



**Setting standards
In analytical science**



Certifying Reference Materials to ISO Guide 34

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Environmental Laboratory Quality Day

17 November 2011



Outline



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- LGC background
- Quality systems - ISO Guide 34 and associated guides
- The production process
- Example
- National and International links

LGC Background



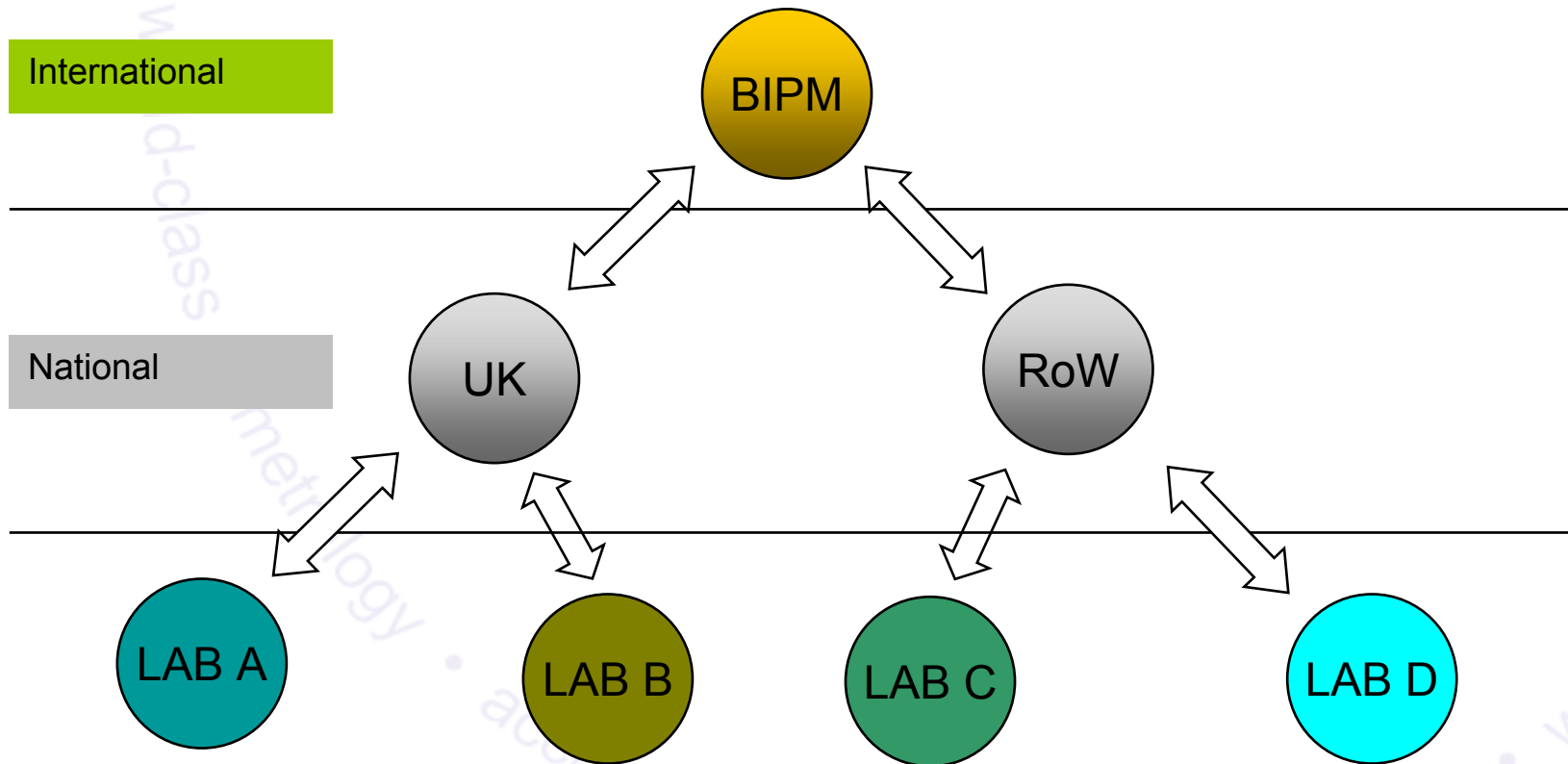
- LGC is the UK's National Measurement Institute (NMI) for Chemical and Bioanalytical measurements
- In this role, LGC develops valid procedures for the precise and accurate determination of key analytes
- Our competency in providing these services is regularly assessed by our participation in high level international inter-comparison studies

