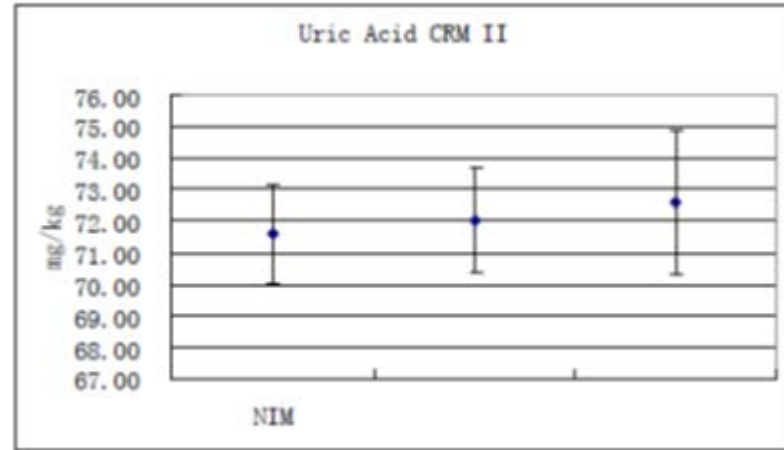
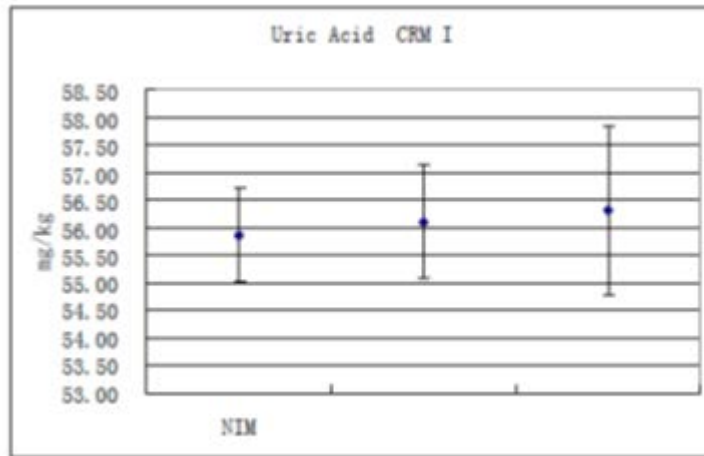
**CCQM Key Comparisons , <http://kcdb.bipm.org/>**

<b>Code</b>	<b>Name</b>	<b>Analyte category</b>
<b>CCQM-K6</b>	<b>Cholesterol in human serum , 2000</b>	<b>Metabolites and substrates</b>
<b>CCQM-K11.1, 11.2</b>	<b>Glucose in human serum , 2005,2013</b>	<b>Metabolites and substrates</b>
<b>CCQM-K12.1</b>	<b>Creatinine in human serum , 2005</b>	<b>Metabolites and substrates</b>
<b>CCQM-K63a</b>	<b>Non-peptide hormones in serum: Cortisol , 2007</b>	<b>Non-electrolyte metals</b>
<b>CCQM-K63b</b>	<b>Non-peptide hormones in serum: Progesterone,2007</b>	<b>Non-electrolyte metals</b>
<b>CCQM-K80</b>	<b>Creatinine in human serum ,2010</b>	<b>Metabolites and substrates</b>
<b>ACRM</b>	<b>co-validation of uric acid and creatinine in human serum</b>	<b>Metabolites and substrates</b>



