The importance and challenges of establishing reference measurement laboratories in IVD manufacturers

Marek Witkowski, MBA
Country Manager Poland

CONTENTS

01

PART ONE

What is RML?

What is RML?

Reference Measurement Laboratory (RML): Laboratory that performs a reference measurement procedure and provides results with stated uncertainties. (ISO 15195:2003)

It is a special type of calibration laboratory. RML intends to accurately measure the biomarkers in clinical samples and thus calibrate the IVD-MD.

The **CRM**, **RMP**, and **RML** form a complete **RMS**, which is the basis for standardization.

RMP
(Reference Measurement Procedure)

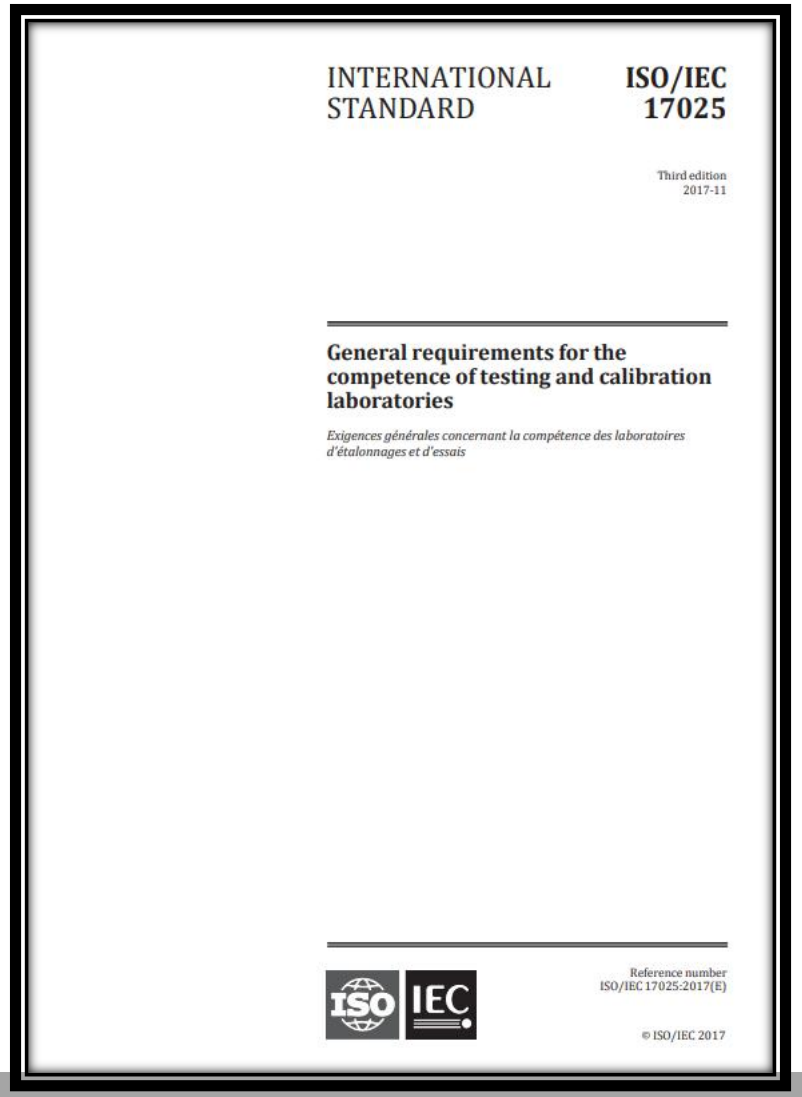
CRM
(Certified Reference Materials)

RML
(Reference Measurement Laboratory)

RMS
(Reference Measurement System)

What is RML?

The RML should be established with a quality management system per specific ISO standards.