Background



- An important role is the dissemination of the traceability gained from these studies to practising analytical scientists in the UK
- This is carried out in many ways, including
 - peer reviewed publications
 - provision of reference values to PT schemes
 - provision of training courses
 - **characterisation of reference materials**

Traceability - providing a common reference point



Our catalogue



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- Single substance materials
 - Purity
 - Melting point
 - Enthalpy of fusion
 - Elemental content
- Matrix materials
 - Food
 - Environment
 - Clinical
 - Industry
 - Forensic

~150 materials

Pure RM production for more than 20
years

What do we make?



Material category:

- Certified reference materials
- Reference materials
- Quality control materials

Category depends on:

- Quality of the data
- Material type

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Identifying needs



- Information from many sources
 - Legislation
 - Analytical challenges
 - Requests from customers
 - Professional contacts

RM Manufacturers



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- Who makes reference materials?
 - National Measurement Institutes
 - Commercial suppliers
 - PT scheme providers
 - 'in house' materials
- What quality criteria are there for assessing the producer?
 - Accreditation

UKAS view



- UKAS policy:
 - Accredited testing and calibration laboratories **shall use**, where available and appropriate, **reference materials or calibrated artefacts** for the verification/validation of critical steps and processes in their methods
 - Laboratories shall ensure that reference materials they purchase are obtained from a **competent producer** of reference materials
- **UKAS recommends the use of accredited reference material producers and calibration laboratories where they exist**



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Quality systems – ISO Guide 34 and related Guides

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metrology • accuracy

accuracy • innovation

innovation • accuracy

accuracy • world-r'

world-r'

RM Production Accreditation



ILAC resolutions (2004):

- **ILAC GA 8.11**
 - *The GA acknowledges that **assessing the technical competence of bodies producing RMs with assigned values is accreditation of a conformity assessment activity.***
- **ILAC GA 8.12**
 - *The GA resolves that **accreditation of technically competent bodies producing RMs with assigned values will be conducted against harmonised criteria based on ISO Guide 34 and ISO/IEC 17025 in combination.***

ISO Guide 34 and ISO/IEC 17025



ISO Guide 34

- Quality system requirements for RM production
 - Organisational requirements
 - Production control