## 2. China's Efforts on IVD traceability

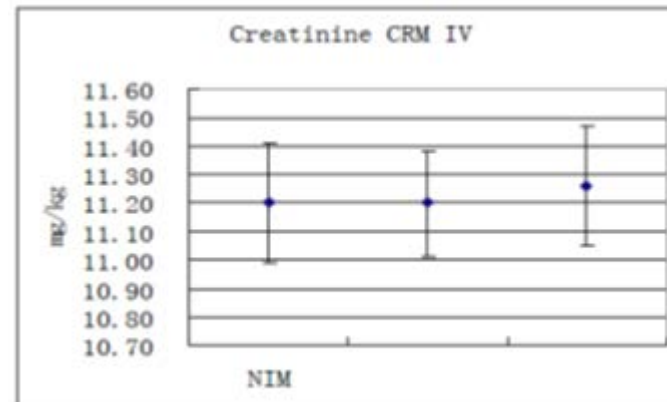
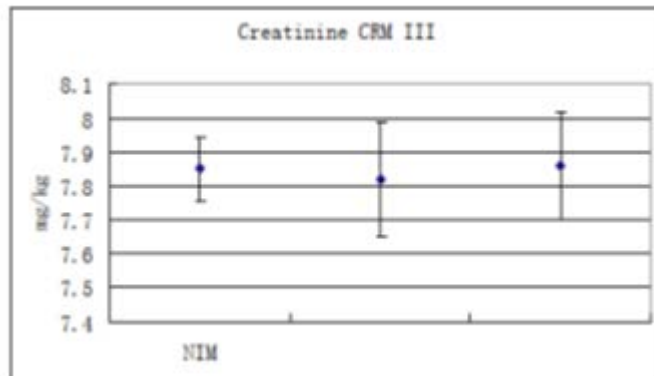
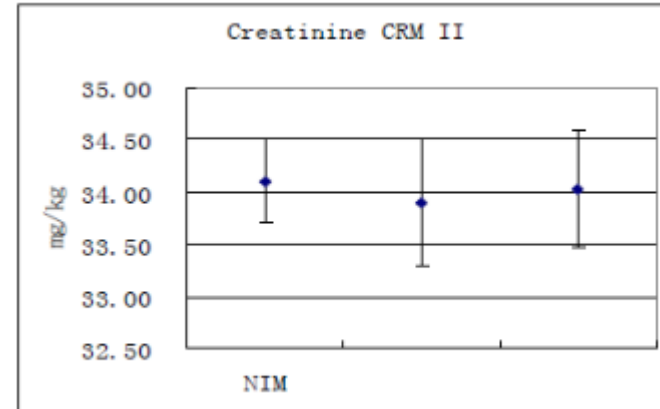
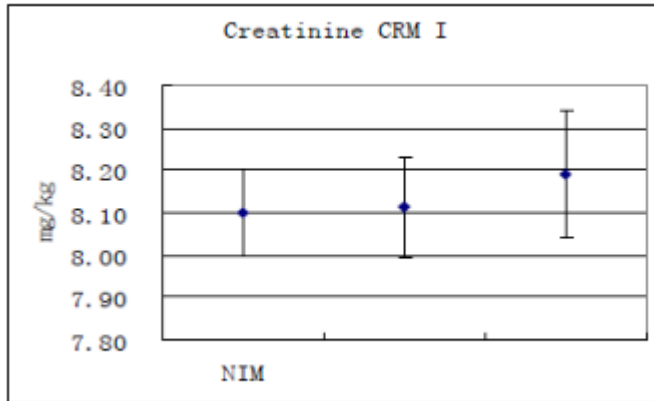
**CCQM Key Comparisons , <http://kcdb.bipm.org/>**



**Co-validation of Uric Acid CRM**

## 2. China's Efforts on IVD traceability

CCQM Key Comparisons , <http://kcdb.bipm.org/>



# Co-validation of Creatinine CRM



## 2. China's Efforts on IVD traceability

Participation in 5 Key Comparisons (IAWG &BAWG),  
<http://kcdb.bipm.org/>

Code	Name	Analyte category
<a href="#">CCQM- K14</a>	Calcium in human serum,2003	Electrolytes
<a href="#">CCQM- K49</a>	Toxic and essential elements in bovine liver,2006	Electrolytes
<a href="#">CCQM- K89</a>	Trace and essential elements in Herba Ecliptae,2011	Electrolytes
<a href="#">CCQM- K107</a>	Elements and Se speciation in human serum,2013	Electrolytes
<a href="#">CCQM- K115</a>	Peptide purity determination - synthetic human C peptide (HCP), 2014	Proteins