INTERNATIONAL STANDARD

ISO/IEC 17025

Third edition
2017-11

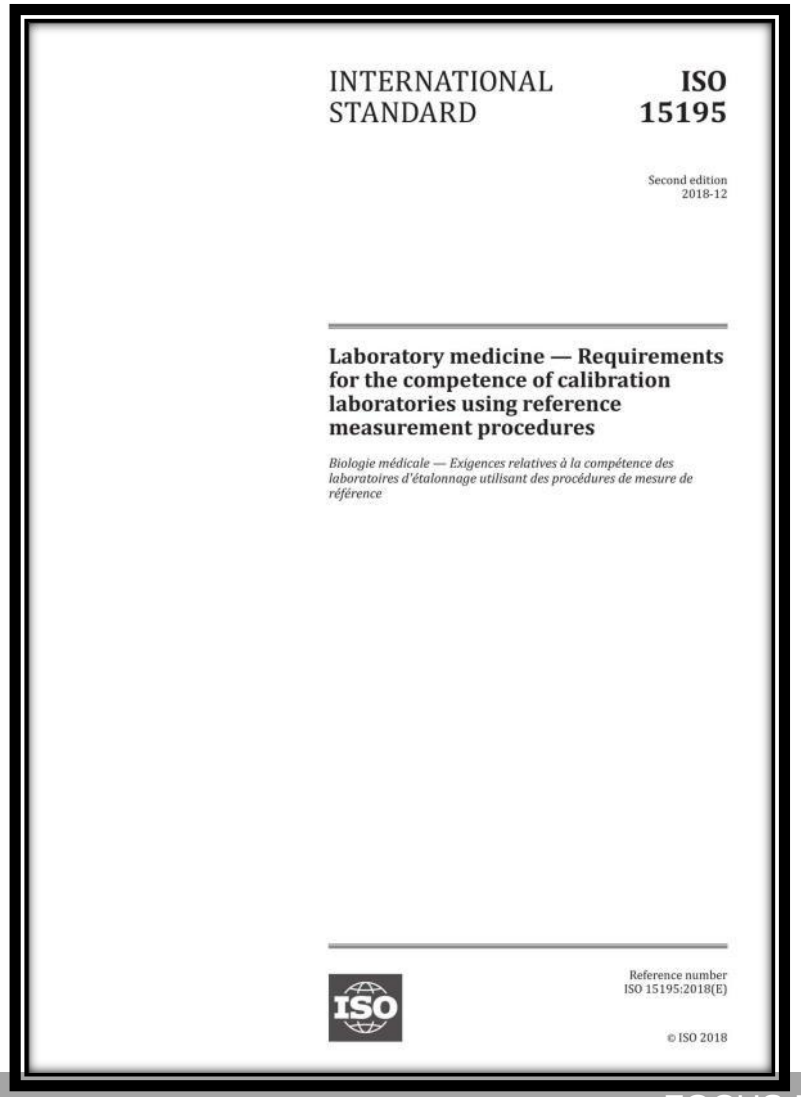
General requirements for the competence of testing and calibration laboratories

Exigences générales concernant la compétence des laboratoires d'étalonnages et d'essais

ISO IEC

Reference number
ISO/IEC 17025:2017(E)

© ISO/IEC 2017



INTERNATIONAL STANDARD

ISO 15195

Second edition
2018-12

Laboratory medicine — Requirements for the competence of calibration laboratories using reference measurement procedures

Biologie médicale — Exigences relatives à la compétence des laboratoires d'étalonnage utilisant des procédures de mesure de référence

ISO

Reference number
ISO 15195:2018(E)

