應用測量科學提升中藥的安全和品質
Enhancing the safety and quality of Chinese medicines by measurement science

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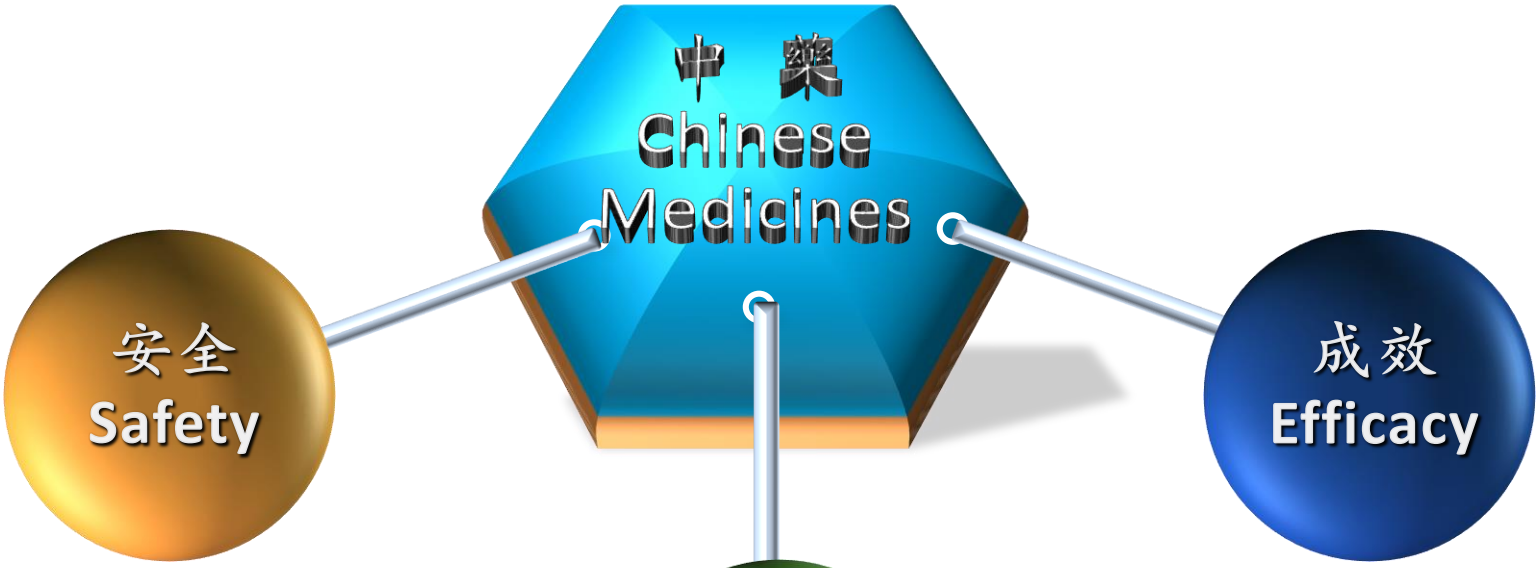
討論的課題 Topics to be Discussed

- 中醫藥現代化的課題
  Issues for Modernisation of Chinese Medicines
- 化學及生物計量學
  Metrology in Chemistry and Biology (MiC)
- 能力驗證計劃（包括指定值）
  Proficiency Testing Programmes (with Assigned Values)
- 有證標準物質
  Certified Reference Materials
- 技術轉移（標準/參考方法）
  Technology Transfer (Standard / Reference Methods)

中 藥 現 代 化
Modernization of Chinese Medicines



- 重金屬/有毒元素
  Heavy Metals/ Toxic Elements
- 農藥殘留
  Pesticide Residues
- 黃曲霉毒素
  Aflatoxins
- 西藥攙雜
  Western Drugs Adulteration
- 中藥中毒個案
  Intoxication cases
  - 替代/攙雜Substitutions/adulteration
  - 炮製不當
    Improper Processing

- 真僞鑑定 Authentication
- 含量測定 Assay
- 化學指標物 Chemical Markers
- 脱氧核糖核酸指紋圖譜
  DNA fingerprinting

- 處方製劑
  Prescription formulation
- 藥效學研究
  Pharmacodynamic studies
- 藥理研究
  Pharmacological studies
- 臨床試驗
  Clinical trial

中　藥　測　試

Chinese Medicines Testing

實現可靠和可追溯的測量
Achieving reliable and traceable measurements

- 制定可靠的方法 Develop reliable methods
  - 適合用途、正確有效的方法 Fit for purpose, properly ***validated methods***
- 使用適當的設施和資源 Use appropriate facilities and resources
  - 工作間、設備/儀器和試劑 Work areas, equipment/instruments and reagents
  - 可溯源校準標準物 ***Traceable calibration standards / reference materials***
- 僱用合格的員工 Employ competent staff
- 建立質量體系 Establish a quality system
  - 常規質量控制、記錄和審計Regular QC, documentation and audits
- 獲取外部審核 Obtain external verification
  - 認可及能力驗證 Accreditation and ***proficiency testing***