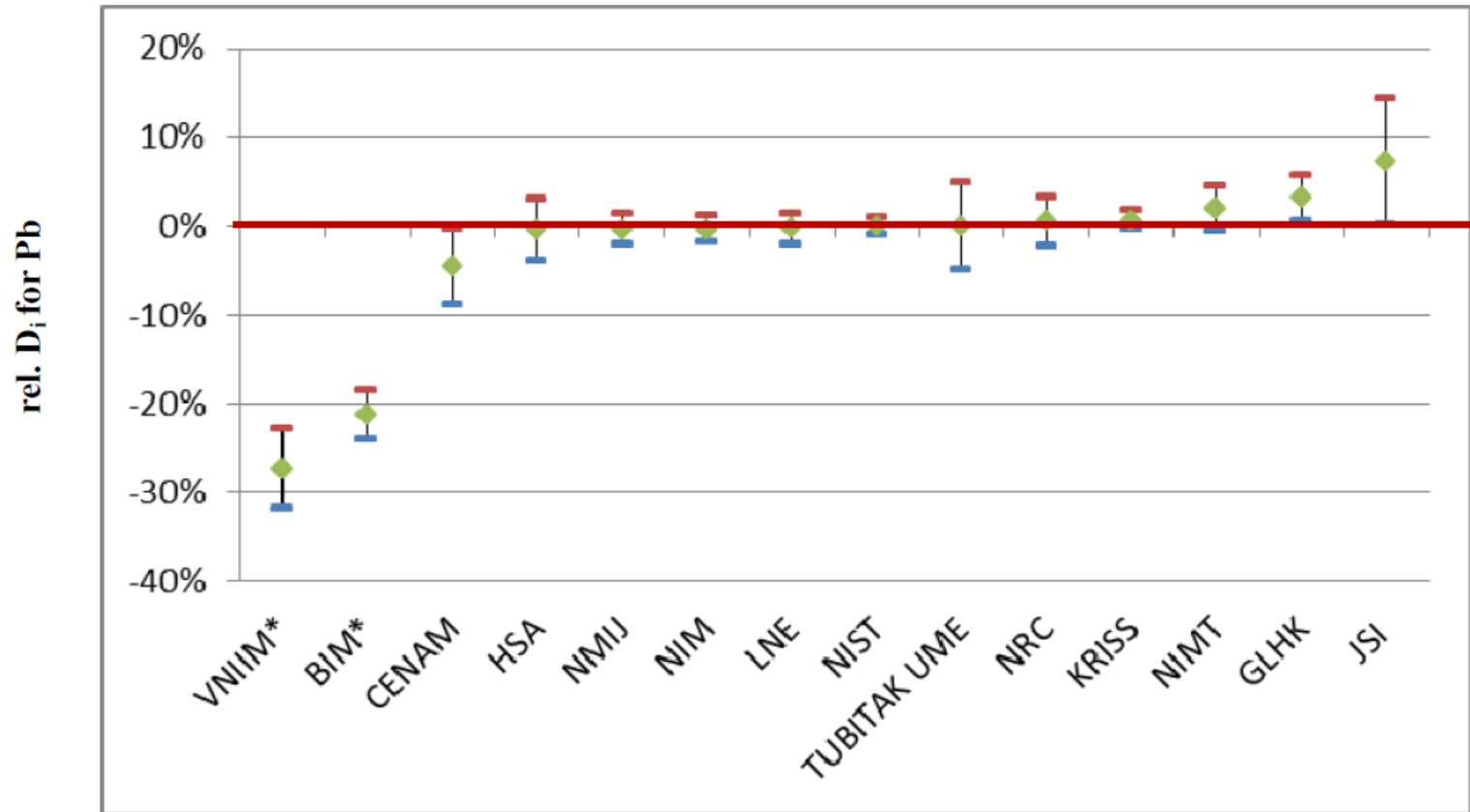




## 2. China's Efforts on IVD traceability

### CCQM K89: Lead measurement results and uncertainties

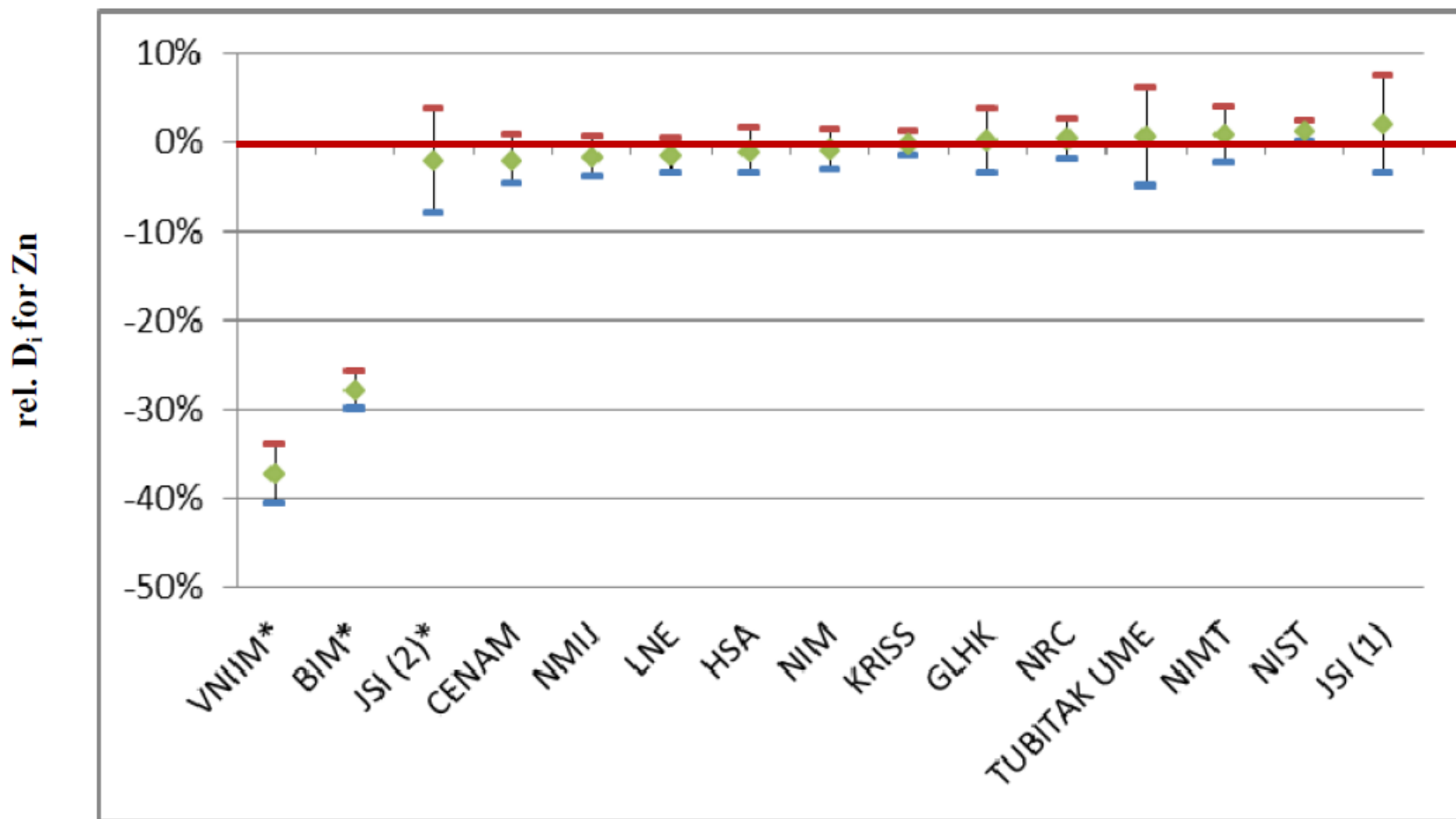
<http://kcdb.bipm.org>



## 2. China's Efforts on IVD traceability

### CCQM K89: Zinc measurement results and uncertainties

<http://kcdb.bipm.org>



## 2. China's Efforts on IVD traceability

### Participation in Pilot Studies

Code	Name	Analyte category
CCQM-P54	DNA primary quantification	Proteins
CCQM-P54.1	DNA quantification (repeat)	Proteins
CCQM-P55	Peptide / protein quantification	Proteins
CCQM-P55.1	Peptide / protein quantification (repeat)	Proteins