© ISO 2018

02

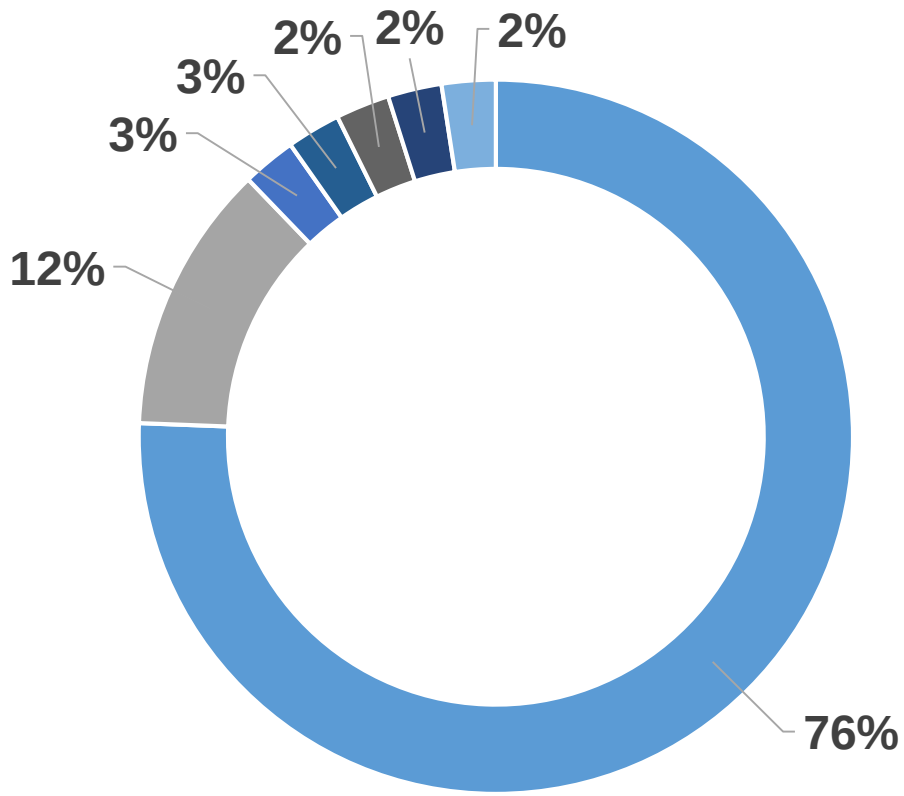
PART TWO

Status quo

Status quo

When establishing an RML, the validity of its QMS should seek to be accredited by authoritative accreditation bodies.

Up to October 2024, 41 RMLs have been accredited in the main countries where China has the most.