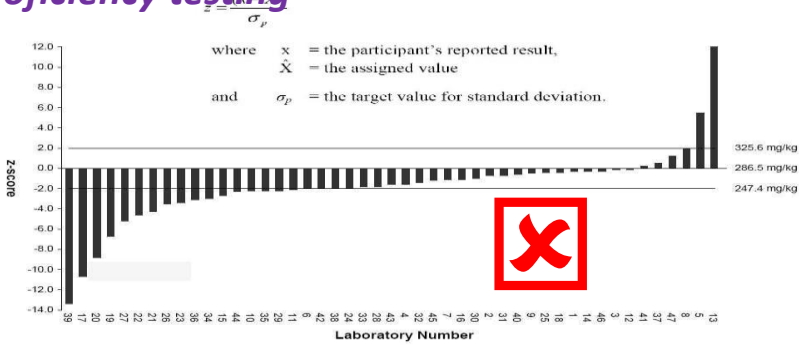
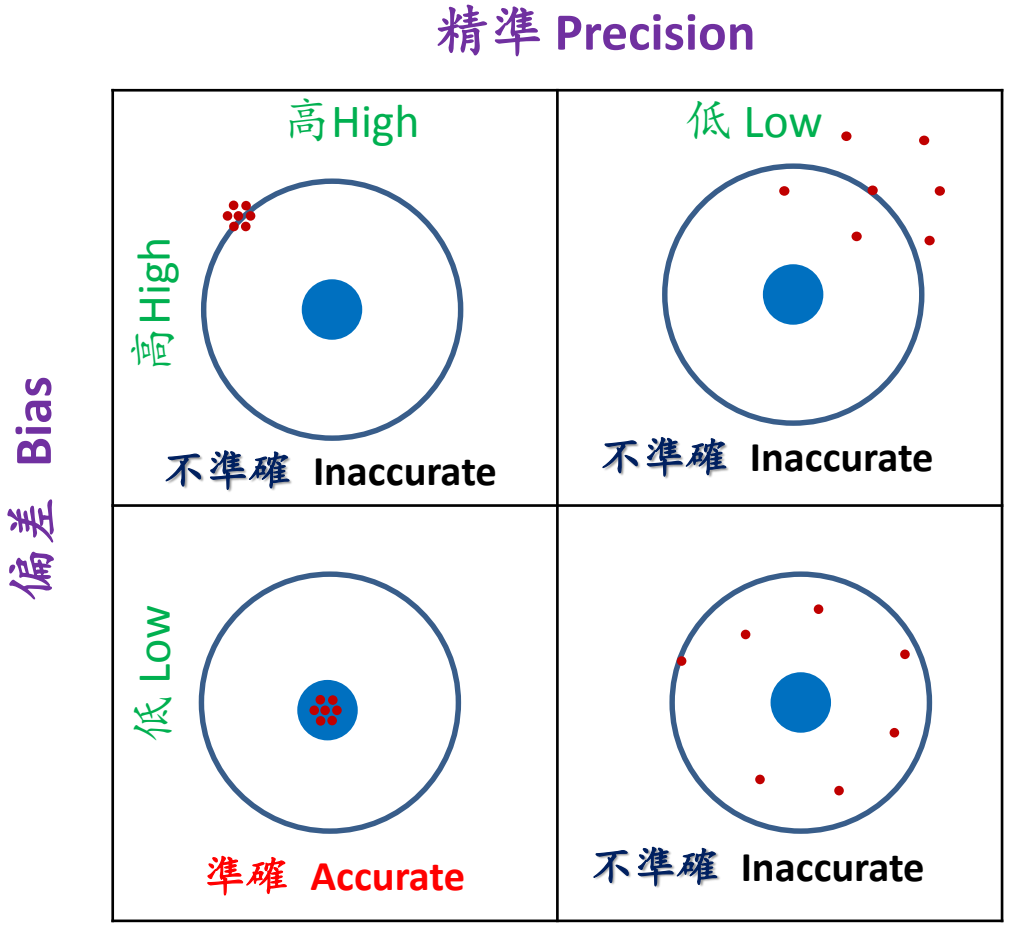


Figure 1: z-Scores for Tin (286.5 mg/kg) in Tomato Purée Test Material (using 'reference value')

準確度 Accuracy



Source: Standard Methods for Examination of Water and Wastewater, American Public Heath Association

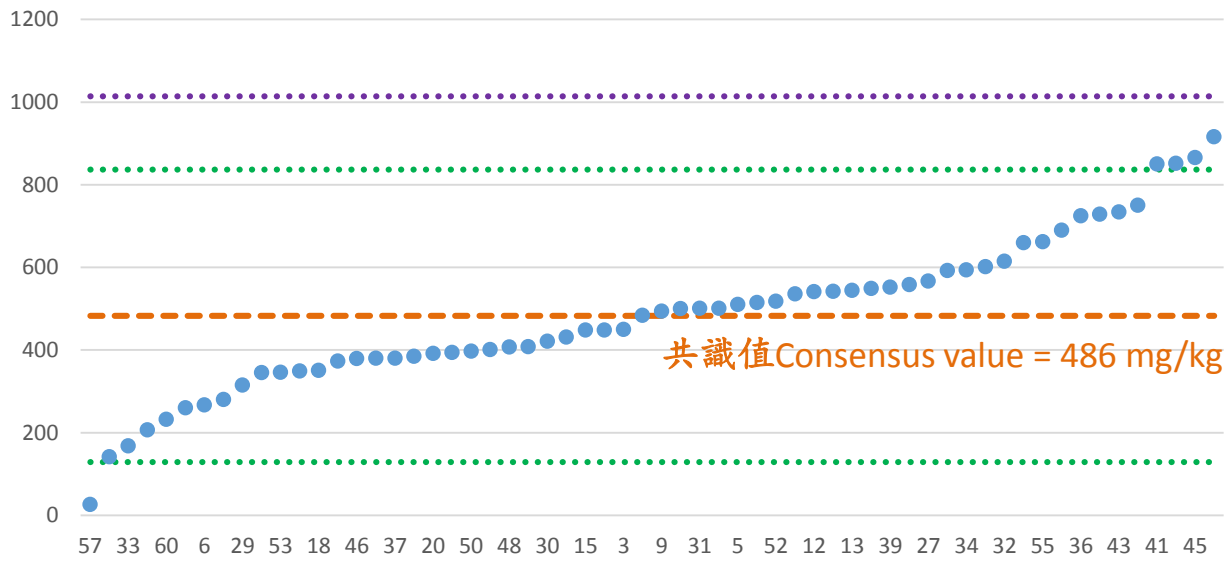
亞太實驗室認可合作組織 – 能力驗證計劃 (APLAC T081)

Asia Pacific Laboratory Accreditation Cooperation – Proficiency Testing Programme

茶葉中有機氯農藥 Organochlorine Pesticides in Tea

(參加的實驗室 participating laboratories : >60)