CCQM-P55.2	Peptide purity determination - synthetic human C peptide (HCP)	Proteins
CCQM-P58	Fluorescence in ELISA	Proteins
CCQM-P58.1	Fluorescencen in ELISA (Stage 2)	Proteins
CCQM-P59	Protein structural measurements by CD	Proteins
CCQM-P59.1	Protein structural measurements by CD (repeat)	Proteins
CCQM-P94	Quantification of DNA methylation	Proteins
CCQM-P94.1	Quantification of DNA methylation	Proteins
CCQM-P94.2	Quantification of DNA methylation	Proteins
CCQM-P102	Quantification of cells with specific phenotypic characteristics	Proteins

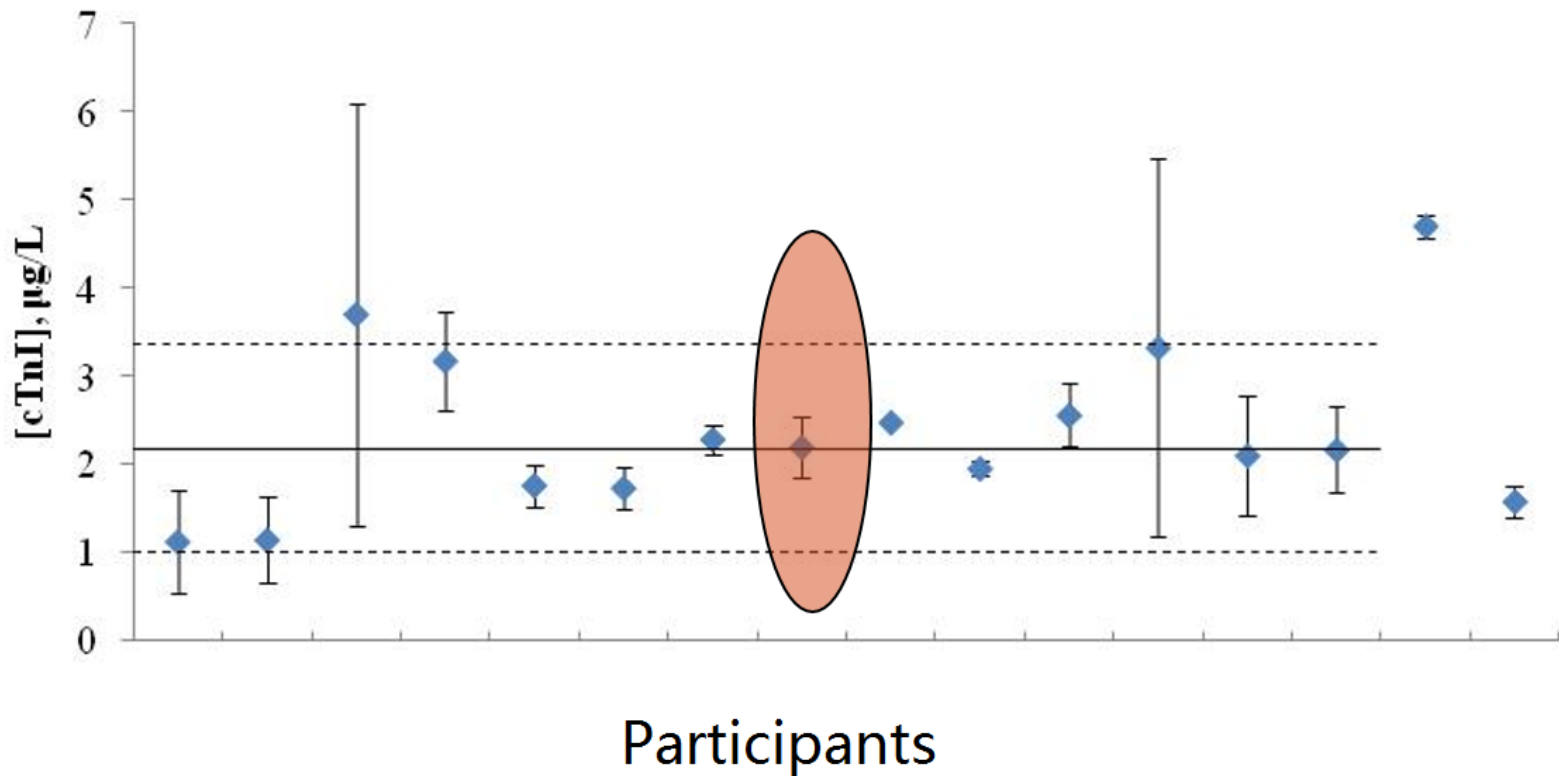
## 2. China's Efforts on IVD traceability