RM production control

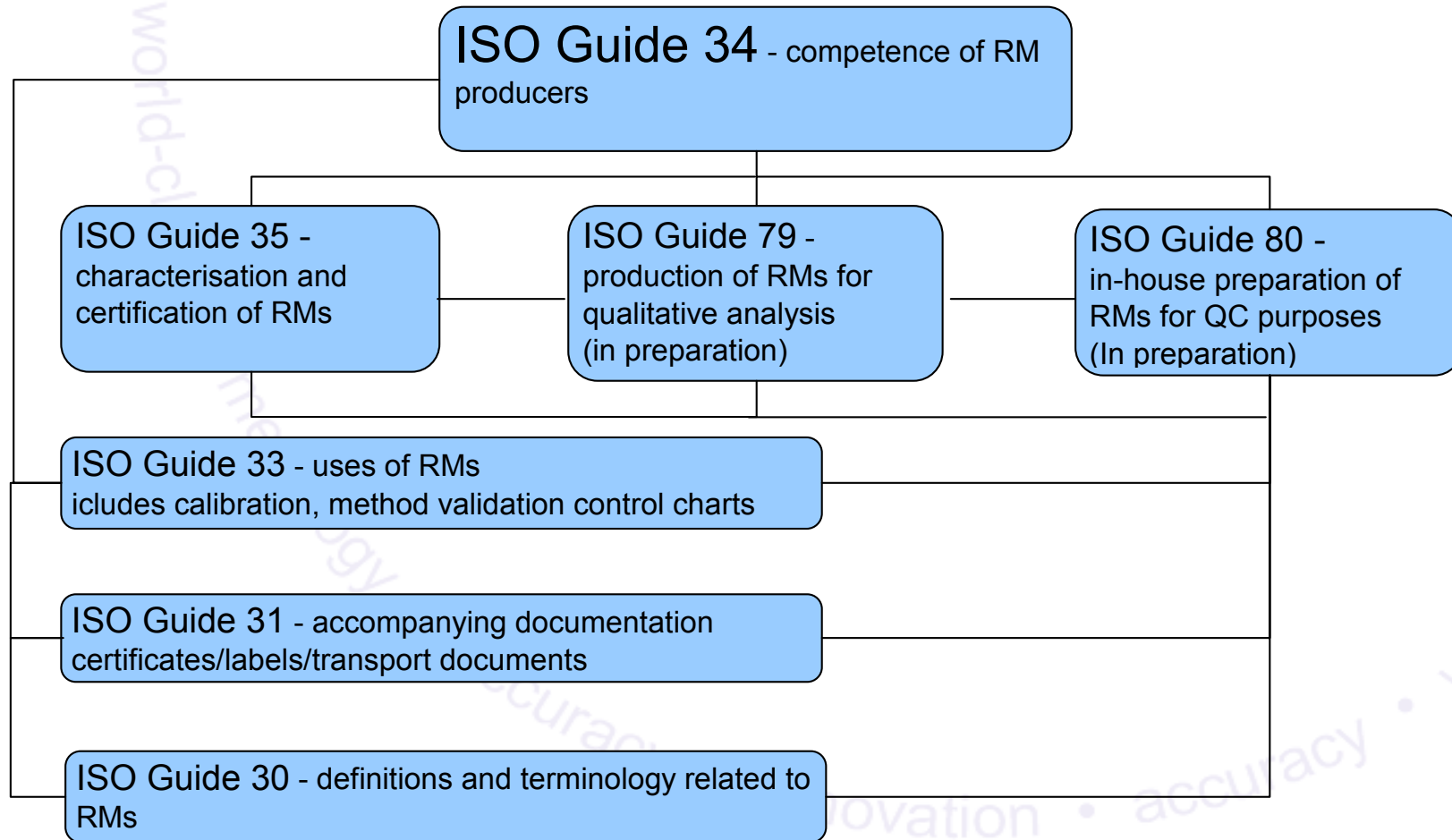
ISO/IEC 17025

- Specifies requirements for competence to carry out tests and calibrations using standard methods, non standard methods and laboratory developed methods
 - Management requirements
 - Technical requirements

Measurement systems control

Significant overlap between ISO Guide 34, ISO/IEC 17025 and ISO 9001 (Quality management systems – Requirements)

The ISO Guides relating to reference materials



LGC Reference Material Production



- Accredited as a calibration laboratory to ISO/IEC 17025 for purity measurements since 1993
 - GC-FID, HPLC/UV, DSC, moisture (Karl Fischer)
- Extensive accreditation as testing laboratory
- Produces reference materials in accordance with ISO Guide 34 and ISO/IEC 17025
 - Audited in March 2006 by UK Accreditation Service (UKAS)
 - Accreditation granted July 2006 (to ISO Guide 34:2000)
 - Surveillance visits each year
 - Reassessment after 4 years
 - Assessment against ISO Guide 34:2009 version in 2011 and accreditation transferred
- Essential elements of LGC approach
 - Planning Form
 - Certification Panel

Documentation relating to ISO Guide 34 accreditation



- ISO Guide 34:2009 and normative references (includes ISO:17025)
- LGC documents
 - Quality Policy
 - Quality Manual which includes:
 - Quality Procedure on production of reference materials
 - Standard Operating Procedures
 - Work Instructions
 - Local Procedures

ISO Guide 34



- Scope
- Normative references
- Terms and definitions
- Organisation and management requirements
 - Includes sections on document control, use of sub-contractors, complaints procedures, corrective actions, internal audits, management reviews
- Technical and production requirements
 - Includes sections on personnel, sub-contractors, planning, production control, material storage, data evaluation, traceability, homogeneity, stability, characterisation assignment of values, distribution.....

