

National Measurement System (NMS)

Valid Analytical Measurement (VAM) Chemical Programme

2003-2006

PUBLIC RELEASE VERSION



Summary

This document describes the work to be undertaken as part of the 2003-2006 Chemical VAM Programme, which was approved by Ministers in October 2003. It provides an overview of the main themes of the programme along with detailed project specifications, which identify the aims, objectives and deliverables of each project to be funded.

Chemical analysis represents a £multi-billion activity in the UK and the decisions taken on the basis of its results influence a significant part on the UK's GDP and its Quality of Life. Thus sound, cost-effective analytical science is required to maintain a competitive, well-regulated UK industry. Through its constituent themes, the programme aims to deliver the total analytical package to help laboratories make accurate and comparable measurements that are fit for their intended purpose.

The programme comprises three main themes, plus an overall programme management and development theme. The three main themes are:

1. **Chemical Metrology**, which is at the heart of the programme. It consists of an integrated set of projects, developing the methods, capabilities and facilities to provide reference materials and standards. These enable the analyst to make measurements that are traceable to internationally recognised standards. With the globalisation of trade and the international mutual recognition of accreditation to ISO 17025, traceable measurements are becoming increasingly important. The highly interactive CM3 sub-theme, focused on the delivery of traceable measurements, has been expanded to include work on the use of new technologies to analyse complex systems, such as nutraceuticals. This will facilitate the uptake of new technology, an area where the programme consultation indicated that the UK was lagging.
2. The **Knowledge Transfer** theme is focused on support for the professional analyst. The shortage of skilled analysts was a consistent message made throughout the consultation. There is work to evaluate the technical performance of UK laboratories, identify areas where support is required and provide a benchmark against which the effect of initiatives to improve performance can be measured.
3. The **Nucleic Acid Measurements** theme has been designed to put key measurement technologies emerging from the science base on a sound footing, so that they can be used with confidence. Included is work to underpin quantification of DNA, which is important for applications such as determining the GMO content of food and in clinical applications such as the measurement of viral load. There is also support for the highly multiplexed array-based technologies, which are used extensively in drug discovery.

Overall, the new programme is designed to help the UK professional analyst capitalise on the recent developments in analytical technology and traceable measurement techniques, enabling their businesses to compete effectively in a global market which is demanding universally assured products and services.

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1. Introduction

1.1 Background

The Chemical VAM (Valid Analytical Measurement programme) forms part of the portfolio of programmes funded by the DTI's National Measurement System (NMS) Directorate. Its focus is on chemical measurements, although previous programmes have also covered some work in the biochemical field, primarily in nucleic acid measurements. This work is expected to transfer to the new Measurements for Biotechnology (MfB) programme in April 2004, but to ensure continuity of the work, the nucleic acid work has been formulated at the same time as the VAM programme.

The fundamental aims of the VAM programme are closely aligned with those of the NMS programmes in general namely:

- To help improve the quality and comparability of measurements made in the UK in order to improve our competitiveness and support regulatory need
- To co-ordinate the UK's measurement system with those of other countries

Like its predecessors, the proposed new programme is scheduled to run for three years from October 2003 until September 2006.

1.2 Context

Chemical measurement is a complex, but critical process. The results can inform decisions whose economic value is many orders of magnitude higher than the cost of the analysis. They can also inform key quality of life decisions, particularly in healthcare.

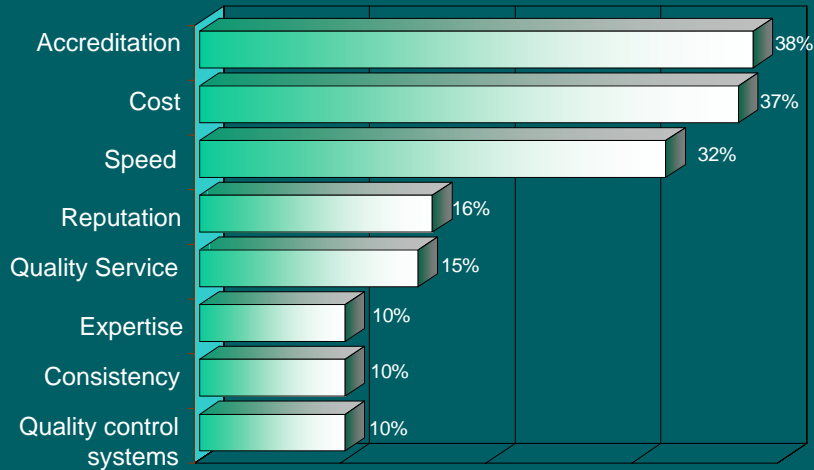
In formulating the 2003-2006 Chemical VAM Programme, particular attention has been paid to the key trends and issues influencing chemical and biochemical measurement. A recent survey by BPRI, the PA Consulting strategic forward look (carried out at the beginning of programme formulation) and the detailed consultation undertaken during programme formulation show that the level of expenditure on analytical measurements continues to grow, particularly in the life science and healthcare sectors as indicated in the panel:

Segment	% of Segment where Analytical Spend has Increased over the Last 5 Yr
Healthcare	68
Pharmaceuticals	60
Chemical/Petroleum	60
Food, Drink & Tobacco	61
Water	50
Life Science	80

Given the critical importance of analytical results, it is not surprising that assurance of the quality of the results through accreditation is uppermost in the list of attributes looked for in laboratories by contractors of analytical work, as shown in the figure.

Qualities looked for in analytical suppliers

Desirable qualities of analytical suppliers include accreditation, competitive costing and the ability to deliver results quickly



Other important factors are cost of the work and the speed of results. Thus we see the key drivers for modern analytical work:

- Quality
- Cost
- Speed

Technological and instrumental developments are helping to address the last two points. Rapid, high throughput methods can dramatically reduce the unit cost of analysis and response times. Thus in the BPRI survey, technological advances were seen as having the most significant impact on the analytical market place over the next ten years (see panel).

Factors Affecting Analysis over Next 10 yr. (Order of Priority)	Major Issues Facing Analysis over Next 10 yr. (Order of Priority)
Technology Advances	Resourcing/Lack of Training
New Legislation	Increasing Legislation
Increased Regulation	Cost of Analysis
Market Changes	New Technology
Increased Testing	Environmental Issues
Environment	Speed of Analysis
Cost of Analysis	Global Competitiveness

More Automation New Methods	Keeping Pace with Change Quality of Service
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However, the search for assured results continues as the demands of analysis (lower levels and increasing complexity) and the consequences of erroneous results in an increasingly litigious and aware society become more substantial. The influence of legislation and regulation figure high on the factors impacting on analysis and the issues facing analytical science (see Panel) and are driving a need for demonstrable quality assurance, particularly via accreditation and proficiency testing.

The acute shortage of skills and resources is a consistent message that has been made throughout the consultation process and it also tops the list of the issues in the BPRI survey. Clearly there is a danger that if staff carrying out the measurements lack the basic understanding, this could have serious implications for the validity of results and the consequential decisions.

Finally, as world trade and industry continues to grow, there is an increasing need to ensure that the results of analysis are valid and comparable on a global scale. International efforts, led by the Bureau of International Weights & Measures (BIPM) and, in particular, through its international Consultative Committee for Amount of Substance (CCQM) to build a global chemical and biochemical infrastructure based on traceable measurements are starting to impact. Key Comparisons, which establish the equivalence of national measurement capabilities and standards, are well under way. For example, Figure 1 shows the results of the cholesterol Key Comparison.

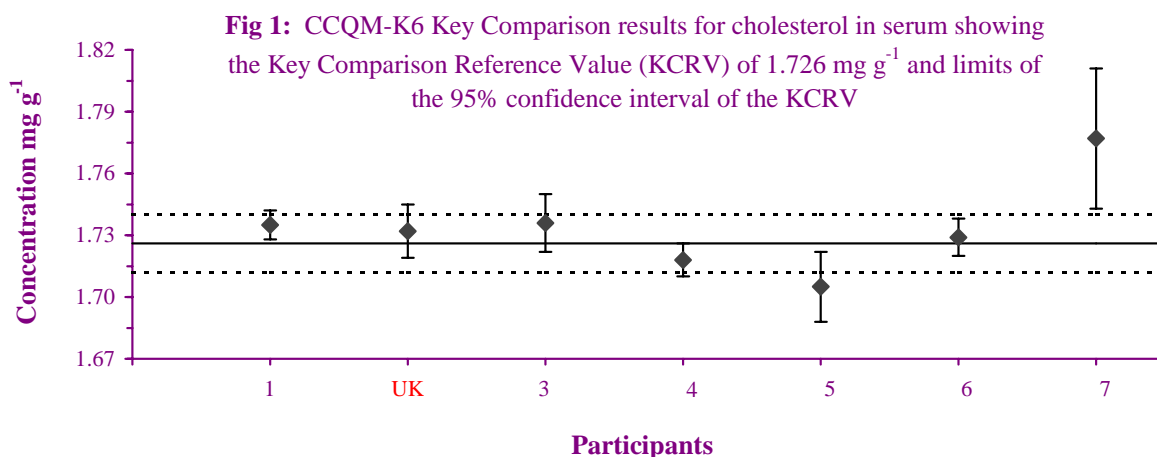


Figure 1 - CCQM-K6 Key Comparison for Cholesterol in Serum

These capabilities and standards are now recognised internationally through a Mutual Recognition Arrangement, which has been signed by the National Measurement Institutes. Another more recent initiative, aimed at assuring comparability in clinical measurements, is the Joint Committee for Traceability in Laboratory Medicine (JCTLM). One of the first tasks of this international body is to identify reference materials of a high order and reference methods, which can be used to support the EC

In Vitro Diagnostic Devices Directive. Thus there is now an opportunity for UK analysts to start benefiting from these initiatives and ensuring that their results are valid and globally acceptable.