### Participation in Pilot Studies

Code	Name	Analyte category
CCQM-P103	Measurement of multiplexed biomarker panel of RNA transcripts	Proteins
CCQM-P103.1	Measurement of multiplexed biomarker panel of RNA transcripts	Proteins
CCQM-P123	Cell quantification on solid substrate	Proteins
CCQM-P137	Clinical amylase measurement	Proteins
CCQM-P154	Absolute quantification of DNA	Proteins
CCQM-P155	Multiple cancer cell biomarker measurement	Proteins
ACRM	Co-validation of Porcine Insulin CRM	Proteins
ACRM	Co-validation of C Reactive Protein	Proteins
ACRM	Co-validation of hGH	Proteins
ACRM	Co-validation of HbA1c	Proteins



## 2. China's Efforts on IVD traceability



**CCQM P58.1 Measurement of cTnI in solution by ELISA**

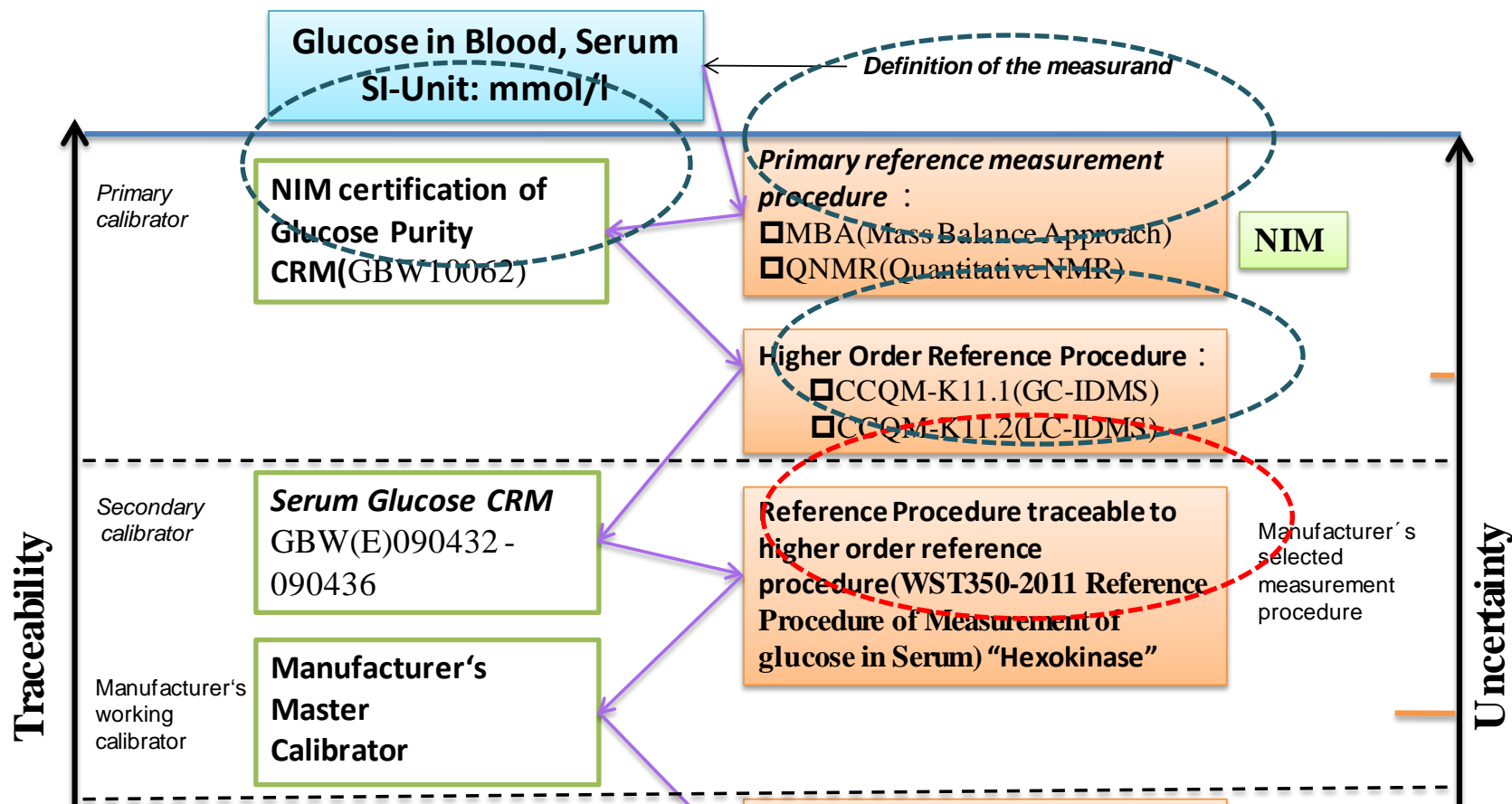
## 2. China's Efforts on IVD traceability