LGC Quality Policy and Quality Procedure for Reference Material Production



- Quality Policy states that materials are made in accordance with Guide 34 and ISO17025. Certificates comply with Guide 31
- Quality Procedure (part of Quality Manual) which describes how requirements of Guide 34 are implemented. Contents include sections on:
 - Project planning
 - Request, tender and contract review
 - Use of sub-contractors
 - Material preparation
 - Characterisation
 - Commutability
 - Information supplied with the material
 - Traceability and uncertainty
 - Storage
 - On-going stability monitoring
 - Customer support

Essential SOPs for Reference Material production to implement ISO Guide 34



- Project planning
- Material specification and procurement
- Material preparation
- Homogeneity assessment
- Stability testing
- Characterisation of certified values
- Commutability
- Storage
- Certificates, labelling and safety data sheets
- Statistics
- Uncertainty & traceability
- Certification
- Reports
- Customer support
- Organisation of inter-laboratory and collaborative studies
- Evaluation of existing materials
- File management
- Product hand-over
- Responsibilities and authorisations
- Stability monitoring

Local procedures



- Management structure and responsibilities
 - Organisation chart
 - List of authorised signatures and initials
 - Delegated authority to sign certificates or measurement and calibration
 - Calibrated equipment
 - Record of staff awareness of quality system documents
 - Staff signatures and initials
 - Training programme for new staff
 - Training plan for the production of reference materials
- plus
- Controlled forms



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The Production Process

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Steps in the production process



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- Project planning including material specification
- Sourcing, preparation and sub-division
- Homogeneity assessment
- Stability assessment
- Characterisation of the assigned value(s)
- Calculation of the assigned value and its uncertainty
- Documentation and storage of the material
- Certification
- Material release
- Post certification work

Planning

- Project manager appointed who prepares for the planning meeting
- Attendees are stipulated in the planning SOP
- At the planning meeting we discuss
 - what we intend to make
 - how we are going to make it
- Decisions are documented in the ‘controlled’ Planning Form
- Changes have to be approved



REFERENCE MATERIAL PROJECT PLANNING FORM: VERSION _	
1. WORKING TITLE	
2. REFERENCE	
3. FILE REFERENCE	
4. PROJECT INFORMATION	
Lead team	Reference Material Production (513)
Project code	
Funding source	
Project team	
External collaborator(s)	
Project manager	
Internal service providers	
Material preparation	
Analytical team(s)	
Technical advice	
Project management	
Storage & dispatch	
Does this work fall within the Reference Material Production scope of accreditation?	<input type="checkbox"/> Yes <input type="checkbox"/> No
(C)RM identifier (LGC number)	
ERM number (where appropriate)	
(C)RM matrix	
CRM	<input type="checkbox"/>
RM	<input type="checkbox"/>
QCRM	<input type="checkbox"/>
Other	<input type="checkbox"/>
Short summary of the project	
Intended use	
Target parameters, uncertainties & traceability	
Signed:	(Planning Meeting Chairman)
Date:	

Sourcing and preparation



- Material source and preparation details may depend on:
 - Matrix type
 - Analyte types and concentration
 - Target uncertainty
 - Number of units
 - Unit size
- Storage requirements (-80°C, -20°C, 4°C and 18°C)
- Containers
- Preparation – purification, drying etc.
- Sub-Sampling

Containers



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- Choice of container affected by
 - potential moisture changes
 - contamination (e.g. by leaching of impurities)
 - light degradation
 - volatility
 - suitable closure



Material preparation



- Processing may involve one or some of the following:
 - Milling & grinding
 - Sieving
 - Mixing
 - Filtration
 - Stabilisation
 - Dispensing into units
 - Sterilisation