The VAM programme seeks to help UK analysts capitalise on these advances and address the issues. It is aimed at helping to ensure that they can consistently achieve valid results, which are acceptable on a global basis. The main mechanisms for achieving this are by:

- Providing UK analytical laboratories with a ‘total analytical package’ to help them achieve valid, globally acceptable results. Key to this is the provision of reference values and tools to help analysts implement the ‘six VAM principles’ for good measurement practice.
- Anchoring the UK measurement system to the emerging global system, through participation in the key international intercomparisons organised by the CCQM
- Developing and maintaining a high accuracy analytical capability to provide values for reference materials of importance to the UK, which are recognised globally
- Evaluating new technology, addressing the associated measurement issues and providing the tools to enable analysts to use these with confidence
- Effective knowledge transfer at both the programme and project level

1.3 Programme Themes

The 2003-2006 VAM programme is broken down into four main themes, namely:

- Chemical Metrology (CM)
- Nucleic Acid Measurements (NM)
- Knowledge Transfer (KT)
- Programme Management & Development (MD)

These are overviewed in Section 2.

2. Overview of Programme Themes

This section gives the context of each theme and an overview of its constituent projects. More detailed information on each project is presented in Annex 1.

2.1 Chemical Metrology (CM)

Background and Context

Consultations with UK experts and with UK and European bodies have highlighted a wide range of measurement issues that should be urgently addressed. The relentless march of European legislation which demands high accuracy analysis at lower levels, whether it be low sulfur fuels, lead in drinking water, or GM food puts increasing demands on the methods used to underpin these measurements. Regulatory bodies are also imposing greater monitoring requirements and the implementation of better control measures. Good examples are the MCERTS scheme introduced by the Environment Agency (EA) and the detailed analytical requirements of the EU *In Vitro* Diagnostic Devices Directive.

At the heart of the Chemical VAM programme is the Chemical Metrology theme, which is aimed at addressing these challenges. A common strand behind much of the work proposed is the requirement to provide laboratories with traceable reference values, either by certification of reference materials or directly through calibration services or appropriate PT schemes. Traceability provides a provenance for the standards and reference materials required to calibrate equipment and test kits and to validate those procedures. Achieving traceable chemical measurements for the UK depends on both establishing an appropriate measurement infrastructure and ensuring that laboratories are willing and able to make use of it. Used together they ensure measurement results, which are both reliable and comparable with results obtained elsewhere; an essential requirement of the 21st Century global economy. Hence, the emphasis in Chemical Metrology Theme is on working with a wide range of UK laboratories to help them achieve this. Practical collaboration and direct involvement in specific tasks is arguably the most effective of all knowledge transfer activities.

The support by the NMS for the continuing development of high accuracy techniques using state of the art instrumentation enables the UK to play a leading international role in the CCQM for both inorganic and organic analysis and ensures that our standards and reference materials are accepted world-wide. Issues associated with the use of reference materials were identified in a specially convened workshop¹ and the difficulties of dealing with the burgeoning need for reference materials were highlighted in PA Consulting's 'Forward Look'². Key issues include:

- There are simply insufficient resources to produce all the materials which may potentially be required, even when producers co-operate to avoid duplication
- Sales of the majority of matrix CRMs and high-purity materials are too small to cover the costs of production, leading to market failure and a need for governmental support

¹ 'RM User Collaboration' – Requirements and Issues' Optimat Ltd, 13 November 2002

² 'Trend Spotting Forward Look: VAM' PA Consulting Group, 23 July 2002

- Many laboratories have inadequate resources and expertise to properly develop and validate their analytical methods, regardless of whether suitable materials are available for purchase

In order to address these issues it is proposed to focus VAM resources on a relatively small number of measurement applications where it is vital to address serious problems or limitations with the methods currently used by laboratories. Priorities for selection of these applications will be in accordance with clear but pragmatic guidelines:

- The application is of major importance to regulatory enforcement, international trade, health and safety, etc
- Where regulators, accreditation bodies, trade organisations, etc require laboratories to use available materials or standards within their analytical processes
- The laboratories themselves have recognised the existence of a measurement problem and are willing to participate collaboratively in the project
- The governmental or industry bodies with responsibility for specific application areas have shown a commitment to the work

The development of new measurement technologies offers opportunities for complex matrix characterisation including trace detection in multi-component samples, identifying specific compounds or determining differences in products or formulations, defining active ingredients in natural products, nutraceuticals or herbal remedies, or profiling metabolites or biomarkers in biological systems. Taken together these applications have economic, public health, regulatory, quality control and production significance.

Projects

The theme is divided into three main areas. Each area contains a number of projects but special attention has been given to integration of all facets of the activities. This is particularly the case with production of reference materials and standards. An aim of this proposal has also been to improve efficiency of RM production by:

- Making maximum use of the high level measurement capabilities developed under previous programmes
- Bringing in appropriate UK partners to work on preparation of the materials and, where necessary, for certification
- Expanding the present high level collaborations with overseas institutes
- Spinning off the capabilities and methodologies developed for the high-level materials to commercial suppliers of "matching" lower level RMs
- Maintaining ongoing or related projects which can build on existing expertise and methodology, rather than starting afresh every three years

This requires a structure within which the suppliers can operate and a means to ensure continuity of the key players maintaining that structure. The structure needs to be scaleable and flexible so that in future it can address all sectors and also embrace:

- All types of materials (from primary standard to QC sample) and also other means of delivering reference values
- A variety of production models, ranging from publicly funded to commercially financed with any combinations in between.
- Seamless integration with the quality and traceability systems within which field analytical laboratories operate.

The main aim of the three projects comprising CM3 “Delivery of Traceable Measurements” is to deliver this requirement.

CM1 Chemical Calibration and Standards

Work in this area is aimed at maintaining the UK’s high-level capability for reference material production and calibration. It includes work to improve the production of reference materials, collaboration with other international producers and work to accredit UK reference material producers. It contains five projects:

CM1.1 Maintenance and Supply of Reference Materials

Approximately 170 materials produced under VAM are still available for sale. The work proposed in this project will ensure the continued integrity of supply.

CM1.2 Development and Improvement of Matrix Reference Material Production and Certification Capabilities

There is an urgent need to develop improved approaches for the production and certification of RMs, in the light of the major revision of ISO Guide 35 (Certification of RMs) and the increasing emphasis being given to traceability issues in chemical measurement. Thus the main aims of this project are to ensure that procedures used to produce and certify matrix reference materials reflect current best practice.

CM1.3 Development and Improvement of Calibration Capabilities for Pure Substances

Pure chemicals (or solutions thereof) form an essential part of many traceability chains in analytical chemistry, since they are frequently used for calibrating analytical instruments. Hence it is important to be able to obtain, or produce high purity materials with reliable and certified values. This project aims to develop improved procedures for the purification and certification of organic compounds for use as calibration reference materials.

CM1.4 UK Chemical Calibration Facility

The main aims of the projects are:

- To transfer expertise obtained from high level metrological studies to UK reference laboratories and to promote a better understanding of the benefits of traceable measurements
- To link UK activities into the international measurement community

Included in this project are activities for European collaboration in order to establish a well-recognised European brand for high quality RMs and participation in the European Virtual Institute for RMs.

CM1.5 *Accreditation of UK Reference Material Producers*

This project aims to look into the practicalities, prospects and benefits of accreditation of reference material producers and, if appropriate, develop a framework for an accreditation scheme for UK producers.

CM2 *Validation of Measurement Methods*

This includes the continued development of high accuracy methods to meet the changing demands and more challenging problems, such as the speciation of organometallic compounds of relevance to environmental analysis. Also included is the participation in CCQM and other intercomparisons. The main aims are:

- To further develop high accuracy methods for the determination of reference values required for the calibration services and RM production
- To undertake related measurement infrastructure activities, particularly participation in UK, European regional, or CCQM interlaboratory comparisons
- To carry out research into specific aspects of the methodology critical to the accuracy and scope of the methods, where possible in collaboration with academic or other research groups
- To ensure the methodology embraces analytes in a wide range relevant to trade, industry, health, food, forensic and environmental applications

Three projects are proposed:

CM2.1 *Development and Validation of Methodology for Accurate Quantitation of Inorganic Analytes*

CM2.2 *Development and Validation of Methodology for Accurate Quantitation of Organic and Organo-Metallic Analytes*

CM2.3 *Development and Validation of Methodology for Determination of Identity, Authenticity and Origin*

CM3 *Delivery of Traceable Measurements*

The benefits of traceable measurements are not always clearly understood in the field of chemical measurement. However, the need for reliable measurement is clearly recognised by all sectors, but one might reasonably ask why at this time traceability should be of particular benefit in achieving reliable chemical measurements? The answer lies partly in the global economy, but also in the increasingly fragmented and competitive nature of the analytical sector and the greatly reduced level of expertise and experience available in many laboratories. Provided appropriate traceable materials and calibration services are available, little extra burden is placed on laboratories.