### GB-T 22576-2008/ISO 15189



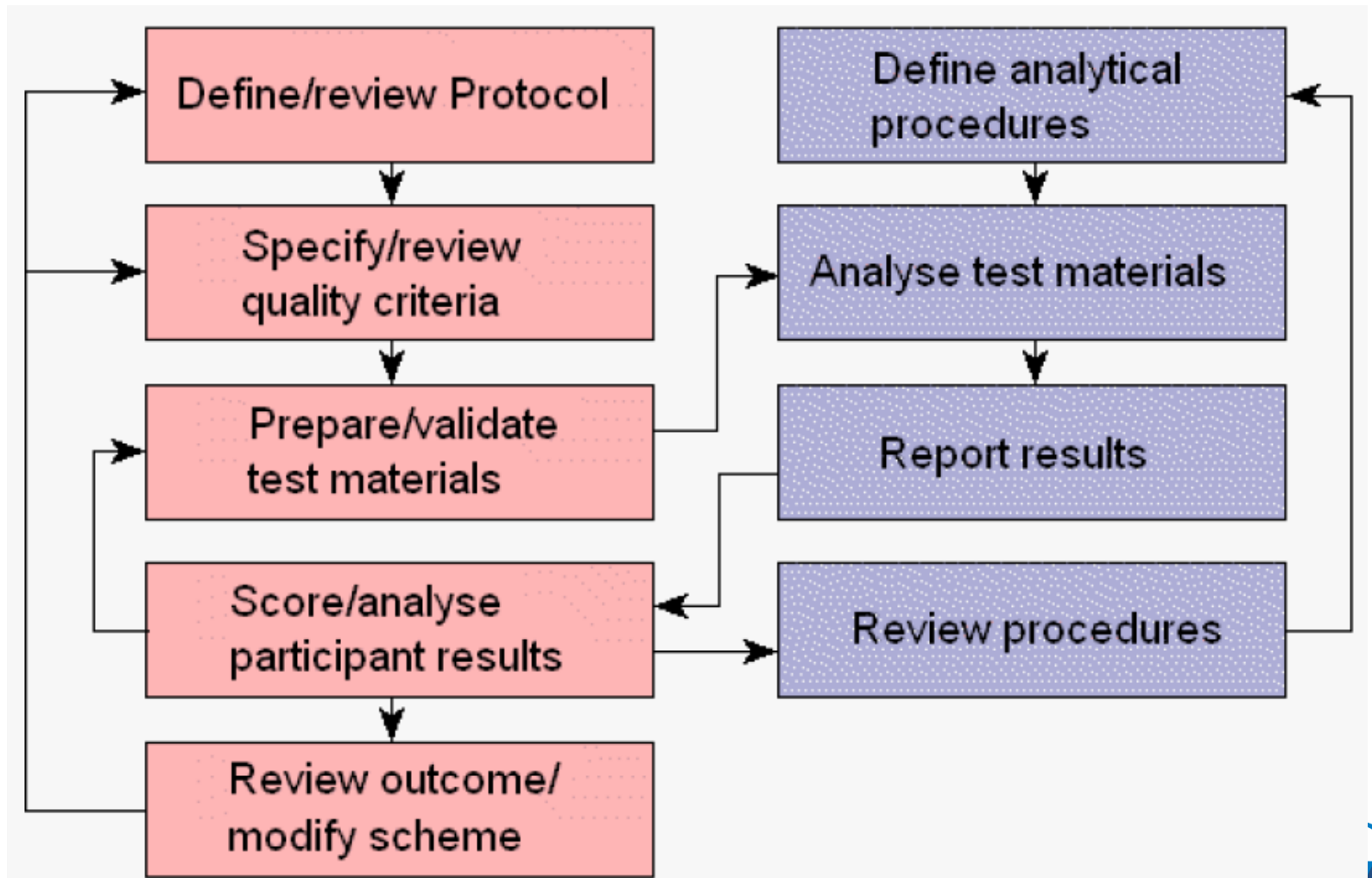


# 2. China's Efforts on IVD traceability



## 2. China's Efforts on IVD traceability

### Organization of Serum Glucose PT





## 2. China's Efforts on IVD traceability

### Proficiency Test for Reference Laboratory

- **2014-2015:** Proficiency testing programs to improve reference laboratories traceability in serum glucose assay
- **Participates:** 11 reference labs
- **Measurand:** Serum Glucose