貝塔硫丹 Beta-endosulfan



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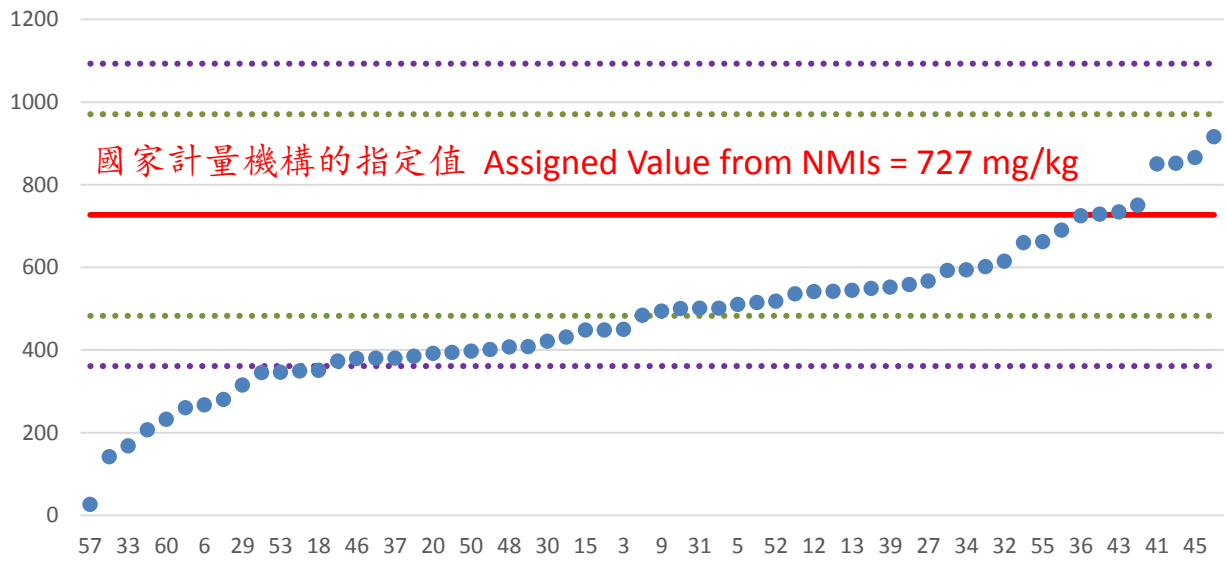

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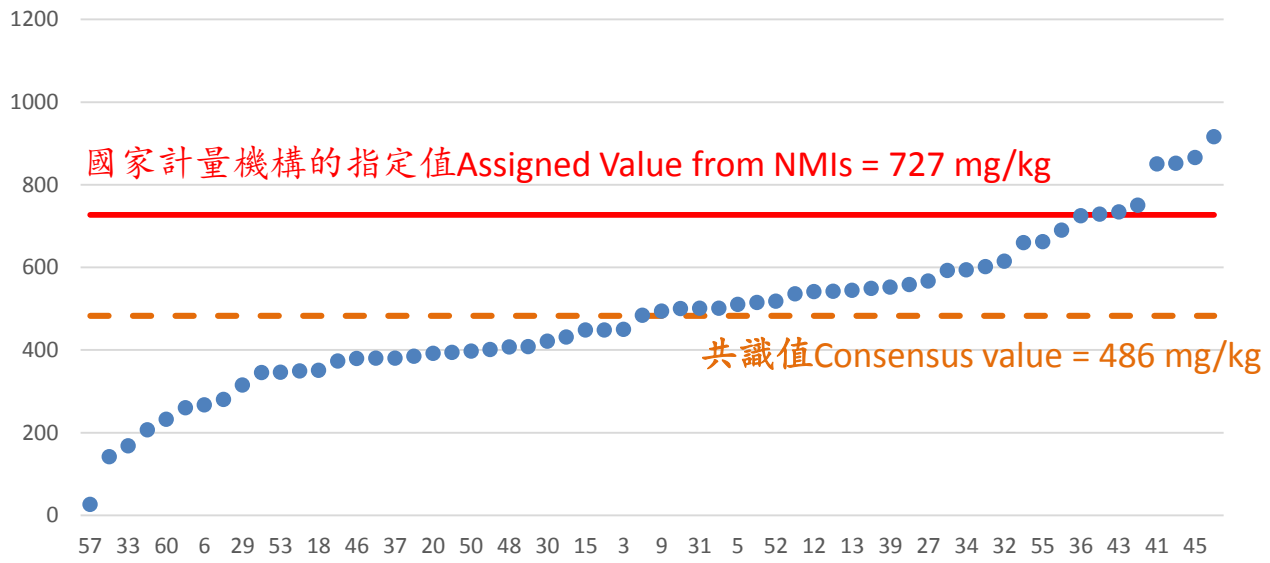


評級變化 Changes in ratings

根據共識值評級 Rating to Consensus Value	根據指定值評級 Rating to Reference Value	受影響驗室數目 No. of Labs affected	百分比 Percent
“合格Acceptable” →	“不合格Unacceptable”	24	40
“不合格Unacceptable” →	“合格Acceptable”	0	0
“合格Acceptable” ↔ “不合格Unacceptable” ↔	“合格Acceptable” “不合格Unacceptable”	36	60

化學與生物計量的工作
Metrology in Chemistry & Biology (MiC) Activities

化 學 及 生 物 計 量 學
Metrology in Chemical and Biology (MiC)

- 計量學是一門研究測量以及其應用的科學
  Metrology is the science of measurement and its application

- 化學及生物計量主要研究 metrology in Chemistry focuses on：
  - 化學及生物測量的可比較性和溯源性study of comparability and traceability of chemical measurements
  - 確保測量數據的可靠性to ensure the reliability of results

- 提供必須的技術基礎 to provide a technical foundation
  - 建立全球測試數據的互認 establishing global mutual recognition of analytical results
  - 利於國際間商貿和監管活動 wider agreements related to international trade, commerce and regulatory issues

- 可比較性和溯源性一般可透過參與以下的比對計劃去建立 Comparability and metrological traceability are normally established through participation in inter-comparisons organized by：
  - 地區計量組織 Local：亞太計量規劃組織 Asia Pacific Metrology Programme (APMP)
  - 國際計量組織 International： 國際計量局 the International Bureau of Weights and Measures (BIPM)

政府化驗所在化學及生物計量的里程碑

Milestones of GL in the field of Metrology in Chemistry & Biology

Mar 1993

國際分析化學溯源合作組織創始成員

Founding member of Co-Operation on International Traceability in Analytical Chemistry (CITAC)

Nov 2004

亞太計量規劃組織正式成員

Full member of Asia Pacific Metrology Programme (APMP)