Work in this area will involve a high degree of collaboration with UK laboratories and will be responsive to their needs. The three projects aim to provide the 'total analytical package' for the analyst including validated methods, reference materials and reference values. This will be accomplished by providing UK field laboratories with the tools required to achieve valid and traceable measurements in key applications within the following sectors:

- Industrial production and consumer safety
- Environment
- Food
- Health
- Forensic

The approach will be implemented by working with laboratories and industry or regulatory bodies to use the expertise developed under VAM to assist in development and validation of specific applications. The outcome will be documented methods validated by round robin and matrix RMs certified by both the participating laboratories and by definitive methods. The latter will ensure traceable data linked into the international measurement system. Thus, information on the RM will include certified values, which have been assigned using 'state of the art' high accuracy methods together with values which indicate the results which could be expected from the more routine techniques used in the laboratory.

A specific study will evaluate the application of new measurement technologies for characterising complex systems, with the aim of demonstrating the potential and increasing the uptake of new technology by UK companies. The relatively slow adoption of new technology in the UK compared with US and other European countries was identified as an issue during the consultation process

[CM3.1](#) *Traceable Measurement of Inorganic Analytes*

[CM3.2](#) *Traceable Measurement of Organic Analytes*

[CM3.3](#) *Traceable Measurement of Chemical Species*

[CM4](#) *Tools for Chemical Metrology*

Quality tools for metrology in chemistry are important both for the UK NMI capability and for calibration laboratories producing chemical measurement standards. This project is aimed primarily at addressing specific and important gaps in existing methodology. In measurement uncertainty estimation, there are current and pressing problems near detection limits, in purity assessment (critical for pure reference material preparation), in experimental design for reliable uncertainty estimates, and in handling correlation routinely at the metrology lab level. The project will also promote chemometrics applications for metrology through improved procedures for measurement uncertainty estimation and traceability through to reference standards.

2.2 Nucleic Acid Measurements (NM)

Background and Context

Technology for nucleic acid measurements is developing rapidly. Significant advances are being made in high throughput, multiplexed measurements and in techniques for detecting Single Nucleotide Polymorphisms (SNPs). The applications of the technology are ubiquitous and growing. Some examples are shown in the panel.

Market Sector	Applications
Clinical	Genetic Diagnostics, Infectious Disease Detection Tissue/Blood Typing
Environmental	Water Quality, Bio-diversity Monitoring
Food	Ingredients – Species, GM, Pathogen Detection
Agriculture	Crop Genetic Engineering, Animal Husbandry
Forensic	Identification
Law Enforcement	Labelling, Authentication, Paternity Testing
Pharmaceutical	Genomics – Drug Discovery, Pharmacogenetics Biopharmaceutical Production

However, the rapid advances and the complexity of highly multiplexed measurements pose some critical issues relating to the validity and comparability of results. In addition, the need for accurate quantitative measurements is growing, but the measurement techniques are not very robust and are struggling to keep up with the regulatory requirements, such as those associated with the labelling of GM food.

Representatives from the key areas and other sectors were included in the consultation process. The consultation has identified a number of common themes, including the need for faster, more sensitive, higher throughput, more cost-effective analysis, with the potential for automation, de-skilling, or on-site testing. Newer genetic measurement technologies have the potential to answer some of these needs, but the associated measurement infrastructure and quality challenges are even greater³.

In formulating the Genetic Measurement theme, account has been taken of the need to strike a balance between building on the substantial outputs from the current programme and addressing new areas of technology in this rapidly developing field.

Projects

The proposed projects for genetic measurements fall into three main categories:

NMI Quantitative DNA Measurements and the Development of Reference Standards

This sub-theme, which comprises four projects, builds on the work of the current programme in moving forward the tools to support quantitative nucleic acid measurements and obtaining valid results from microarray based measurements. Both areas received strong support from the consultation.

³ CB Epstein and RS Butow Current Opinion in Biotechnology 2000 **11** 36

[NMI.1](#) *International Standards and Performance Indicators for Nucleic Acid Measurements*

Work started under the 2000-03 programme will trial the use of a 2 plasmid based system for DNA quantitation. The proposed project will extend the evaluation of the system as a performance indicator for quantitative nucleic acid measurement and produce an optimised material for distribution.

[NMI.2](#) *A Primary Method to Produce Standards for DNA Quantitation*

The ultimate underpinning of quantitative nucleic acid measurements is to anchor them to the SI units. This can be achieved through the use of high accuracy, primary methods of analysis. Work initiated under the 2000-03 VAM programme has shown the potential of isotope dilution mass spectrometry (IDMS) as a primary method for DNA quantitation ⁴.

The main project aims are:

- To complete the development of an IDMS based method for DNA quantitation
- To produce a set of quantified reference standards for use with common methods
- To validate through international trials a reference measurement system for DNA quantification, based on real-time PCR

[NMI.3](#) *Development of Standard Units to Measure Gene Expression*

Gene expression profiling using, for example, microarray technology has become an indispensable approach for gaining insights into cellular regulation. As such, underpinning activity in this area has a significant impact on the economics of major areas of UK industry (e.g. pharmaceutical, healthcare and agrochemical) and on the understanding of disease states with longer-term benefits in human wellbeing. The successful future application of these technologies will depend on the ability of the individual laboratories to produce valid and comparable data.

This project will seek to co-ordinate, evaluate and develop potential approaches that will facilitate the ultimate goal of achieving a standard unit of measurement for gene expression, thus facilitating the generation of comparable results.

[NMI.4](#) *Specificity Standards and Reference Indicators for Arrays*

Proprietary standards exist but are not available to use across formats. A major success of the current Bio-VAM programme has been the development of a set of specificity standards, which can be used as performance indicators for array based analyses. These standards will be validated, produced and made available for more general use under this programme.

The work will also investigate the potential of emerging techniques for the preparation of targets for array-based genotyping based on whole gene amplification.

⁴ G O'Connor et al. Anal Chem 2002 **74** 3670

NM2 Comparability, Quality and Interpretation of Genetic Measurements

The discussions with end users of genetic measurement have highlighted the widespread recognition of the imprecise nature of current methods, and the need for a greater understanding of statistics and measurement uncertainty as applied to quantitative technologies. Accordingly, the requirement for standardised procedures and reference materials has increased but appropriate materials and validated procedures are not yet available for most applications. An awareness of the limitations of methodologies is central to meaningful interpretation and application of genetic measurement data. Other issues such as ensuring the quantitative accuracy, comparability and reproducibility of data still require effective solutions for many applications.

Feedback from participants in a prototype general EQA/Proficiency Testing (PT) for DNA analysis, which was undertaken as part of the current programme, included strong endorsement for the utility of such schemes. They allow benchmarking across labs working on a variety of applications, and are also of use for researchers working on unusual/niche applications. They complement specific schemes, which have been introduced for those analyses where the quality and accuracy of the results is critical, such as in clinical diagnostics, or the determination of the GM content of food. Examples include the EQA schemes run by UK NEQAS for molecular analysis of genetic disorders and the CSL-run FAPAS®/GeMMA schemes for quantitative GM analysis.

This sub-theme consists of two projects, which build on work in the current programme.

NM2.1 Comparability and Consistency of Genetic Measurements

This project aims to:

- Promote appropriate use of molecular biology methods and technology
- Develop a truly generic PT scheme for DNA analysis, to provide the tools for cross-sectoral benchmarking of laboratory performance
- Facilitate introduction of quality systems, especially within start-up SMEs and academic laboratories

NM2.2 Critical Data Analysis for Low Level DNA Measurement

The project is aimed at addressing the potential issues associated with low level genetic measurements, including a significant improvement to the method for the non-invasive prenatal diagnosis of inherited diseases.

2.3 Knowledge Transfer (KT)

Background and Context

Although there are specific knowledge transfer activities within each project, there is a need to undertake knowledge transfer activities at the programme level. The VAM programme has always placed a high level importance on proactive and effective knowledge transfer – not just simply producing guides and publications, but ensuring that the key elements are absorbed through direct interaction. This can be in the form of training courses, workshops and practical exercises. The value of work in this area

has consistently been endorsed by strong support during consultation and programme prioritisation.

The current programme has demonstrated the success of sector-based networks as a means to develop and transfer best practice in analytical measurement. Consultation has also reinforced the need to adopt a more sectoral approach to knowledge transfer. It is therefore proposed to increase the focus on sector-based knowledge transfer activities, both in the provision of support for professional analysts and in the promotion of the programme. Sector based networks are also being used in some of the Chemical Metrology projects and these networks will also be targeted for the wider knowledge transfer activities.