## 2. China's Efforts on IVD traceability

### Proficiency Test for Reference Laboratory

$$\text{z-score} = \frac{x - X}{\sigma_p}$$

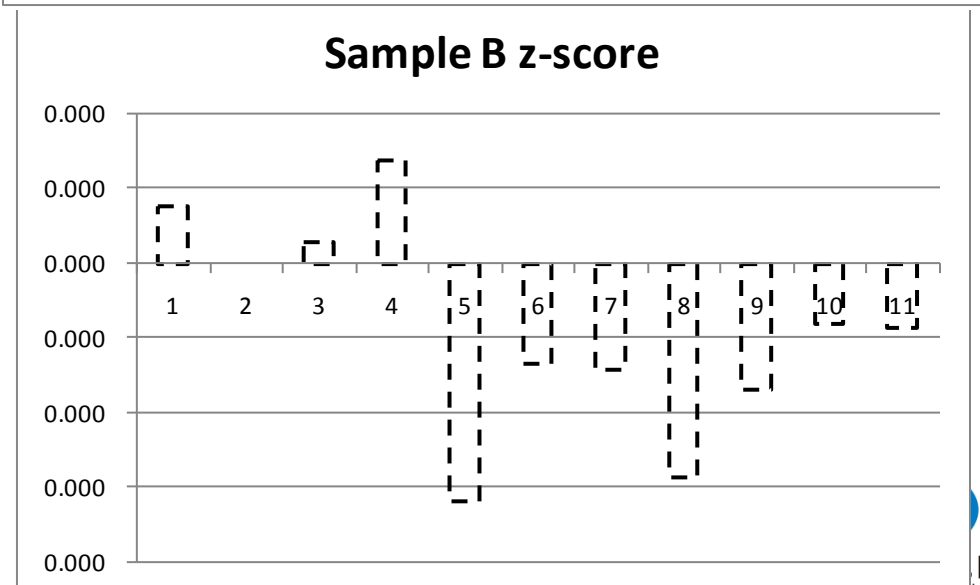
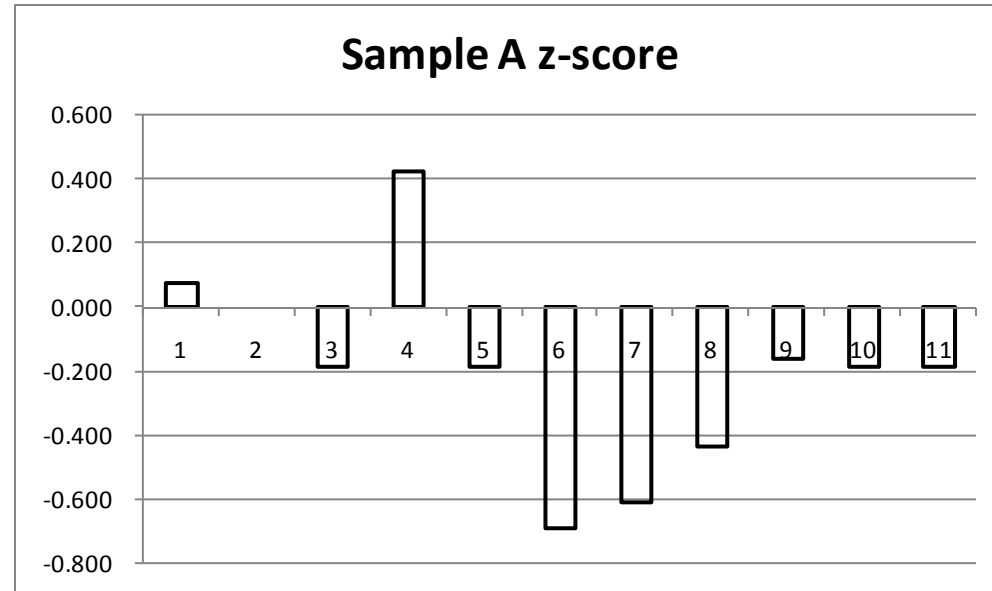
$x$  is the participant's reported results.  
 $X$  is the assigned value.  
 $\sigma_p$  is the standard deviation for proficiency assessment

$|z| \leq 2$ : "Satisfactory" ("S") performance.

$2 < |z| < 3$ : "Questionable" ("Q") performance.

$|z| \geq 3$ : "Unsatisfactory" ("U") performance.

No outliers



## 2. China's Efforts on IVD traceability

### Proficiency Test for Reference Laboratory

- 2008-2009: Proficiency testing programs to improve reference laboratories traceability in Clinical Enzyme assay
- Participates: 12 reference labs
- Measurands: lactate dehydrogenase(LDH ), creatine kinase (CK)



## 2. China's Efforts on IVD traceability

### New entries for Reference Measurement Laboratory Services

Analyte Category	Analyte	Location of Laboratory
Enzymes	Alanine aminotransferase	China
	Alkaline phosphatase	
	Alpha-amylase	
	Aspartate aminotransferase	
	Creatine kinase	
	Gamma-glutamyltransferase	
	Lactate dehydrogenase	
	Alkaline phosphatase	Spain
Metabolites & Substrates	Glucose	Italy
	Glucose	China
	Urea	
	Total glycerol	Germany
	Uric acid	
Non Peptide Hormones	Thyroxine	Germany
	Testosterone	
Proteins	HbA1c	France
	Total protein	China