Sub-sampling



- Aim is to maintain homogeneity during sub-sampling
 - volatility
 - separation
- Good practice to:
 - complete sub-division as soon as possible
 - maintain homogeneity of bulk during sampling
 - discard last 10% of the bulk material (and in some cases the first 5-10%)

Homogeneity testing



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- All materials are tested for homogeneity
- All analytes of interest are tested
- Usually 10 to 30 units analysed in triplicate
- Units analysed in random order, not 'as bottled'
 - Separate analytical drift from bottling trends
- Statistical analysis (ANOVA) used to obtain S_{method} (the method standard deviation) and S_{bb} (the between unit standard deviation)
- The larger of $(S_{\text{method}}/\sqrt{n})$ and S_{bb} is used to estimate u_{hom} (*the contribution to the combined uncertainty from possible inhomogeneity*)
- Assists in the assessment of the statement of minimum weight on the certificate

Approaches to stability assurance



- Prior information
 - Use data from related materials
 - Use published and/or readily available information
- New stability studies
 - Accelerated testing
 - Long-term testing
 - Isochronous testing
- Determine a value for u_{lts} (the contribution to the combined uncertainty for possible long-term instability)

Characterisation approaches



- Single primary method in one laboratory
 - cost effective if methodology and equipment is readily available
e.g ID-ICP-MS
- Two or more independent methods in one or more laboratory
 - Requires detailed uncertainty information for methods
- Consensus certification
 - Multiple laboratory study using competent laboratories
 - Sometimes free choice of method
 - Sometimes method specified

Commutability



- To be fit for its intended purpose, a reference material must have test properties that are comparable to the properties demonstrated by authentic samples.
 - i.e. the properties must be commutable
- Originally a problem identified in the clinical laboratory measurement sector, the potential implications of commutability in other measurement sectors are now being looked at by ISO REMCO