One of the concerns that came out of the PA Consulting's Forward Look was how to balance the value of training and education in good laboratory and measurement practice, against the role of the NMI at the top of the measurement pyramid. PA had identified a skills gap and it is clear from all the other consultations that this is one of the most serious issues in all sectors.

In order to answer the question, 27 individuals from academe and the public and private sectors were contacted to identify the requirements for training and education projects in the VAM Programme. In addition, a Focus Group was convened to look specifically at how best to balance the VAM work on training and education in good measurement practice. The Focus Group concluded that:

- Knowledge transfer at the programme level, through training and education helps to disseminate the outputs from the other projects by presenting them in a form which is more easily understood by 'field' laboratories
- It is important to improve the uptake of the VAM principles within the university sector
- Training networks are an effective means of knowledge transfer, but it is important to ensure that any output from the networks is disseminated as widely as possible
- In order to gain leverage, there should be a focus on 'training the trainers' through, for example, the instrument suppliers and trade associations
- There is a need to educate customers, possibly by holding joint network meetings where both laboratories and customers are present
- There is a need to facilitate lectures on VAM issues to as wide a range of audiences as possible, e.g. at sector events. Dissemination of the VAM message could be improved by forging links with other stakeholders, such as research associations

One of the enduring themes of the VAM programmes has been the development of tools to help the analyst to consistently obtain valid results. The focus has been on making implementation of best practice easier and less burdensome to busy analytical laboratories. The dissemination of the work has consisted of guides, training courses and some software, such as the VAMSTAT statistical training package. The essential universal IT availability in laboratories leads to a great, but so far little tapped, potential for delivering tools in the form of software. Internet use has also become the norm, and has become the de facto medium for delivery of international harmonisation documents. It is also practical to implement some less critical tools via

the web, though it will be some time yet before long-distance communications allow the guaranteed immediate and rapid access to web-based tools that could replace local laboratory software.

A clear understanding of the actual performance of laboratories is essential in setting regulation based on analytical results and identifying priorities for improvement. Thus the examination of UK PT results is a potentially valuable means of assessing the broad performance of UK analytical labs, understanding where mistakes occur, identifying measures to improve the performance where necessary and examining the effectiveness of these measures.

Projects

The Knowledge Transfer theme covers three main areas: Programme-wide Knowledge Transfer, Training & Education and National & International Harmonisation.

KT1 *Publicity and Promotion*

The Programme-wide knowledge transfer will promote the uptake of the outputs of the programme through an interactive VAM web-site, publication of the popular VAM Bulletin, articles in a variety of publication and attendance at high profile events and the publication of a VAM Programme brochure.

The main aims of the project are:

- To increase the number of organisations benefiting from the VAM Programme
- To raise awareness of the importance of valid analytical measurement
- To improve understanding of what constitutes a valid analytical measurement

KT2 Training and Education

The key issue for Training and Education is where the limited effort available under the Programme should be targeted. It has been decided to focus the majority of the effort on support for the professional analyst in order to obtain maximum leverage for the work. The projects will concentrate on delivering training, coaching and supporting material through sector-based networks established under the UK Chemical Calibration Facility (Project CM1.4). In addition, they will produce a range of tools (software, guidance notes, books etc) which support analysts in implementing the VAM principles. Work with schools and universities will focus on supporting teaching staff and continuing the successful PT competition in chemical analysis for schools.

There are four projects in this theme covering: schools and colleges, universities, professional analysts, the technical performance of UK laboratories. Most of the effort proposed will be focused on supporting working analysts, because analytical skill shortages were consistently identified as a key issue during consultation.

[KT2.1](#) *Support for Schools and Colleges*

[KT2.2](#) *Support for Tertiary Education*

[KT2.3](#) *Support for Professional Analysts*

[KT2.4](#) *Evaluating the technical performance of UK laboratories*

KT3 *National & International Harmonisation*

Work under the National & International Harmonisation project is aimed at maintaining UK international influence on the development of international standards and quality developments, helped by feedback and input from UK stakeholders. This involves active participation in international meetings, the development, maintenance of national networks, working with organisations such as BSi, CEN, ISO etc. and the dissemination of international developments.

The main aims are:

- To develop and maintain the UK's international credibility and influence on policy and strategic analytical measurement issues through proactive participation in key European and international organisations
- To provide the UK with increased value for money through fostering collaboration and facilitating co-ordination and harmonisation with other countries and regions
- To communicate to UK stakeholders regular information on representational activities undertaken and provide feedback on the significance and consequence of developments

2.4 Programme Management & Development (MD)

Background and Context

Work under this theme will ensure that the projects are co-ordinated and managed effectively in order to deliver a seamless, value for money programme. It will also ensure a close interaction between those delivering the Chemical VAM programme and other cross-programme NMS initiatives. Provision has also been made for a project starting in Spring 2005 to identify the requirements for the next 2006-2009 programme.

Projects

MD1 *Programme Management*

The main aims of this project are:

- To provide co-ordinated management and delivery of all VAM projects to ensure the delivery of this work to quality, time and budget
- To ensure that the 'Chemical' VAM Programme projects are co-ordinated with other National Measurement System (NMS) programmes and initiatives

- To provide effective co-ordination and collaboration with other VAM contractors with the aim of delivering a seamless VAM (Chemical & Physical) programme

MD2 Programme Development

The aim is to assist the DTI in the development of the 2006-2009 Chemical VAM Programme, specifically in the identification and procurement of the most effective programme of work for the available budget, consistent with DTI's NMS objectives.

The main task during programme formulation is the iterative production and revision of a series of programme documents (specifications) which evolve during the course of the programme development cycle (orientation – consultation – prioritisation – approval).

3. Glossary

BIPM	International Weights & Measures Organisation
CCQM	BIPM committee responsible for chemical and biochemical measurements
CEN	European Standards Organisation
CIA	Chemical Industries Association
CONTEST	An environmental PT scheme organised by LGC
CPACT	Centre for Process Analytics and Control Technology
CRM	Certified Reference Material
CSL	Central Science Laboratory of DEFRA
DAPS	A Distilled Spirits PT scheme
DSC	Differential Scanning Calorimetry
EA	Environment Agency
EMTN	VAM Environmental Measurement & Testing Network
ESI	Electrospray Interface
FAPAS	A food PT scheme organised by CSL
ICP-OES	Inductively Coupled Plasma Optical Emission Spectroscopy
IDMS	Isotope Dilution Mass Spectrometry
IRMPD	Infrared Multiphoton Dissociation
IRMS	Isotope Ratio Mass Spectrometry
ISO	International Standards Organisation
IQC	Internal Quality Control
IVD	<i>In Vitro</i> Diagnostics Device
JCTLM	Joint Committee for Traceability in Laboratory Medicine
MCERTS	EA Sponsored Certification Scheme
MRA	NMIs Mutual Recognition Arrangement
NIST	USA's NMI
NMI	National Measurement Institute
FT-MS	Fourier Transform Mass Spectrometry
OGD	Other Government Department
PCR	Polymerase Chain Reaction, a propriety DNA amplification technology
POCT	VAM Point of Care Testing Network
PT	Proficiency Testing
RM	Reference Material
RT-PCR	'Real Time' PCR, a version of PCR used for DNA quantification
SNP	Single Nucleotide Polymorphism (Single DNA Base Difference)
UKAS	UK Accreditation Service
UK NEQAS	UK National External Quality Assessment Scheme (Clinical)
WEQAS	Wales External Quality Assessment Scheme (Clinical)
WGA	Whole Genome Amplification

Annex 1 - Project Descriptions

Project CM1.1 Maintenance of Supply of Reference Materials

Aims & Objectives

A reference material is the most common way for a laboratory to link its measurements to those made in other laboratories, provide data for the calculation of measurement uncertainty, to validate a method and to provide 'traceability'. It is therefore essential that materials prepared under the VAM programme and the infrastructure around the materials are maintained to ensure user confidence. The work proposed under this programme should ensure the integrity of the supply of materials following certification.

Deliverables

Deliverable	Description	Due
CM1.1/1	Stability tests on at least 105 RMs	Sep 06
CM1.1/2	9 replacement RMs produced and available for distribution	Sep 06
CM1.1/3	Updated safety data sheets and labels, which address changes in legislation, for 90 RMs	Sep 06
CM1.1/4	Updated certificates conforming to international agreements on the amount and format of the information produced for 60 RMs	Sep 06
CM1.1/5	An effective technical support service for handling and responding to customers enquiries as evidenced by positive customer feedback	Sep 06
CM1.1/6	Promotion of VAM RMs through the publication of 3 articles in the scientific press and the publication of 70 RM certificates on the web-site	Sep-06

Background

The vast majority of chemical reference materials produced under the VAM programme are stored and sold by LGC. At present, there are approximately 170 materials on sale which have been funded by VAM covering a wide range of material types and analytical areas. This number will increase as more materials are prepared under the programme. Currently, the income from sales of the materials is used to maintain the service, but the income does not fully fund all the activities necessary to maintain a reputable supply of good quality materials.