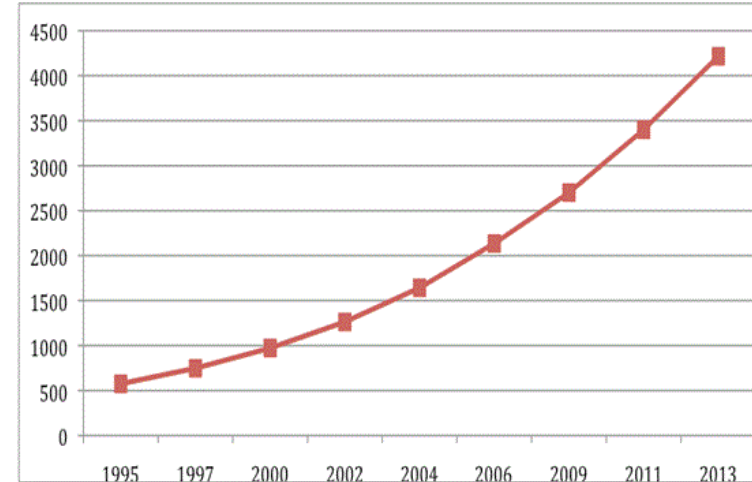
### 3. Future Demands and Tendency

# Market for IVD in China

Statistics from the Ministry of Health show that: China's medical devices industry has made rapid progress and the annual growing rate has reached 15% ~ 20% since 2001.

In 2008, the gross output value of medical devices reached 300 billion Yuan.

by 2020, China will become the world's second largest healthcare market.



The growth of China's IVD market chart(millions US dollars)

<http://mcevoyandfarmer.com/china.html>





# 3. Future Demands and Tendency

## IVD document standards

### Priority

Biochemical diagnosis

Immunodiagnosis

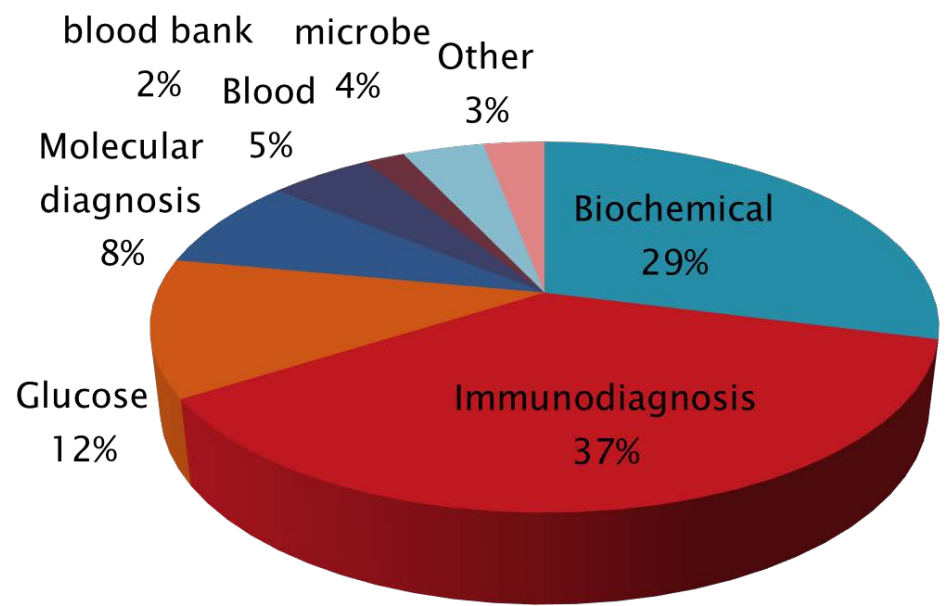
Molecular diagnosis

~20 items/year

~100-120 items (2016-2020)

~ 75% product standards

~ 25% management standards





### 3. Future Demands and Tendency

# IVD Quality Assurance - CRMs

## □ Fundamental Research

- Primary methods
- Biosimilar
- Commutability

## □ CRM production (including pure CRM and Serum matrix CRMs)

- Critical disease biomarker CRMs,  
such as tumor, cardio-cerebrovascular disease and

diabetes.





### 3. Future Demands and Tendency

## IVD Quality Assurance – Verification and Calibration

#### □ Verifications

- Biochemical diagnosis devices, eg. Automatic biochemistry analyzer;

#### □ Calibration Specifications

- Immunodiagnosis devices, eg. Micro plate chemiluminescence analyzer;

- Cytodiagnosis devices, eg. Urinary sediment analyzer.







# 3. Future Demands and Tendency

## IVD Quality Assurance – Standards & CRMs

~600 Clinical inspection items by WS/T 102-1998

~120 Products Standards By the end of 2014	~100-120 new Standards in the next 5 years	Gap of document standards!	
~50 Clinical CRMs By the end of 2014	~50 Clinical CRMs In the next 5 years	~100-120 New Gap of Clinical CRMs To support IVD standards!	Gap of total clinical CRMs

A long way to go!





*Thank you for your Attention!*