May 2005

國際計量委員會互認協議特派計量機構

Designated Metrology Institute under CIPM MRA

Aug 2006

認可能力驗證提供者

Accredited Proficiency Testing Provider

Dec 2008

完成第一次同行評審

First peer review

Sep 2009

認可能力驗證提供者

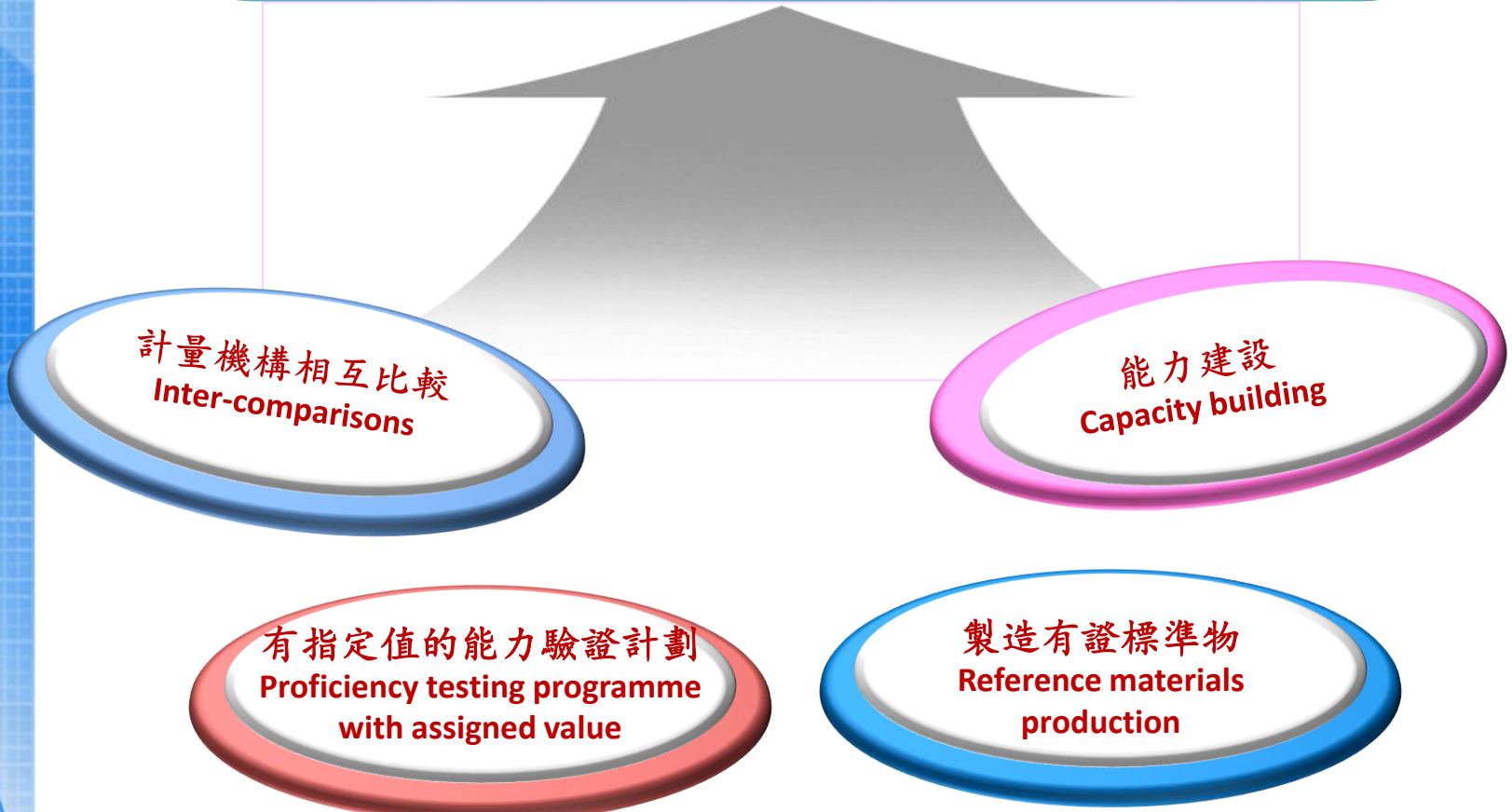
Accredited Proficiency Testing Provider

Nov 2010

認可參考物質生產者

Accredited Reference Material Producer

化 學 與 生 物 計 量
Metrology in Chemistry and Biology (MiC)



測 量 校 準 能 力
Calibration and Measurement Capabilities (CMCs)

- 在國際間公認為計量機構所能擁有最好的檢測能力
  internationally recognized as the best measurement capability that a metrology institute could possess
- 在國際計量組織舉辦的關鍵比對中得到滿意成績
  With support of the results obtained from key comparisons organized by international metrology organizations
- 計量機構可透過以下途徑把有關測試的溯源性傳向客戶：
  NMI/DI can disseminate traceability to its customers through services such as:

  1. 提供校準或參考值 provision of calibrations or reference value

  2. 提供有證標準物質 provision of certified reference materials (CRMs)
- 政府化驗所共取得39項測量校準能力聲明 (截至2015年的1月)
  totally 39 CMC claims have been approved (as at Jan 2015)
  - 包括高純度化學品、無機溶液、水、pH值、聚合物和塑料、生物流體和材料、食品和土壤
    covering High Purity Chemicals, Inorganic Solutions, Water, pH, Polymers and Plastics, Biological Fluid and Materials, Food, and Soil.

有指定值的能力驗證計劃

Proficiency Testing Programmes with Assigned Values

能力驗證計劃的目的
Objectives of PT Prgrammes

- 評價實驗室能力的一個寶貴工具
  A valuable tool for the evaluation of the performance of testing laboratories

  - 協助參與實驗室證明他們的技術能力
    Assist participating laboratories in demonstrating technical competence

  - 查明問題和給機會自我改進
    Identify problems and opportunities for self-improvement

能力驗證提供者的認可範圍
Scope of Accreditation for Proficiency Testing Provider

中藥 Chinese Medicine	(a) 農藥殘留 Pesticide Residues (b) 重金屬及有毒元素 Heavy Metals and Toxic Elements
環境 Environmental	Sediment: Polynuclear Aromatic Hydrocarbon
食品 Food	(a) Elements (b) Malachite Green (c) Melamine (d) Organochlorine Pesticide Residues (e) Radionuclides: ^{131}I, ^{134}Cs and ^{137}Cs
法證 Forensic	Drugs in Biological Matrix