China

UK

Germany

Japan

USA

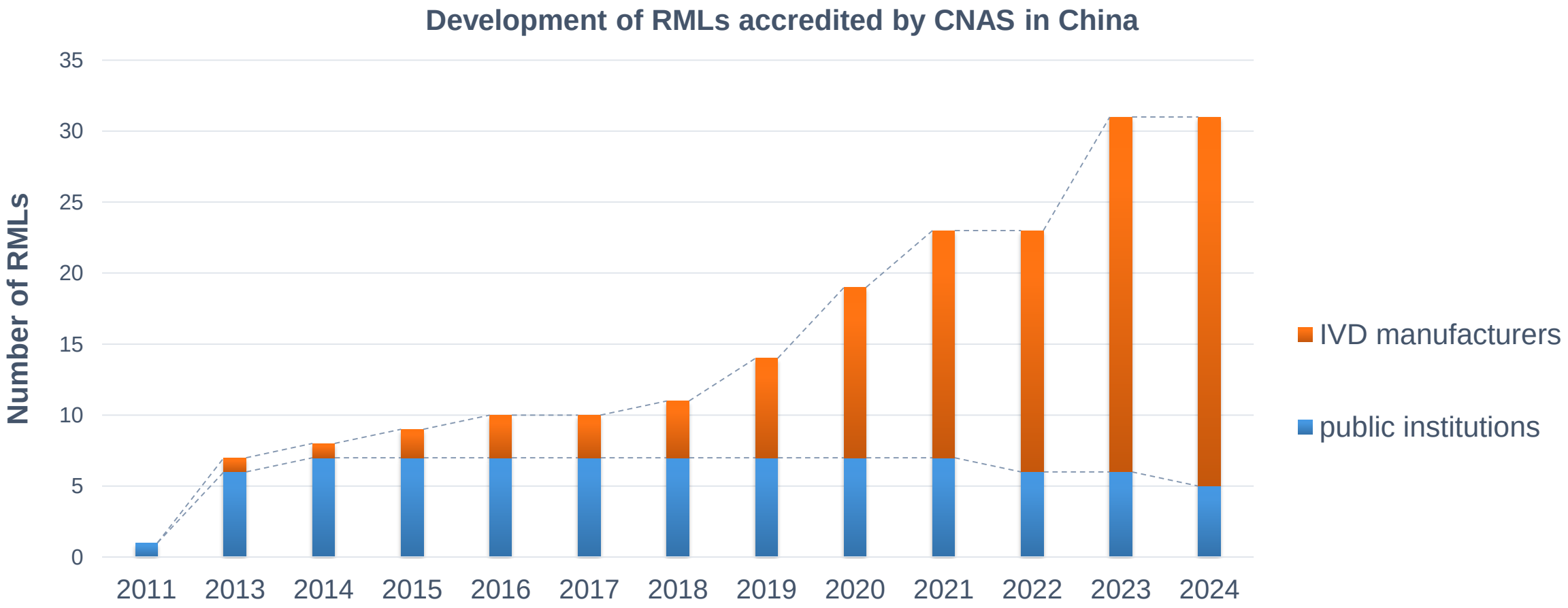
Belgium

France

Data collected from accreditation bodies' database on 2024.10

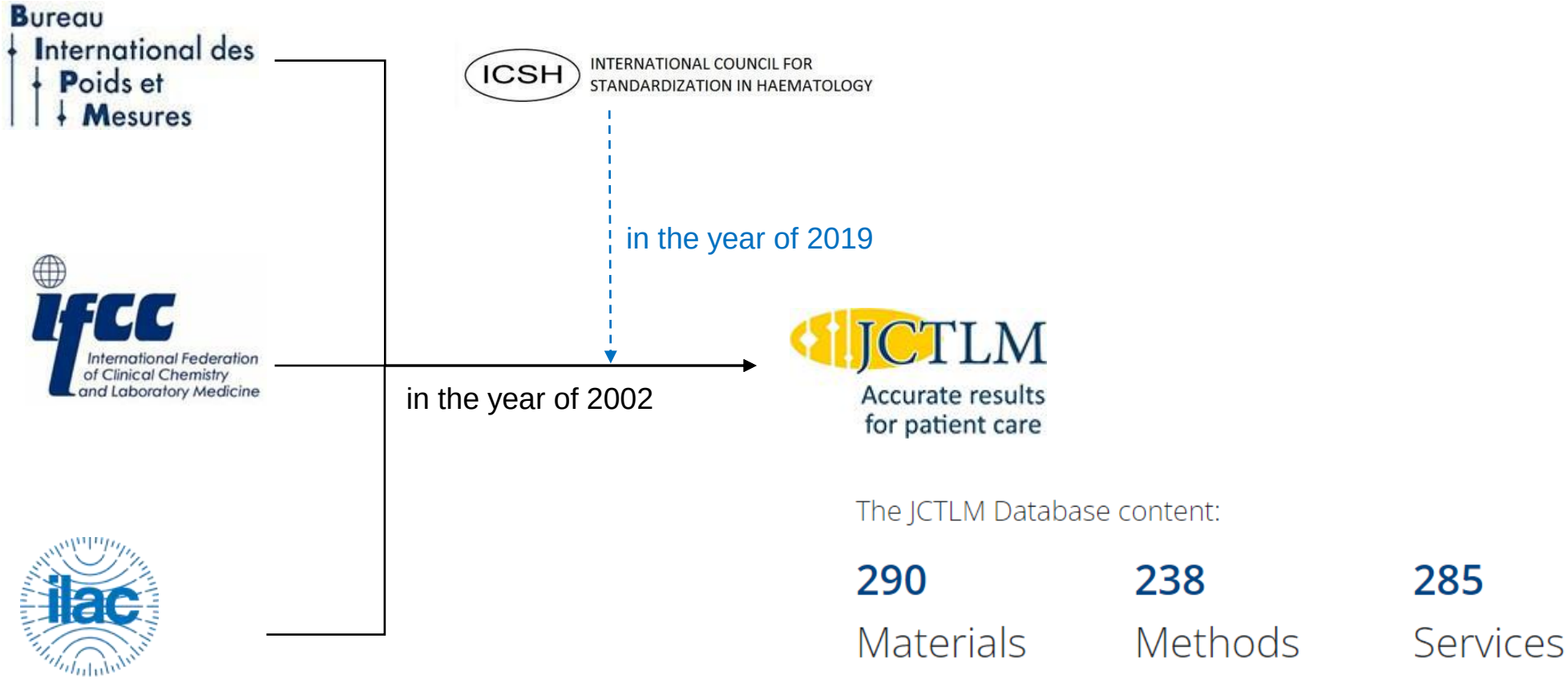
Status quo

In China, the RMLs have grown quickly in recent years. Most of them are established by IVD manufacturers.