Commutability - definition

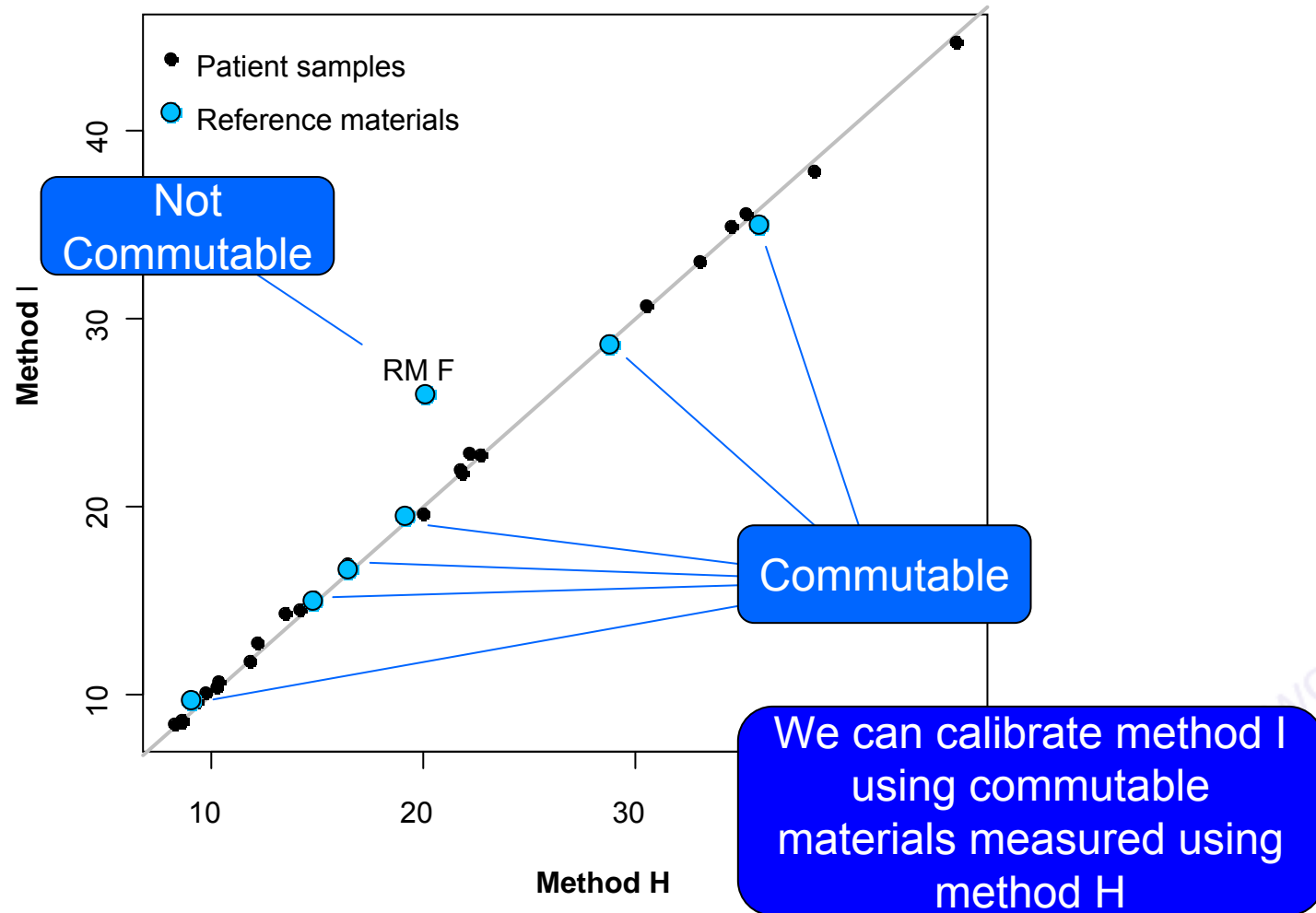


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- Commutability of a reference material (Clinical Laboratory Standards Institute (CLSI))
 - A property of a reference material demonstrated by the equivalence of the mathematical relationships among the results of different measurement procedures for a reference material and for representative samples of the type intended to be measured
- Notes
 - A general property
 - Demonstrated by a particular test
 - With results specific to the procedures tested
 -unless the procedures also form a 'representative set'

The pictorial explanation

CLSI Example: Methods H and I



Uncertainty



- Calculated from the standard uncertainties associated with the:
 - Homogeneity assessment
 - Characterisation measurements
 - Possible long-term instability
 - Other contributions
- Contributions are combined and expanded to give a 95% confidence interval (quoted on the certificate)

Material certification



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- Carried out by LGC Certification Panel
- Permanent members are:
 - Principal Scientist – Reference Materials
 - Head of Reference Material Production
 - Quality team representative
- plus
 - Relevant Science Leader
 - Project team members including project manager
 - Independent experts (e.g. statistics)

Activities of In House Certification Panel



- Reviews:
 - intended use/original specification of the material
 - expertise of the RM producer / subcontractors
 - records on the sourcing and preparation of the RM
 - approaches used to assess homogeneity and stability
 - approaches used to characterise the property values
 - supplementary information from the characterisation studies
 - statistical processing of raw analytical data and results
- Records the essential details of the review and examination of data
- Approves documentation for the reference material
- Authorises the release of the RM for use

In addition.....



- For higher level materials a second stage approval
- LGC is part of the European Reference Materials Co-operation
 - A joint collaboration of three major European reference materials producers
- IRMM (The Institute for Reference Materials and Measurements of the European Commission's Directorate General Joint Research Centre, Belgium)
- BAM (The Bundesanstalt für Materialforschung und –prüfung, Germany)
- LGC, United Kingdom

- **Peer-review** of CRMs by the European Reference Materials technical committee ensures highest quality and reliability
- **Full transparency** of the certification principles, and the evaluation report, provides valuable insight to help analysts get the maximum benefit from the use of the material. Principles of production and certification are based on ISO Guide 34
- Clearly defined and stated **traceability** of the certified values ensures applicability of the materials to the respective analytical problem.
- **Internationally recognised values** underpinned through the participation of the producing institutes in the key comparisons organised by the Bureau International des Poids et Mesures

- Materials to be sold as ERMs undergo a 2 stage review
 - Technical review by experts from BAM and IRMM
 - ERM Panel approval