有關中藥的能力驗證
Chinese Medicines related PT

- 人參中的有機氯農藥 Organochlorine pesticides in ginseng root (APLAC T059)
- 茶葉中的有機氯農藥 Organochlorine pesticides in tea* (APLAC T081)
- 廣金錢草中的鎘和鉛 Cadmium & lead in *Herba Desmodii Styracifolii* 廣金錢草(APLAC T043)
- 墨旱蓮中的重金屬及有毒元素Heavy metal and toxic elements in *Ecliptae Herba* 墨旱蓮* (APLAC T065)

** 有指定值的能力驗證計劃 PT with assigned value*

國際/地區工作
International/Regional Activities

APMP PT 11-02 programme
- 參與實驗室participants: 17
- 完成日期 completed in : 2013

(來自發展中經濟體的專家實驗室 expert labs from developing economies)

APLAC T081 programme
- 參與實驗室participants: 65
- 完成日期 completed in : 2013

(一般實驗室 field labs)

Ref. values

國際計量機構
NMIs/DIs
worldwide

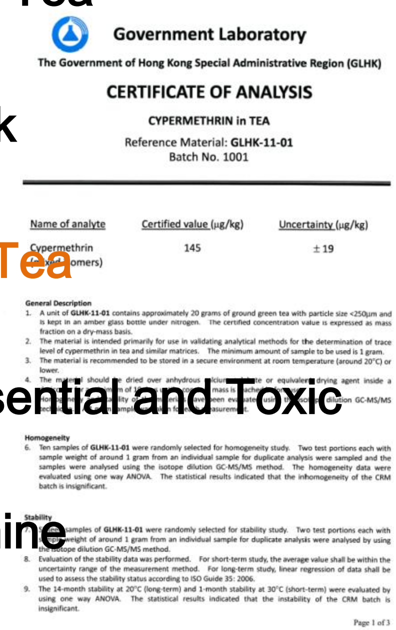
CCQM 重點比較
A CCQM Key Comparison
(CCQM K-95):
綠茶中的農藥
（β－內硫丹和硫丹硫酸鹽）
Pesticides
(beta-Endosulfan and Endosulfan Sulphate) in green tea

* CCQM: 物質量諮詢委員會 – 化學及生物計量
Consultative Committee for Amount of Substance - Metrology in Chemistry and Biology

有證標準物
Certified Reference Materials

政府化驗生產的有證標準物
Certified Reference Materials by GL

- GLHK-10-01: 廣金錢草中的鎘和鉛 Cadmium and Lead in Herb (*Herba Desmodii Styracifolii*)
- GLHK-10-02: 墨旱蓮中的微量和必需金屬元素Trace and Essential Elements in *Herba Ecliptae*
- GLHK-11-01: 茶葉中的氯氰菊酯 Cypermethrin in Tea
- GLHK-11-02: 牛奶中的三聚氰胺 Melamine in Milk
- GLHK-11-03: 茶葉中的有機氯農藥 Pesticides in Tea
- GLHK-11-04: 海產品中的必需/有毒金屬元素 Essential and Toxic Elements in Seafood
- GLHK-01-01: 高純度三聚氰胺 High Purity Melamine



Government Laboratory

The Government of Hong Kong Special Administrative Region (GLHK)

CERTIFICATE OF ANALYSIS

CYPERMETHRIN in TEA

Reference Material: **GLHK-11-01**

Batch No. 1001

Name of analyte	Certified value (µg/kg)	Uncertainty (µg/kg)
Cypermethrin ([illegible]omers)	145	± 19

General Description

1. A unit of **GLHK-11-01** contains approximately 20 grams of ground green tea with particle size <250µm and is kept in an amber glass bottle under nitrogen. The certified concentration value is expressed as mass fraction on a dry-mass basis.
2. The material is intended primarily for use in validating analytical methods for the determination of trace level of cypermethrin in tea and similar matrices. The minimum amount of sample to be used is 1 gram.
3. The material is recommended to be stored in a secure environment at room temperature (around 20°C) or lower.
4. The ma[illegible] should [illegible] dried over anhydrous [illegible]te or equivalen[illegible] drying agent inside a [illegible]
5. [illegible] dilution GC-MS/MS [illegible]

Homogeneity

6. Ten samples of **GLHK-11-01** were randomly selected for homogeneity study. Two test portions each with sample weight of around 1 gram from an individual sample for duplicate analysis were sampled and the samples were analysed using the isotope dilution GC-MS/MS method. The homogeneity data were evaluated using one way ANOVA. The statistical results indicated that the inhomogeneity of the CRM batch is insignificant.

Stability

7. [illegible] samples of **GLHK-11-01** were randomly selected for stability study. Two test portions each with [illegible] weight of around 1 gram from an individual sample for duplicate analysis were analysed by using the [illegible]otope dilution GC-MS/MS method.
8. Evaluation of the stability data was performed. For short-term study, the average value shall be within the uncertainty range of the measurement method. For long-term study, linear regression of data shall be used to assess the stability status according to ISO Guide 35: 2006.
9. The 14-month stability at 20°C (long-term) and 1-month stability at 30°C (short-term) were evaluated by using one way ANOVA. The statistical results indicated that the instability of the CRM batch is insignificant.

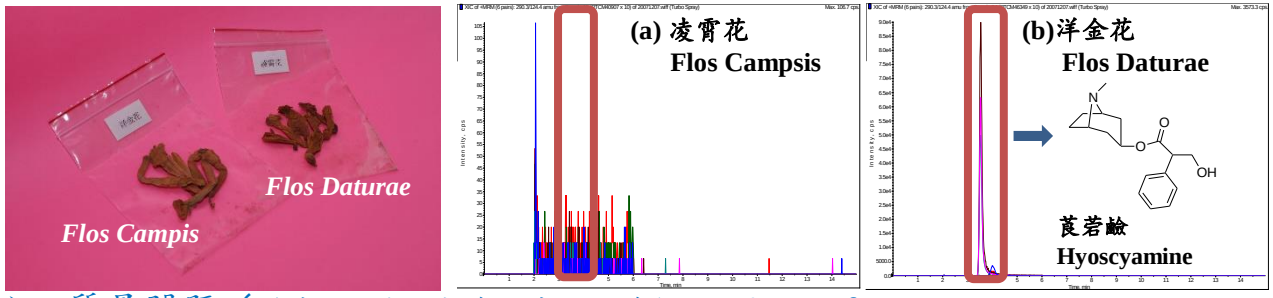
Page 1 of 3

中毒個案調查
Intoxication Investigation

◆ **藥物不良反應的可能原因 Possible causes of adverse drug reactions:**

- ➢ 錯誤替換（歸因於外觀類似）Erroneous Substitution (attributed to similar physical appearance)
  - 如有毒洋金花(茄屬生物鹼)替代凌霄花e.g. substitute Flos Campsis by toxic Flos Daturae → solanaceous alkaloids