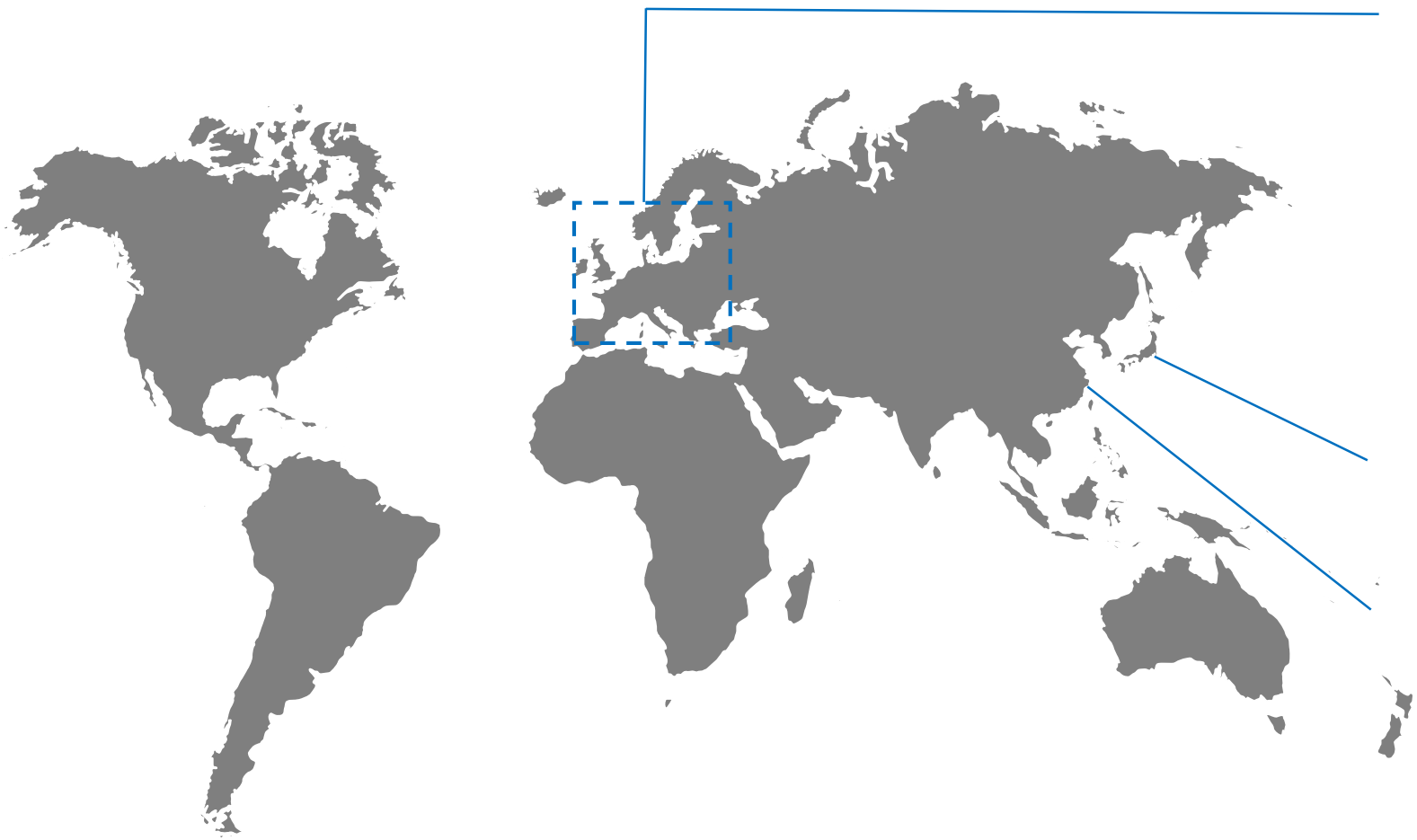
Status quo

The JCTLM was established in 2002 through a declaration of cooperation between BIPM, IFCC, and ILAC. Since its founding, the role of the JCTLM has expanded to become a global resource for implementing metrological traceability in laboratory medicine.



Status quo

RMLs can apply to be listed in the JCTLM database after being accredited by domestic accreditation bodies, and offer reference measurement services globally.



Germany (5): INSTAND, SPMD-Rfb, Roche…

Belgium (1): Ugent-Ref4U

France (1): LNE

United Kingdom (1): WEQAS

Japan (1): ReCCs

China (19): NCCL, SCCL, GPHCM, Snibe,…

Data collected from JCTLM database on 2024.06

03

PART THREE

The vital role of RML

The vital role of RML

Have you ever met the following problems in your routine work?

- The test results from different commercial reagents are discrepant even though they declare the same traceability.
- Lot-to-lot differences were often observed in some manufacturers' products.

Incorrect traceability methods!

Bad quality control !

Non-commutable CRMs!

There's little can be done by end-users. And the best way to solve these problems is:

BUY GOOD PRODUCTS!

For IVD manufacturers, how to produce such GOOD PRODUCTS? The best way is:

SET UP A REFERENCE MEASUREMENT LABORATORY!