Main Activities

Stability testing. It is essential that the materials offered for sale have not changed in composition since they were issued. The shelf-life of a material is considered during production but the certified / assessed values must be checked periodically to give confidence in the supply. Any changes which occur can then be detected at an early stage and action taken to avoid loss of user confidence. The frequency of testing depends on the product type and the analyte of interest. The procedures in place to monitor materials follow on from a recent project 'Predicting the Shelf-life of Reference Materials'.

Replacement. Replacement materials are required when either all stocks have been sold or the composition of a material has started to change. Continuity of supply is important to users and a replacement programme needs to be in place to ensure a

rapid transition between batches. Although the method of production of a replacement material would usually be very similar to the original batch, there is an investment required which may not be repaid by sales income for many years.

Safety data sheets and labelling. Of the 170 (approx) materials on sale, about 70 require safety data sheets before they can be sold/transported both nationally and internationally. A safety data sheet is prepared as part of the production process using the expertise of staff within LGC, but there is a need to update the sheets to reflect changes in legislation (e.g. the new CHIP legislation requires more details of hazards to the environment). Similarly, the labelling of a material needs to include hazard information, where applicable, and a review system should be in place to ensure compliance with current legislation.

Certificates. The certificate or statement supplied with a reference material is the primary source of information for users regarding how the material was prepared and certified, and how it should be used. It is important that the documentation issued reflects international agreements on the amount and format of information supplied. A review system should be in place to assess the need and implement the requirements for updating.

Customer enquiries. LGC receives many enquiries from current and potential users regarding VAM reference materials. These range from how a material was prepared, how it should be stored, which procedures were used to certify the material, interpretation of analytical results to the certified values themselves. Sometimes analyses are required to investigate queries. This is a responsive service requiring expert knowledge of the materials and the production processes involved.

Promotion. For a material to be used by the scientific community analysts need to know of its existence and be confident in the way it has been produced. Although LGC Promochem carry out marketing exercises in collaboration with the production team, these are mainly focussed on catalogues and exhibitions. The production of VAM reference materials needs to have more coverage in the form of articles in the scientific press giving details of the production process and this is particularly important for matrix materials which have a shorter shelf-life and cannot wait for other methods of communication of their availability. In addition, more information needs to be included on the web so that users can make more informed choices about the materials they buy. The publication of all certificates on the web-site is of high priority.

Project CM1.2 Development and Improvement of Matrix Reference Material Production and Certification Capabilities

Aims & Objectives

To ensure that procedures used to produce and certify matrix reference materials reflect current best practice, as presented in international documents and guidelines. In particular, procedures for stability testing, calculating certified values and uncertainties and establishing traceability require investigation and up-dating.

Deliverables

Deliverable	Description	Due
CM1.2/1	A work plan which addresses those aspects of RM production needing improvement, or redesign following the publication new international guidelines, such as the revised ISO Guide 35	Jul 04
CM1.2/2	A report on recommended procedures for RM certification including improved approaches to stability testing and the use of weighted/unweighted data to calculate certified values	Jan 05
CM1.2/3	A report which identifies the main gaps in the current RM preparation facilities in the UK and recommends how these should be addressed	Mar 06
CM1.2/4	A report on the use of interlaboratory data to assign reference values, which examines ways of establishing the traceability of certified values, the no. of laboratories needed for a valid value and the consistency over space and time of independent laboratory studies based on 3 matrix reference materials	Sep 06

Background

There is now an urgent need to examine and develop improved approaches for the production and certification of matrix reference materials, in the light of current international debate on this issue. Of particular importance is the major revision of ISO Guide 35 (Certification of Reference Materials), that will be completed in 2003 and the increasing emphasis being given to traceability issues in chemical measurement.

Main Activities

- Review the requirements of the new edition (2003) of ISO Guide 35, and other relevant recent publications, in terms of reference material production and certification issues.
- Investigate the use of isochronous stability testing and evaluate the relative merits and applicability of this approach compared to conventional stability testing.
- Investigate the application of a linear model to assess long-term stability and shelf-life and to estimate the uncertainty contribution arising from stability effects.
- Optimise procedures for post-certification stability monitoring, particularly in terms of testing protocols, testing intervals and data evaluation procedures.

- Investigate and compare procedures for calculating certified values and uncertainties from weighted and unweighted results.
- Investigate alternative approaches to estimating the uncertainty of certified values derived from an interlaboratory study.
- Investigate ways of establishing the traceability of certified values derived from an interlaboratory study, including the use of a common calibration material that is itself traceable.
- Investigate the number of laboratories required for an interlaboratory study to provide a valid, traceable certified value, particularly in terms of the between-laboratory variation observed in the data.
- Review the availability of facilities and equipment in the UK and Europe for the preparation of bulk quantities of candidate reference materials and the feasibility of making use of these facilities. Identify any critical gaps in equipment availability.

Project CM1.3 Development and Improvement of Calibration Capabilities for Pure Substances

Aims & Objectives

To develop, where necessary, improved procedures for the purification of organic compounds for use as calibration reference materials. To develop improved procedures for the certification of pure organic compounds, or their solutions, taking account of new measurement techniques.

Deliverables

Deliverable	Description	Due
CM1.3/1	A report on significantly improved methods for determining the purity of organic pure substance standards, including the use of FT-ICR-MS for organic impurities and cold –on column GC-ICP MS combined with GC-MS for elemental detection and confirmed mass.	Sep 04
CM1.3/2	A report on two new, or substantially improved methods for purifying organic compounds to >99%	Apr 05
CM1.3/3	A report on an improved method for routine metrological determination of moisture in RMs, including the evaluation of new approaches such as Near IR. Two methods will be initially screened, but only one selected for full development	Jul 05
CM1.3/4	Publication of a detailed protocol and application notes for confirming the identification of a pure organic compound that is to be certified, including measurement of thermal properties	Nov 05
CM1.3/5	A UKAS accredited calibration method for the certification of aqueous ethanol reference materials based on IDMS	Jan 06
CM1.3/6	Published spreadsheets and guidance for use for combining values from different techniques to provide an overall certified value and uncertainty	Sep 06

Background

Pure chemicals (or solutions thereof) form an essential part of many traceability chains in analytical chemistry, since they are frequently used for calibrating analytical instruments. Accordingly it is important to be able to obtain or produce high purity materials with reliable and traceable certified values. Areas of considerable importance include the provision of pure organic substances with certified purity values and certified melting point values. Another important area is our measurement capability for the provision of ethanol in water reference materials.

Purification of organic compounds and certification of their purity to produce primary chemical standards has been of concern to a relatively small number of NMIs for many years. There have been few recent improvements in methodology and most institutes (including LGC) rely on classical chemistry for purification and a small number of "traditional" techniques (principally DSC, FID-GC and Karl Fisher) for certification. However, it is now timely to investigate new approaches to a problem which underpins all analysis of organic compounds. LGC has expertise in a number of powerful instrumental techniques which have not until now been applied to this problem by any NMIs. These include FT-ICR-MS for identification and possible quantification of organic impurities, NIR for water determination, use of cold on

column GC-ICP-MS (to detect all the elements present) combined with GC-MS (for confirmed mass), and (provided small amounts of a primary pure standard are available) high accuracy IDMS for assay of the major constituent.

With regard to the provision of small amounts of primary pure standards, it is proposed to build on the experience of the pharmaceutical industry in determining the identity, purity and quantity of compounds synthesised by combinatorial methods. In particular, preparative scale LC should allow purification of small quantities of primary organic standards (including isotopically labelled materials) with much greater speed and effectiveness than traditional approaches. Application of LC for purity determination has been hampered by the lack of a suitable "universal" detector equivalent to the FID used for GC. However, work in the pharmaceutical industry has shown the value of LC systems combining multiple detectors, eg a UV detector (purity estimate), a mass spectrometer (confirmation of identity), and multi-channel evaporative light scattering detectors (quantitation). These approaches should be particularly attractive for organo-metallic compounds which are difficult to handle by conventional techniques.

Main Activities

- Investigate and develop a modern procedure, such as preparative LC, for purifying organic compounds to a purity of >99%.
- Develop improved procedures for determining the purity of organic compounds, based on those techniques currently in use, such as GC, HPLC and DSC.
- Investigate the potential for using additional techniques, such as LC/MS, NMR, TGA for establishing purity values.
- Further development of methodology for moisture determination, with emphasis on accurate determinations for low moisture levels and/or small samples.
- Investigate procedures for identifying impurity species.
- Develop a protocol for confirming the identity of a pure organic compound that is to be certified as a reference material.
- Assess the availability of equipment and services for assigning certified melting point values to organic compounds and the feasibility of setting up a UK reference melting point facility.
- Critically compare the primary dichromate titration method for the certification of alcohol in water reference materials with the IDMS primary method that has been the subject of CCQM key comparisons. Evaluate any relative bias and if appropriate quantify a correction factor.
- Investigate procedures for combining purity estimates, or other values, obtained by different techniques, to provide an overall certified value and uncertainty.