LC-MS/MS 圖譜chromatograms of (a)凌霄花 Flos Campsis and (b)洋金花 Flos Daturae

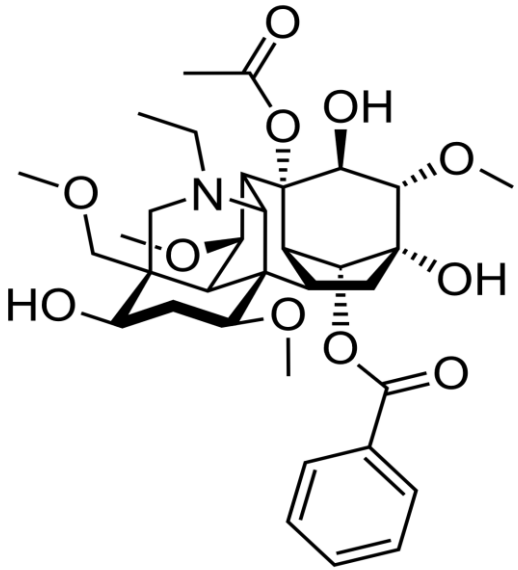


- ➢ 質量問題（對毒性/烈性中藥的處理不當）Quality Defect (attributed to improper processing of toxic/potent Chinese medicines)
  - 如附子/草烏/附子的炮製→烏頭類生物鹼 e.g. processing of aconite roots: *Radix Aconiti / Radix Aconiti Kusnezoffii / Radix Aconiti Lateralis Preparata* → aconitum alkaloids

- ➢ 濫用或過量（從業者或消費者的疏忽）Misuse or overdose (attributed to negligence of practitioners or consumers)

化學指標物
Chemical Markers

- 供應 Availability
- 純度 Purity
- 可溯性 Traceability



中 成 藥
Proprietary Chinese Medicines

◆註冊要求 Registration Requirements

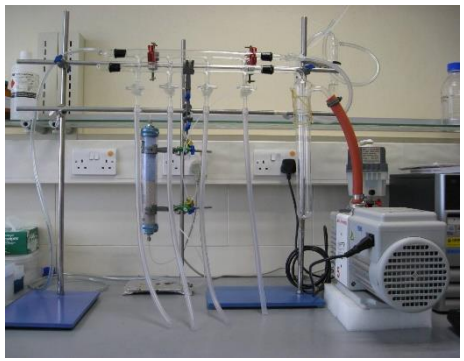
- 鑑定 **Identification**
- 含量分析 **Assay**
- 穩定性及其他質量控制
  Stability & other quality control

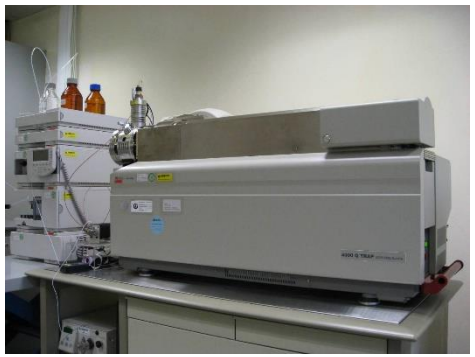
◆化學指標物 Chemical Markers

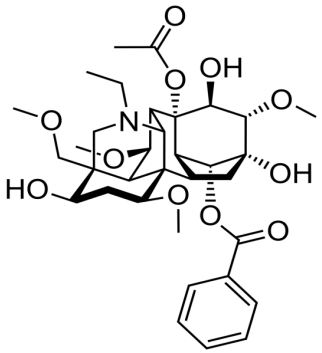
使用有證標準物質確保結果的有效性！
Use of Certified Reference Material to ensure the validity of result!

有證標準物質純度評估
Purity Assessment of CRM

參　數 Parameters	儀　器　技　術 Instrumental Techniques
(1)有機雜質 Organic Impurities	高效液相色譜 HPLC-UV, 液相質譜 LC-MS/MS
(2)無機雜質 Inorganic Impurities	電感耦合等離子體質譜 ICP-MS, 離子色譜 Ion Chromatography
(3)揮發性有機化合物 Volatile Organics	氣相質譜 GC-MS
(4) 水份 Moisture Content	氣相熱導檢測法 GC-TCD, 卡爾 – 費歇爾法 Karl-Fischer Coulometry





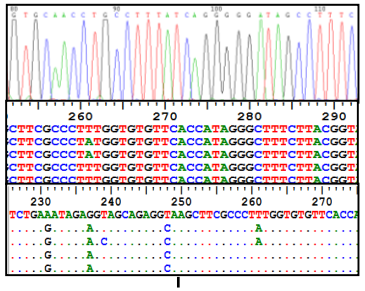


中藥材的DNA條形碼
DNA barcoding of Chinese medicines

DNA條形碼：利用一個標準基因組區域中的很短基因序列作為物種鑑定

DNA barcoding: use of a short gene sequence from a standardized region of the genome as a tool for species identification

樣品採集和製備 ***Sample collection and preparation*** → DNA提取 ***DNA extraction*** → 聚合酶鏈反應和電泳 ***PCR and electrophoresis*** → 排序 ***Sequencing*** → 數據分析 ***Data analysis***