The vital role of RML

With RML, the manufacturers can

- **Establish traceability chains correctly**

  Traceable to SI unit and achieve mutual recognition of results

  Correction of bias caused by non-commutability of CRM during calibration

- **Improve products' quality**

  Help recognize defects regarding specificity during IVD MD development

  Help inspect the quality of different lots of raw materials and reagents

- **Meet requirements of IVD MD regulations**

  Traceability implementation and declaration are required in many regional regulations around the world

Value transfer ↓ ↑ Traceable to

RML

Establish traceability chain by ISO 17511

Value transfer ↓ ↑ Traceable to

Clinical test results

How to establish a traceability chain for IVD-MD

What an RML usually does in-house

Measurement Procedure (mp.)

mp.1
Fit for purpose mp(s), e.g. qNMR

mp.2
Primary RMP

mp.3
RMP-ISO 15193 conforming

mp.4
Manufacturers selected MP

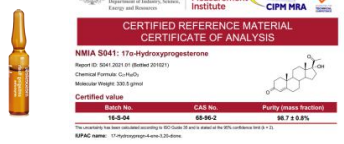
mp.5
Manufacturers standing MP

mp.6
End-users IVD-MD

uncertainty

Material (m.)

m.1
CRM-ISO 15194 conforming



m.2
Primary calibrator-prepared as solution m.1 in suitable solvent

m.3
Secondary, commutable CRM, or pooled human blood

m.4
Manufacturers working calibrator

m.5
Product calibrators for end-user IVD

m.6
Human sample with result

ISO 17511 1st calibration hierarchy

The vital role of RML

Other benefits:

Promote technological innovation

- Develop new methodology to improve test accuracy

Academic collaborations

- Assist and take part in standardization projects
- Joint development of candidate reference measurement procedures
- Contribution to the writing and revision of International standards

Follow the trend of precision medicine

- Accurate and consistent results can help doctors better diagnose and follow up on the efficacy of treatment

Spread influence

- Consistent accurate and comparable results will convince the end-users. This is especially important for transnational companies.