Project CM1.4 UK Chemical Calibration Facility

Aims & Objectives

- To transfer expertise obtained from high level metrological studies to UK reference laboratories and to promote better understanding of the benefits of traceable measurements with the UK analytical community.
- To link UK activities into the international measurement community

Deliverables

Deliverable	Description	Due
CM1.4/1	A report which identifies the gaps and issues associated with the quality, availability and suppliers of pure calibration standards and solutions	Sep 04
CM1.4/2	A report covering the food and environmental sectors, plus two others on the experience and benefits of using the guidance developed under the previous programme for implementing traceability and the further development of sector-specific guidance	Jan 05
CM1.4/3	5 established calibration services used by an average of 5 clients pa who pay for the direct cost of the calibrations	Oct 05
CM1.4/4	Active participation in the CCQM meetings, including providing the Chair and Secretariat for the Inorganic WG and related EUROMET activities, support for European initiatives for RMs including the EU Virtual Institute and the ERM consortium.	Sep 06
CM1.4/5	The operation and establishment of four sector specific user groups and networks (two current networks, plus two new ones), which are electronically networked, aimed at providing a better understanding of the benefits of traceable measurements and transferring expertise in high accuracy measurement. At least six network meetings to be held per year.	Sep 06

Background

It is essential to ensure that the work undertaken to establish an infrastructure for traceable measurements produces real benefits through improved reliability and comparability of everyday measurements. This depends on laboratories making an increasingly wide range of chemical measurements which are soundly-based on traceable standards, reference materials, or reference values. This can only be done through provision of artefacts, services and collaborations which link a wide range of materials, methods and laboratories to the relatively small number of international key comparisons which are planned.

Work is required to develop UK services to deliver this horizontal broadening and to encourage laboratories, accreditation bodies, and other relevant organisations to use them. It is also essential to show how these developments can be implemented in a cost-effective manner at the working laboratory level and to promote their value amongst the various stakeholders. This also needs to be done in close collaboration with analytical and reference laboratories and accreditation bodies.

We aim to develop the UK capability for "in-house" RM production by assisting in sourcing of materials for this purpose and continuing to involve a wide cross-section

of laboratories in our round robins, the on-going "user group" networks, or other aspects of RM production.

Internationally, close co-operation with overseas institutes and organisations is essential to ensure a strong UK voice in the development of the chemical measurement system and the support the practical collaborations in studies and CCQM key comparisons. Efficiency gains are also being achieved by collaboration with overseas institutes in the production of the 'high level' materials and related activities.

The UK Chemical Calibration Facility provides a focal point to facilitate achievement of these goals. Within the UK, it offers a means of providing internationally-recognised traceability for reference materials and calibration standards produced by of a wide variety of suppliers and laboratories, as well as assisting in their effective co-ordination. Externally, the Facility engages in collaboration with overseas institutes to ensure more efficient production of high-level materials and to maintain the necessary links between UK chemical measurements and the international measurement system.

Main Activities

- Develop the portfolio of calibration services and promote their uptake
- Establish collaborative relationships with standards suppliers, PT scheme organisers, reference laboratories and analytical laboratories in major UK industrial companies
- Participate in international fora and develop overseas collaborations
- Support relevant European activities such as the EU Virtual RM Institute and development of a European RM "brand"
- Further develop UK guidance and provide advice on implementation of traceable measurements, particularly within the context of ISO 17025 accreditation
- Establish and maintain sector specific networks which will provide laboratories with a better understanding of the benefits of traceable measurements and good analytical practice in general. (*Training and coaching activities will be supported through project KT2.3*)

Project CM1.5 Accreditation of UK Reference Material Producers

Aims & Objectives

- To examine the feasibility and benefits of an accreditation scheme for reference material producers and, if appropriate, to develop a framework for implementing an accreditation scheme in the UK.

Deliverables

- To be agreed

Background

There is currently a great deal of deliberation going on around the world with respect to the appropriate route for the accreditation of Reference Material Producers. Within Europe (4E-RM WG) there does not appear to be a clear consensus on which standard is the most appropriate, or whether a combination of standards should be considered. International standards and guides (notably ISO Guide 34 and ILAC-G12) have been produced although, with the exception of certain accreditation bodies (e.g. within Australia and USA), these have not been wholly adopted by National Accreditation Bodies. There is apparent agreement that some of the existing 'accreditation' standards, currently covered by MRAs, would satisfy many of the issues associated with RM Producers, and that accreditation by these in association with ISO Guide 34/ILAC-G12 may provide the assurance that is being sought. However it could be that flexibility within the approach is needed, matching the standard(s) to the needs of the individual RM Producer. It is important that the benefits and risks of each issue are considered carefully and that an international consensus is reached leading to harmonised approaches and cross-border recognition.

National Measurement Institutes (NMIs) throughout the world have established a mutual recognition arrangement (MRA) in relation to the standards and calibration services underpinning national measurement systems. The National Physical Laboratory (NPL) is the lead institute for the UK and has nominated LGC as a partner for the chemical measurement system. However, inclusion within the MRA is essentially confined to those organisations (usually NMIs) and those measurements that have been the subject of international key comparisons. Such key comparisons are necessarily limited in extent and will not cover all measurements and organisations concerned with reference material production and certification. It is, however, important to ensure that all reference materials and values provided by UK organisations are linked into this international system for traceable measurements.

Accreditation of reference materials producers will provide a potential mechanism for international recognition of competence on a wide basis, embracing a large range of reference materials and certification measurements. The traceability of data provided by accredited producers will in time be established through links to organisations within the MRA.

Furthermore, accreditation will fulfil one essential requirement for the inclusion of reference material producers within the MRA, namely the requirement for a quality

system subject to accreditation or peer review. Accreditation of a reference material producer, combined with successful participation in appropriate MRA key comparison exercise(s), would also serve to include the producer within the MRA where the producer and the NMI agreed that this was desirable. Such inclusion within the MRA would cover the particular measurement that was the subject of the comparison and other generally similar measurements that were considered to be embraced by the comparison exercise(s).

Main Activities

- Investigate likely uptake and value for RM producer accreditation, in consultation with producers and accreditation bodies
- Develop a framework for implementing an accreditation scheme for UK RM producers

Project CM2.1 Development and Validation of Methodology for Accurate Quantitation of Inorganic Analytes

Aims & Objectives

- To further develop high accuracy methods for the determination of reference values required for the calibration services and RM production
- To undertake related measurement infrastructure activities, particularly participation in UK, European regional, or CCQM interlaboratory comparisons
- To carry out research into specific aspects of the methodology critical to the accuracy and scope of the methods, where possible in collaboration with academic or other research groups.
- To ensure the methodology embraces inorganic analytes in a wide range trade, industry, health, food, forensic and environmental applications.

Deliverables

Deliverable	Description	Due
CM2.1/1	Published methods based on multicollector ICP-MS for at least two applications capable of achieving a five-fold reduction in uncertainty	Jul 04
CM2.1/2	Published methods based on multicollector ICP-MS which are capable for use with 129I and 32P spike isotopes when only extremely small amounts of material are available and the isotope ratio is significantly different from the ideal 1:1, as required for certain clinical applications	Jan 05
CM2.1/3	A report on the working approach to the reduction of interferences to a metrologically usable level using collision cell and high mass resolution ICP-MS for three applications required by the UK Chemical Calibration Facility	Apr 05
CM2.1/4	New IDMS-based methodology required for biological and environmental matrices, which is suitable for applying to an international comparison, with validated preparation and equilibration stages	Jul 05
CM2.1/5	ICP-OES and ICP-IDMS methodology for the accurate and precise quantification of P and S in bio-assays acceptable for the certification of these elements in matrix RMs and/or the provision of reference values	Nov 05
CM2.1/6	Pilot-tested methodology for certifying metals in matrices such as car catalysts, high performance alloys, polymers and soft tissues using quantitative laser ablation ICP-MS	Apr 06
CM2.1/7	Validation of the new methodology through the successful completion of 3 CCQM or EUROMET key comparisons, or studies in relevant fields	Sep 06

Background

The overall focus of the work is the requirement to deliver improved methodology where the instrumental measurements are based on conventional mass spectrometry (MS), isotope ratio mass spectrometry (IRMS) and isotope dilution mass spectrometry (IDMS). The research is not, however, restricted to these mass spectrometry

techniques; all aspects of the methodology needed to develop complete, validated analytical methods will be investigated, and specific illustrative applications will also be addressed. Where relevant other instrumental techniques (eg ICP-OES, ion chromatography) will also be used.

A key aspect of the present proposals is to improve the UK's chemical metrology capability by development of the new Finnigan Neptune multi-collector ICP-MS instrument at LGC. Several instruments of this type are available in the UK but are used primarily for geochemical-type applications or academic research; this will be the first UK facility aiming to exploit its unique capability for metrology applications. As in other areas, formal collaboration with the manufacturer will facilitate this development and improve the value-for-money of VAM delivery.

The IDMS protocol used at LGC has been well established in previous VAM projects but we need to stretch our capability to new elements. One important progression is to provide accurate elemental analysis of elements with biological and pharmaceutical relevance. The Neptune permits extreme isotopic ratios to be measured with good precision. This allows us to use spikes such as ^{129}I and possibly ^{32}P that are safe to handle in small quantities. The LGC matched IDMS protocol means that absolute spike abundance 'cancels' in the IDMS equation and therefore decay is not an issue providing sample and calibration blends are prepared at the same time. Iodine analysis provides a high accuracy quantification of thyroid drugs and similar pharmaceuticals and this will link with a current EU programme where we are already contributing organic IDMS. Current organic IDMS methodology at LGC provides an uncertainty of ~2% for assay of iodine-containing drugs; an inorganic approach could improve that value to <0.5 %.