DNA條形碼核 DNA Barcode Nuclear ITS2, *rbcL*, *matK* and *trnH-psbA*

經過身份驗證的樣本
Authenticated Samples

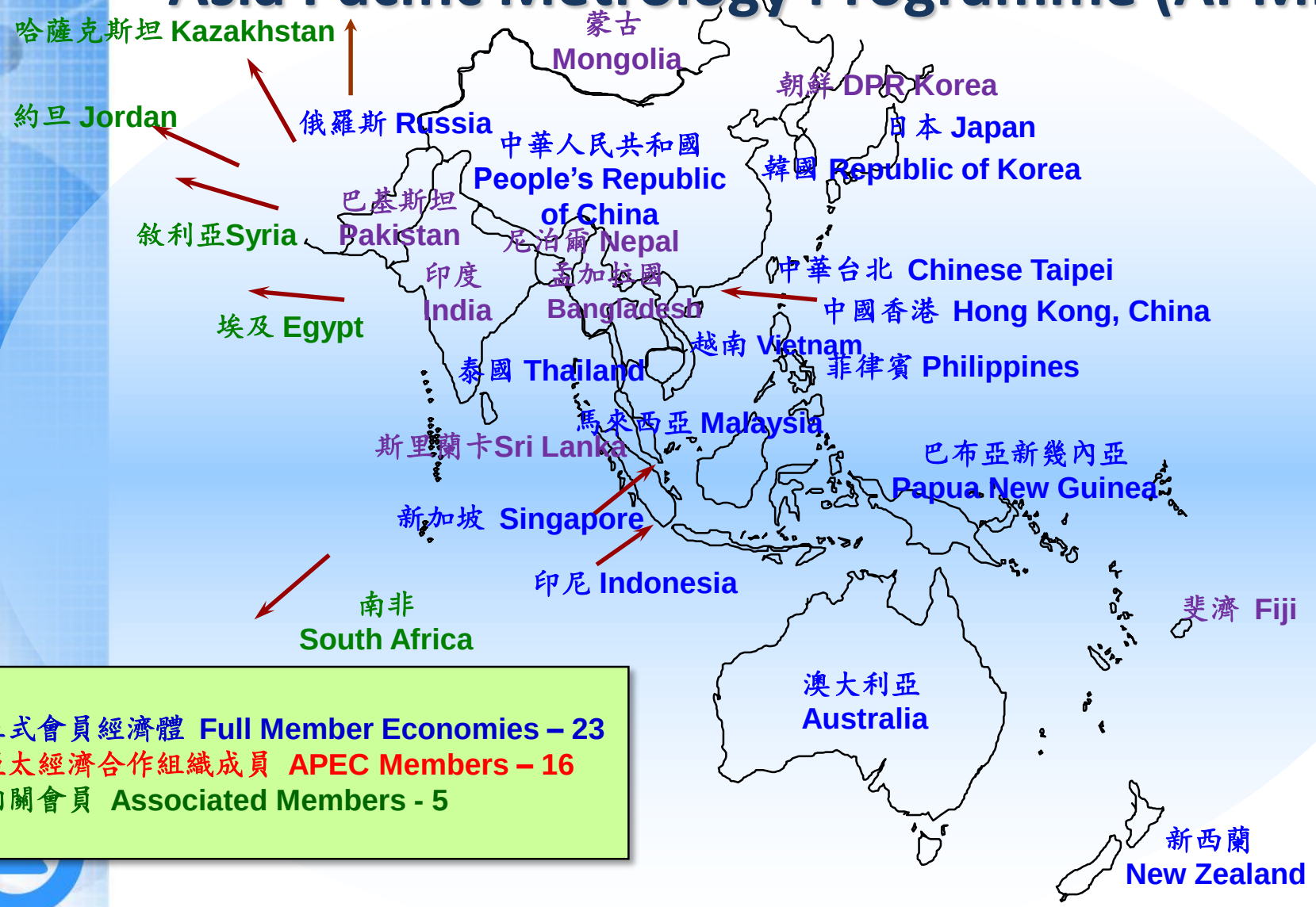
溯源 Traceability?

DNA條形碼序列數據庫
DNA barcode sequence database

CCTATACCTAATCTTCGGAGCATGAGCGGGCATGGTAGGC....

技術轉移 –建立實驗室測試能力
Technology Transfer
- laboratory capacity building

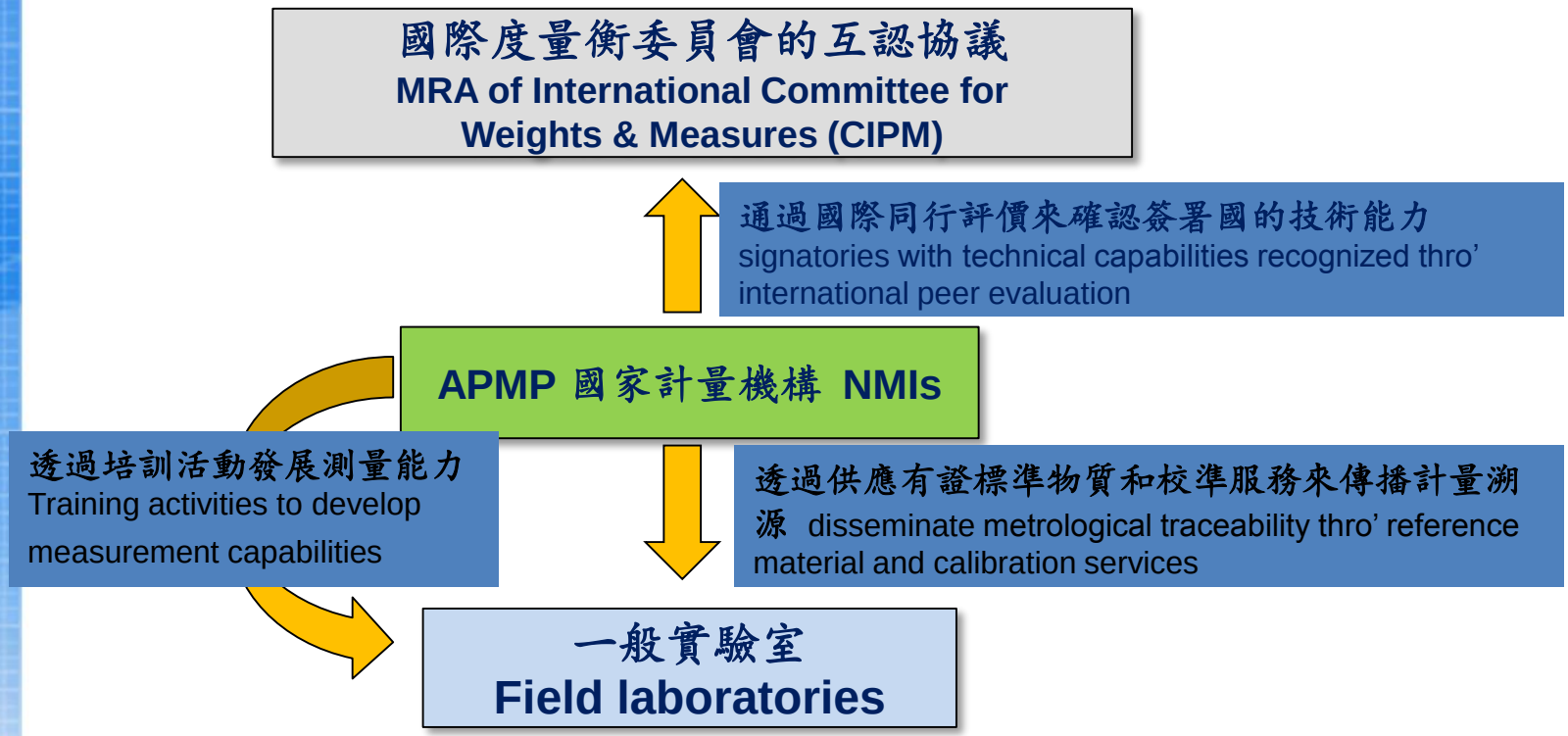
亞太計量規劃
Asia Pacific Metrology Programme (APMP)