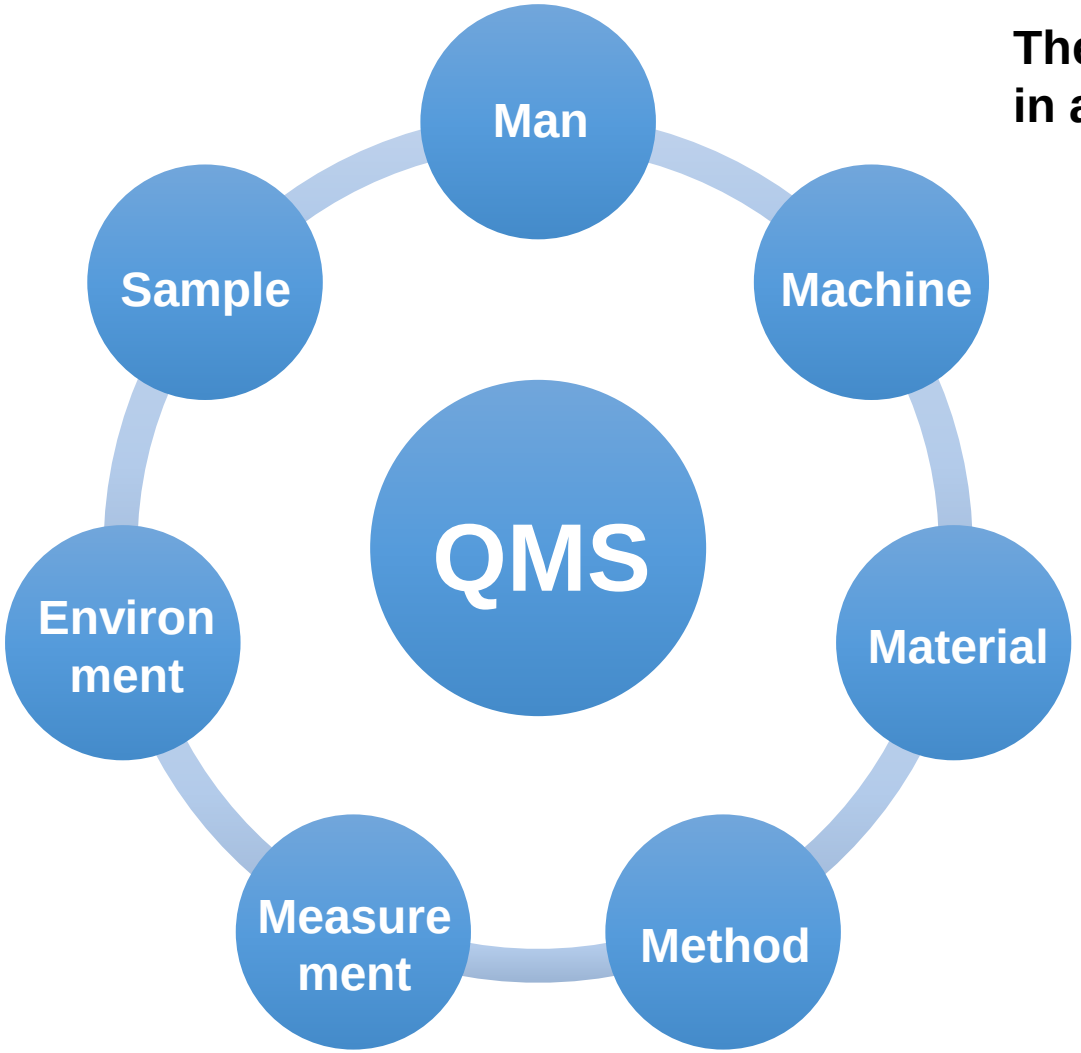
04

PART FOUR

Challenges

Challenges

Despite so many benefits, it's not easy to set up an RML.



The Quality Management System of RML shall be established in accordance with ISO/IEC 17025 and ISO 15195.

QMS elements: 5M1E+1S

Man — personnel requirements

Machine— equipment selection, calibration and maintenance

Material — CRM, reagents, consumables

Method — reference measurement procedure

Measurement — process requirement

Environment — facilities and environmental conditions

Sample — handling of samples

Challenges

You will need:

Well-trained professionals

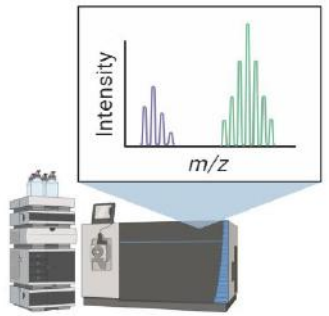
+

Expensive CRMs

+

RMPs

+



Expensive measurement instruments

+

Strict environment control

+

Valid calibration of devices

+

Rigorous sample management

and

Continuous running
Participating PT/EQA

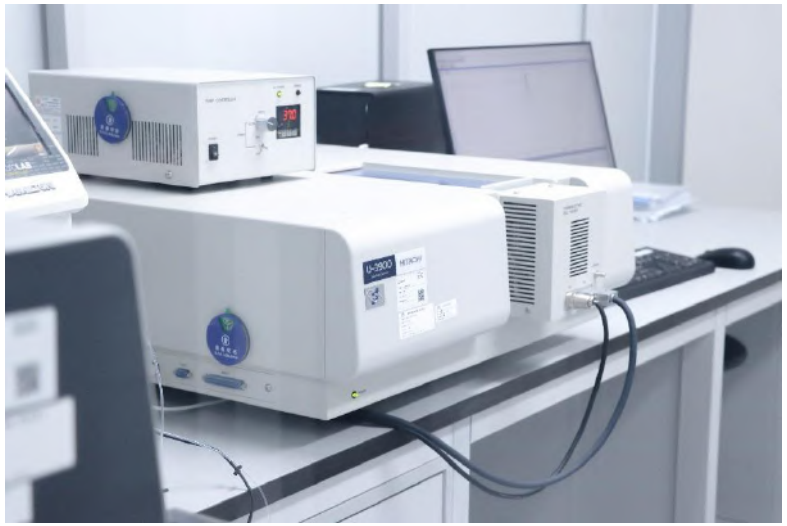
High cost, but little direct economic output! Wise man sees underlying values!

05

PART FIVE

Introduction of Snibe RML

Introduction of Snibe RML



Introduction of Snibe RML

ID-LC-MS/MS

- 25(OH)D
- 17α-OHP
- ALD
- Estradiol
- Progesterone
- Testosterone
- T3
- T4
- FT4
- Folic acid
- Tacrolimus
- Cyclosporine
- Everolimus
- Sirolimus
- ……

Reference Measurement Platform

UV-VIS

- ALT
- α-AMY
- γ-GGT
- ALP
- AST
- LDH
- CK

Thanks

FOCUS MAKES PROFESSION