Depleted uranium currently has high health and political profile and is therefore likely to form part of a forthcoming CCQM pilot study. It is important for the UK to take part in such a study given the need for UK measurements in this area to be internationally traceable. Given the availability of the Neptune, we can not only develop the high-accuracy isotopic ratio measurements needed for this work but can also investigate accurate quantification of depleted uranium by IDMS. This study would build on our experience in actinide analysis and IDMS and use the unique potential of the Neptune for multiple ion counting.

The Neptune also provides an opportunity to further extend the capability to supply and certify isotopic spike standards, an area where LGC has developed a reputation for speciation standards. Synthesis is best contracted to a third party and it is therefore essential that the isotopic composition of the spike is determined after synthesis. This capability is especially important for standards of the lighter isotopes such as S or Ca which are thermally fractionated. The Neptune can provide primary measurement of isotopic enrichment without the need to rely on a traceable isotope producer such as Oak Ridge. This is very important for mass produced spikes where we can source enriched isotopes from the cheapest suppliers but incorporate our own full uncertainty in the finished product.

A further collaboration, with Agilent Technologies, has resulted in installation of a laser-ablation ICP-MS at LGC. Qualitative use of this technique is relatively common, but it is proposed to work with Agilent to develop high-accuracy quantitation of solids and surfaces. At present the only metrology capability of this type is at NIST who maintain a restricted bank of basic matrix materials such as rock

samples and glass. However, laser performance is highly matrix dependent and current standards are not suitable for industrial applications or soft-tissue analysis.

Important industrial applications of this capability with hard materials include car catalysts and high performance alloys (developing current collaborations with artificial hip manufacturers). The Agilent 213nm laser is also ideally suited to soft tissue samples. It is proposed as part of this project to upgrade the laser with cryo-cell capability. This would allow development of high accuracy solid analysis protocols for soft-tissue standards such as cellulose which can be underpinned by conventional IDMS digestion of the same material. Provided this research is successful, the ultimate goal would be to provide laser sampling of a soft tissue such as proteins doped with an inorganic tracer (such as ^{32}P) to provide traceable assay using bio-assay methods such as 2D gels.

Main Activities

- Investigate the application of multi-collector ICP-MS for high accuracy IDMS
- Extend current capability for high accuracy ICP-OES, notably for mono-isotopic elements
- Study the application of collision cells to reduce interferences in high accuracy ICP-MS, including IDMS measurements
- Investigate quantitative analysis of solid samples using laser ablation ICP-MS, with particular emphasis on development of standards
- Study errors and uncertainty arising during sample preparation, including methodology needed for multi-element IDMS
- Participation in CCQM and other international comparisons

Project CM2.2 Development and Validation of Methodology for Accurate Quantitation of Organic and Organo-Metallic Analytes

Aims & Objectives

- To further develop high accuracy methods for the determination of reference values required for the calibration services and RM production
- To undertake related measurement infrastructure activities, particularly participation in UK, European regional, or CCQM interlaboratory comparisons
- To carry out research into specific aspects of the methodology critical to the accuracy and scope of the methods, where possible in collaboration with academic or other research groups.
- To ensure the methodology embraces organic and organo-metallic analytes in a wide range trade, industry, health, food, forensic and environmental applications.

Deliverables

Deliverable	Description	Due
CM2.2/1	A report on a feasibility study identifying the options for accurate quantification using FT-ICR-MS, including MALDI applications	Sep 04
CM2.2/2	A developed method, presented at a suitable scientific conference, on the accurate quantification of a difficult organic analyte, such as a steroid, in the absence of isotopically labelled analogues	Nov 04
CM2.2/3	Documented approaches, including generic labelling, degree of labelling and spike equilibration, to the selection and handling of internal standards for optimum quantitation by IDMS using LC-MS and LC-MS-MS	Apr 05
CM2.2/4	Published recommendations for the scope of application and optimum operation for IDMS accurate quantification using fast GC-TOF-MS, which will be applied to one or two application areas	Sep 05
CM2.2/5	New methodology based on hyphenated techniques such as LC-MS-MS for Sn and As in clinical samples and Se in dietary substances, validated through appropriate international comparisons	Jan 06
CM2.2/6	A report on a survey conducted in collaboration with OGDs on organo-metallic species of importance in consumer products	Jul 06
CM2.2/7	Successful completion of 3 CCQM or EUROMET key comparisons or studies in fields such as pollutants, pesticides and purity determinations	Sep 06

Background

The overall focus of the work is the requirement to make end measurements based on conventional mass spectrometry (MS), isotope ratio mass spectrometry (IRMS) and isotope dilution mass spectrometry (IDMS). The research is not, however, restricted to these mass spectrometry techniques; all aspects of the methodology needed to develop complete, validated analytical methods will be investigated, and specific illustrative applications will also be addressed.

The Finnigan FT-ICR-MS facility implemented at LGC under the DTI VIMMS project is a unique facility amongst all chemical metrology institutes world-wide and will play a major role in delivery of both this project and the related on Development and Validation of Methodology for Determination of Identity, Authenticity and Origin. The investigation of FT-ICR-MS for quantitation will be a novel piece of work, undertaken in collaboration with Finnigan. The FT-MS technique will be investigated for dynamic range of quantitation and also for the suitability of the wide range of experimental procedures used to trap, accumulate and detect ions in the spectrometer cell. The collaboration with Finnigan will also provide a MALDI source with applicability to molecules of a wide size range. The nature of MALDI has made it the source of choice for many high throughput laboratories but recent advances (eg choice of analyser, total spot consumption) and increased use have resulted in MALDI being used to provide semi-quantitative information. A study into the possible uses of MALDI quantitation, including the benefits/pitfalls of the source for this purpose, is an important aspect of the proposed research.

Efforts under the previous two VAM programmes have provided a substantial pool of expertise for organic IDMS, including development of the "exact matching" technique. It is essential, however, to undertake further research to extend the capability enable us to offer better calibration services for a wider range of analytes/matrices and, in particular, to reduce the cost and time required in applying this capability as part of the UK Chemical Calibration Facility. With regard to improving the capability, it is proposed to investigate a "Static IDMS" technique based on LC-MS. The use of column switching and peak parking technologies will be investigated for continuous ratio measurements on LC peaks. The advantage of this would be the removal of on column fractionation normally observed in transient IDMS analysis. Monitoring of the ratio in a continuous manner should also, in theory, reduce the isotope ratio uncertainty.

Fundamental work on spike equilibration was undertaken in the last VAM programme but from the perspective of elemental IDMS. Work on applications such as PCB's in sediment has shown, however, that further research on understanding spike equilibration steps for labelled organic molecules is also desirable. The use of ToF and ion trap analysers have been considered unsuitable for IDMS measurements in the past because of doubts over reproducibility of instrument response and the effect of extraneous ions on instrument response. The instrumental features causing many of the historical problems with the use of these analysers for quantitation have, however, rapidly evolved. The availability, for example, of features such segmented channel plate multipliers in ToF and selective ejection techniques in ion traps warrants the reinvestigation of these technologies for IDMS applications.

Labelled materials are expensive and often need to be synthesised specifically for an IDMS application. It is proposed to look at generic reaction mechanisms for attaching (isotopically) labelled and non-labelled tags to pure compound standards and also samples. As well as IDMS applications, this could also be used for the tagging of analyte groups (e.g. sulphur drugs). A separate approach is to reduce the consumption of expensive labelled materials as internal standards for IDMS. Exact matching IDMS has been shown to reduce systematic bias and increase precision but it often requires the use of large amounts of labelled material. Investigation into a number of aspects will be undertaken, including the degree of spiking, the increased uncertainty associated with non-exact matching, and the effect of key instrument parameters (eg.

the change of observed isotope ratio with scanning speed of quadrupole MS instruments).

An important aspect of this project will be to build on expertise in speciation developed under previous VAM projects, particularly in the context of multi-element speciation techniques. This will include further development of the GC-ICP-MS capability to include Se, Hg, S, pesticides, and identification of previously uncharacterised species, e.g. As-species in marine samples such as algae, by FT-MS and MS-MS techniques. Current speciation research on Sn and As will be extended into the clinical field by applying/adapting methodologies developed during the previous VAM programme. Sample matrices of interest include serum, blood, urine and tissues if available. In addition, speciation of different organo-metallics (Hg, Se, etc.) are of growing interest in both these samples and others such as herbal or alternative medicines on sale in the UK. The latter are already screened for total metal content by LGC for the Medicines Control Agency (MCA). Existing collaboration with Agilent Technologies and their clients will provide an important contribution for this work. Additional collaborations will be set up with appropriate laboratories and hospitals that have expertise or interest in this field. Screening of consumer products is a related area of major importance which requires further research on both new species and matrices such as food commodities, food supplements, drinking water etc. There is growing interest in obtaining data on a wide range of organo-metallic species of toxicological importance, including TBT, TPhT, As(III), As(V), and MeHg. Collaborations will include regulatory bodies such as the DTI Consumer Safety Unit and the Food Standards Agency (FSA) in order to target efforts and objectives with the needs of regulators, industry and consumers.