正式會員經濟體 Full Member Economies – 23
亞太經濟合作組織成員 APEC Members – 16
相關會員 Associated Members - 5

亞太計量規劃組織
Asia Pacific Metrology Programme - APMP

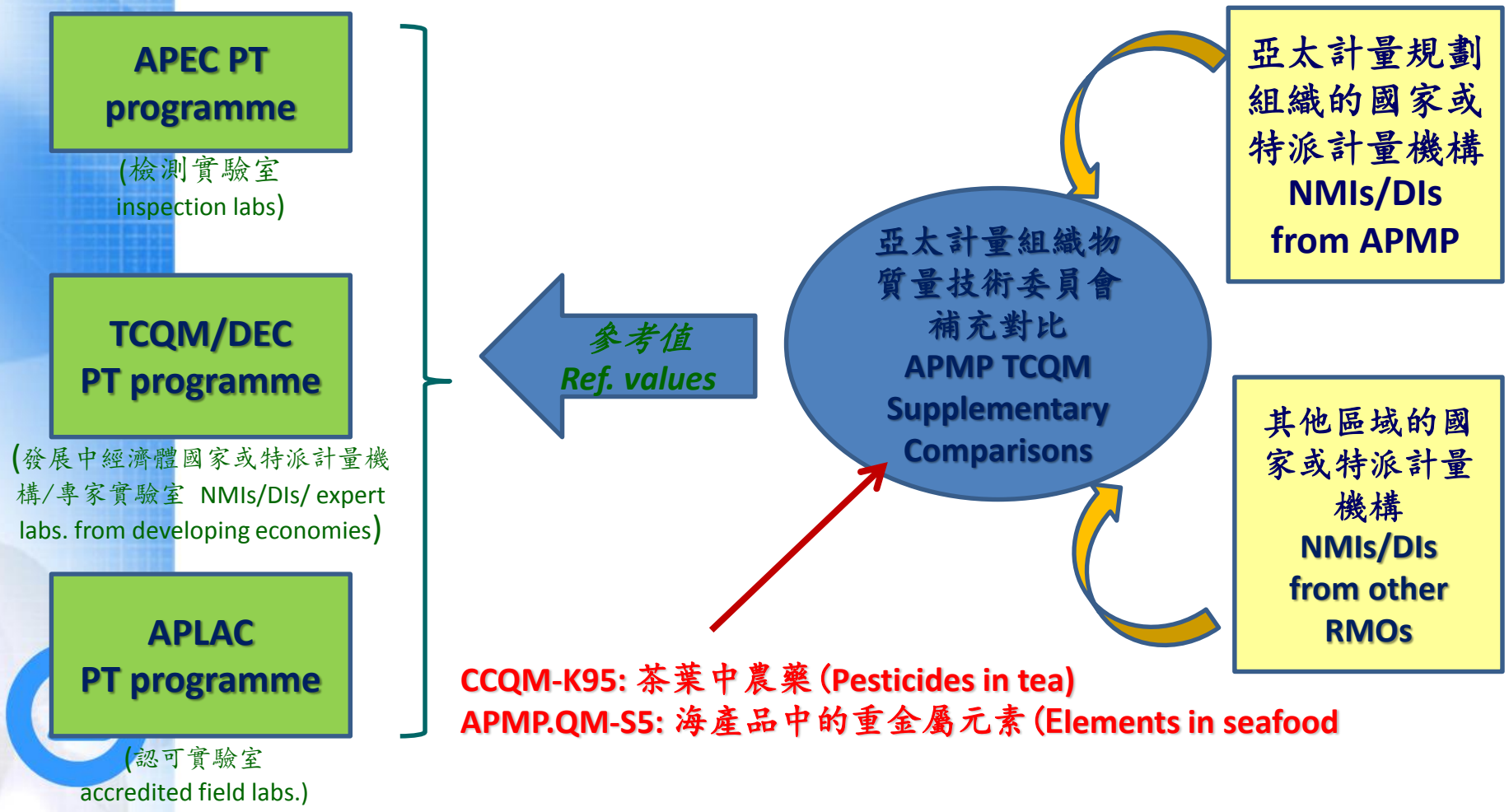
- 通過國家計量機構之間的合作，推動並建立一個區域測量基礎設施 To promote and support a measurement infrastructure in the region through collaboration between National Metrology Institutes (NMIs)



培訓師培訓計劃
Train-the-trainer programme

- 2010年9月，於馬來西亞舉行的分析方法驗證培訓課程
  Analytical Method Validation Training course held in Malaysia, Sep 2010
- 政府化驗所派出兩名導師
  Two instructors from GL
- 來自10個經濟體的21名專家參與該課程培訓
  21 participants from 10 economies

亞太計量規劃組織(APMP)物質量技術委員會(TCQM)/發展中經濟體委員會 (DEC)/亞太實驗室認可合作組織(APLAC)/亞太經合組織(APEC)聯合工作(Joint Activities)



謝謝
Thank You