Content of certificate



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- Essential information (ISO Guide 31)
 - Name and description of the material
 - Reference number and/or batch number
 - Reference value(s)
 - Uncertainty of the reference value(s)
 - The minimum quantity of material to be used
 - Storage instructions
 - Information on expected shelf-life
 - Instructions and intended use of the material
 - Analytical procedures used to establish the reference value(s)
 - Names of laboratories taking part in the characterisation of the material
 - Date of issue of the Certificate / Statement of Measurement
 - Name and address of the issuing organisation
 - Signatory for the issuing organisation

Branding

- ERM (European Reference Materials)
- LGC



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CERTIFICATE OF ANALYSIS

ERM[®] - AC404e

Reference Spirit – 5 % ABV (Alcohol by Volume)			
Parameter	No. of Determinations	Certified Value (at 20°C)	Uncertainty
Alcoholic Strength (% ABV)	10	4.97	0.04
Density (in air) (kg/m ³)	10	990.05	0.04

1. The material was certified gravimetrically with all weighings traceable to the International System of Units (SI).

2. The uncertainty quoted is the half-width of the expanded uncertainty calculated using a coverage factor of two (k=2), which gives a level of confidence of approximately 95%. The uncertainty evaluation has been carried out in accordance with UKAS requirements.

This certificate is valid for 12 months from the date of shipment, provided the sample is stored with the crimp cap intact under the recommended conditions.

The minimum amount of sample to be used is 2 mL.

NOTE

European Reference Material ERM[®]-AC404e was produced and certified under the responsibility of LGC according to the principles laid down in the Technical Guidelines of the European Reference Materials[®] co-operation agreement between BAM, LGC and IRMM. Information on these guidelines is available on the Internet (<http://www.erm-crm.org>).

Accepted as an ERM[®] Teddington, January 2008.

Signed: _____

Dr. John Marriott, UK Government Chemist
LGC Limited
Queens Road
Teddington
Middlesex
TW11 0LY, UK



All following pages are an integral part of the certificate.
ERM[®] - AC404e
Page 1 of 2
Queens Road, Teddington, Middlesex TW11 0LY, UK Tel: +44 (0)20 8943 7000 Fax: +44 (0)20 8943 2767 Web: www.lgc.co.uk

Certificate of measurement



Contaminated Clay Loam Soil – Extractable Metals,
PAHs and Inorganics
Certified Reference Material LGC6145

Certified Values

Constituent	Certified value ^{1,2} (mg/kg)	Uncertainty ^{3,4} (mg/kg)	Weight of sample ⁵ (g)
Arsenic	38.7	1.2	3
Cadmium	0.65	0.07	3
Chromium	47.0	1.6	3
Copper	62.2	3.6	3
Lead	46.1	2.3	3
Nickel	30.0	2.5	3
Selenium	1.81	0.18	3
Vanadium	53.9	2.3	3
Zinc	137	6	3

Assessed Values

Constituent	Assessed value ^{1,2} (mg/kg)	Uncertainty ^{3,4} (mg/kg)	Weight of sample ⁵ (g)
Naphthalene	0.3	2.3	1
Acenaphthylene	0.73	0.11	1
Phenanthrene	325	26	1
Anthracene	8.4	1.6	1
Chrysene	45	9	1
Benzo[b]fluoranthene	12	3	1
Indeno[1,2,3-cd]pyrene	0.97	0.28	1
Water soluble chloride	85	9	10

Constituent	Assessed value ^{1,2} (g/L)	Uncertainty ^{3,4} (g/L)	Weight of sample ⁵ (g)
Water soluble sulfate	5.3	0.7	10

NOTE

- Traceable to SI reference standards.
- For the metals the values are traceable to SI via the calibration solutions used.
- For the metals the relative uncertainty of the participating laboratories was established by one or more of the following:
 - Accreditation to ISO/IEC 17025.
 - Satisfactory performance in the measurement of a GC provided by LGC.
- Values reported on a dry weight basis.
- The uncertainty quoted is the half-width of the expanded uncertainty interval calculated using a coverage factor of 2, providing a level of confidence of approximately 95%.
- The uncertainty quoted is the half-width of the expanded uncertainty interval calculated using a coverage factor of approximately 2, providing a level of confidence of approximately 95%.
- Weight of samples taken for homogeneity assessment.
- The water soluble sulfate content was determined using a 2.1 (molar acid) extraction.

Date of issue: July 2007
Revision date: February 2008
Format revised: December 2008

Signed: _____
Gill Holcombe (Mrs)
for the Government Chemist

Material number: LGC6145
Batch number: 001
Page 1 of 2



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quality • safety • service • analysis

Distribution



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- All materials distributed through LGC Standards
- All stored in controlled conditions in Teddington apart from one petrol material





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Post Production

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Information



- All information relating to the production of a material is retained for the lifetime of the material, and beyond.....
 - Helps with any queries
 - Assists in the production of replacement batches

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Stability monitoring



- Continues once the material is on sale
- Frequency of testing depends on
 - the analyte
 - the matrix
- For the lifetime of the material
- Costs may be high

Customer support



- ISO Guide 34
 - Reference material producer should also provide an advisory service to offer guidance (including a complaints procedure) and technical services to the users.....
- What does this mean?
 - Expertise / knowledge available for lifetime of material
 - collate and store all enquiries
 - act on information received



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Example – LGC6115 Contaminated Soil Characterised for PAHs and PCBs

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LGC6115 Contaminated Soil Characterised for PAHs and PCBs



PAHs

	Certified value (mg/kg)	Uncertainty (mg/kg)
Phenanthrene	178	6
Fluoranthene	312	7
Benzo[a]anthracene	36	1
Benzo[a]pyrene	0.13	0.02
Benzo[ghi]perylene	0.33	0.06

Analytical procedure for PAHs



- Sub-sample packed into cell for accelerated solvent extraction
- Spiked with equimolar amounts of isotopically labelled analytes of interest
- Extraction carried out
- Analysis of resultant solution by GS-MS

- Method previously used successfully in a CCQM study
- Blanks, calibration standard and QC material taken through whole procedure

Analytical procedure for PCBs



- Sub-sample packed into cell for accelerated solvent extraction
- Spiked with equimolar amounts of isotopically labelled analytes of interest
- Extraction carried out
- SPE step
- Analysis of resultant solution by GS-MS

- Method previously used successfully in two CCQM studies
- Blanks, calibration standard and QC material taken through whole procedure

Combined uncertainty



Analyte	U_{char} (mg/kg)	U_{hom} (mg/kg)	U_{lbs} (mg/kg)	U_{moisture} (mg/kg)	U_{crm} (mg/kg)	k	U_{crm} (mg/kg)
Phenanthrene	2.02	1.41	1.41	0.24	2.84	2	5.70
Fluoranthene	2.54	1.25	1.25	0.42	3.09	2	6.40
Benzo[a]anthracene	0.17	0.25	0.25	0.05	0.38	2	0.76
Benzo[a]pyrene	0.0040	0.0058	0.0058	0.0002	0.01	2	0.02
Benzo[ghi]perylene	0.0135	0.016	0.016	0.0004	0.03	2	0.05

Confirmation



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	LGC IDMS Certified value $\pm U_{\text{char}}$ mg/kg	CONTEST data grand robust mean \pm grand robust sd mg/kg	LGC GC-MS Mean \pm sd mg/kg
Phenanthrene	178 \pm 2	166 \pm 37	164.7 \pm 2.8
Fluoranthene	312 \pm 3	303 \pm 32	311.0 \pm 4.9

National and International links



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Include

- UKRMWG
- UKAS
 - Technical Advisory Committee
- BSI Committee on Reference Materials RMI/1

- ISO REMCO
- ERM
- CCQM

Summary

- LGC background
- Accreditation of RM producers
- LGC's accreditation for the production of reference materials to ISO Guide 34:2009
- Looked at the steps in production
- Links with other UK and International organisations





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Any questions?

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