Further research is also proposed on the critical area of extraction techniques for speciation as well as on separation and detection of species, especially using LC and GC coupled to ICP-MS and/or organic tandem-MS. This last point highlights the importance attached under the new project to establishment of a combined speciation facility at LGC, i.e. to develop a centre of excellence in speciation based on our unrivalled expertise in both organic and inorganic mass spectrometry. A vital goal will be development of organo-metallic species extractions and separations which can be applied unchanged to analysis by all the techniques.

Main Activities

- Investigate sample preparation problems arising with accurate analysis of labile organic and organo-metallic compounds
- Study errors and uncertainty arising during sample preparation including methodology needed for IDMS applications
- Develop methodology for accurate speciation of additional organo-metallic compounds, based on both inorganic and organic mass spectrometry
- Investigate techniques for enabling quantitation using high resolution FT-ICR-MS, including development of IDMS applications
- Develop IDMS methodology of organic analytes based on Maldi solid-phase sampling, using FT and/or TOF mass spectrometry
- Participation in CCQM and other international comparisons

Project CM2.3 Development and Validation of Methodology for Determination of Identity, Authenticity and Origin

Aims & Objectives

- To further develop a range of methods for the determination of identity, authenticity and origin of chemical substances
- To carry out research into specific aspects of the methodology critical to the accuracy and scope of the methods, where possible in collaboration with academic or other research groups.
- To ensure the methodology embraces organic and inorganic analytes for a wide range trade, industry, health, food, forensic and environmental applications.

Deliverables

Deliverable	Description	Due
CM2.3/1	A peer-reviewed publication on the instrumental operation of the FT-ICR-MS instrument for the accurate molecular weight determinations of organic species, including medium to high molecular weight compounds in a range of matrices	Sep 04
CM2.3/2	A report on a study on alternative MS-MS approaches including IRMPD and electron capture dissociation by FT-ICR-MS and the instrumental factors which give reproducible and quantitative spectra suitable for spectral libraries	Jun 05
CM2.3/3	New methodology for purity and impurity assays, suitable for international comparisons and certification of pure primary standards based on HPLC with UV and ESI-MS in parallel	Dec 05
CM2.3/4	A report on a feasibility study of laser ablation ICP-MS for forensic fingerprinting of materials such as glass and bullets	Sep 06
CM2.3/5	A published, fully evaluated method for sulfur, suitable for metrological applications and capable of determining geographical origin based on multi-collector ICP-MS	Sep 06

Background

The use of accurate isotope ratio methodology is rapidly expanding from the traditional geo-science applications to a wide range of regulatory problems such as origin, authenticity and speciation of natural products or forensic identification of banned substances. This has stimulated a need for compound-specific standards and highly accurate (low uncertainty) rather than merely very precise measurements of isotope ratios. The work will underpin the determination of reference values for application in areas such as the origin of steroids (e.g. in sports drug samples and in animal testing), geological origins (e.g. of oil-bearing minerals), and detection of authenticity and adulteration in the food industry.

The scope of the current project on mass spectral libraries will be extended to cover MS-MS on different instrumentation and also the possibilities resulting from use of IRMPD on the FT-MS. In addition electron capture dissociation MS-MS, which is also only available on FT instruments, has a similarity to electron impact dissociation and may yield MS-MS spectra similar to EI and therefore searchable in EI databases.

This would be ideal for structural characterisation, e.g. for pure primary organic compounds. Peptide libraries are currently based entirely on mass. Investigations into the use of accurate mass measurements to reduce the number of candidate searchable peptides would be of benefit to those using peptide fingerprinting for protein identification.

Accurate mass measurement of small molecules in mixtures (i.e. contaminants) will again build on work in the previous VAM project. This application will require substantial development in collaboration with Finnigan and will be a test even for the FT-MS instrumentation as space charge effects and detector dead time are serious issues in trap and ToF analysers. The proper assessment of the measurement uncertainty would be an important aspect of this work. Investigation of the uncertainty of measurement on multiple charged ions (ESI) and large singly charge ions (MALDI) would also be of value.

An important aspect of the research with inorganic analytes will be to develop enhanced capability based on the new Finnigan Neptune multi-collector ICP-MS instrument which has been purchased by LGC. This instrument is now (January 2003) being installed and will be fully tested and operational for VAM 2003-6. Important industrial applications of this capability with hard materials include measurement of the rare earth elements used to prevent fraud by fingerprint CDs. The capability to work with hard laser targets such as glass and bullets would also extend the capability for authenticity and fingerprinting, using trace elemental and/or isotopic composition. This would be building on the capability in natural isotope ratio analysis from earlier VAM programmes.

Main Activities

- Extension of work on use of "AccMass" measurements determination of molecular weight / chemical formula of medium-large chemical molecules
- Application of high resolution FT-ICR-MS for determination of purity and identification of unknowns
- Development of spectral libraries and databases for identification of unknowns using LC-MS independently of ionisation techniques or specific instrumentation
- Determination of authenticity and origin based on measurement of natural isotope ratios by multi-collector ICP-MS

Project CM3.1 Traceable Measurement of Inorganic Analytes

Aims & Objectives

- To provide UK field laboratories with the tools required to achieve valid and traceable measurements of inorganic analytes in key applications within the following areas:
 - Industrial production and consumer safety
 - Environment
 - Food
 - Health
 - Forensic

Deliverables

Deliverable	Description	Due
CM3.1/1	A pure dibutyl sulphide standard certified for sulfur content and gasoline RMs certified at two sulfur concentrations plus the validation of industry-standard methods for sulfur in fuel and metals in alloys through the provision of reference values	Sep 05
CM3.1/2	Validated and documented methods, QC materials, RMs and CRMs from three collaborative studies with environmental laboratories, UKAS and EA to support accreditation to the contaminated land MCERTS scheme for inorganic analytes	Sep 06
CM3.1/3	Trace metal reference values for clinical PT schemes and a clinical CRM produced through two collaborative studies with UK and European laboratories and WEQAS and NEQAS	Sep 06
CM3.1/4	Validated methods for toxic and nutritional elements in food, reference values for PT schemes and CRMs produced through collaboration with FAPAS and food laboratories	Sep 06
CM3.1/5	Acting as the pilot lab, complete and report on two CCQM studies such as sulfur in fuel, iodine in a simple matrix or the elemental composition of car catalysts	Sep 06

Background

The benefits of traceable measurements are not always clearly understood in the field of chemical measurement. Quality systems and accreditation provide an assurance that measurement procedures are well-documented and correctly undertaken. Traceability provides a provenance for the standards and reference materials required to calibrate and validate those procedures. Used together they ensure measurement results which are both reliable and comparable with results obtained elsewhere, an essential requirement of the 21st Century global economy.

The need for reliable measurements is widely recognised by all sectors, but one might reasonably ask why at this time traceability should be of particular benefit in achieving reliable chemical measurements. The answer lies partly in the global economy but also in the increasingly fragmented and competitive nature of the

analytical sector and the greatly reduced level of expertise and experience available in many laboratories. Hence, measurements and standards come from an ever-broadening range of suppliers, users have ever-decreasing experience with which to judge their worth. As noted above, traceability provides a provenance which together with quality systems and accreditation can help to redress the balance.

Provided appropriate traceable materials and calibration services are available, little extra burden is placed on laboratories. Clearly, however, their own results will not in turn demonstrate traceability unless they undertake proper calibration and validation of their methods. Achieving traceable chemical measurements for the UK thus depends on both establishing an appropriate measurement infrastructure and ensuring that laboratories are willing and able to make use of it. Hence, the emphasis in this project on working with a wide range of UK laboratories; practical collaboration and direct involvement in specific tasks is arguably the most effective of all knowledge transfer activities.

In order to achieve valid and traceable measurements, UK analytical laboratories need fit-for-purpose standards and CRMs for key applications, e.g. where there are measurement problems, regulatory requirements, or a need for acceptance of UK data by trading partners. However, even with the availability of such materials laboratories frequently still experience serious problems in developing appropriate methods, either individually or in collaboration. What laboratories really want in key application areas are "total analytical packages" which can provide:

- a documented and validated method of known uncertainty
- one or more CRMs to validate the in-house implementation of the method
- low cost RMs for routine QC checks of the method
- a PT scheme with traceable reference values to confirm the correct, on-going application of the method
- international acceptance of the resulting data

This project will implement this approach by working with laboratories and industry or regulatory bodies to use the expertise developed at LGC under VAM to assist in development and validation of specific applications. The outcome will be documented methods validated by round robin and matrix RMs certified by both the participating laboratories and definitive methods at LGC. The latter will ensure traceable data linked into the international measurement system.

Extensive consultation with environmental regulators and laboratories, together with UKAS, has highlighted the need to underpin measurements related to contaminated land analysis. The key issue here is the impending MCERTS scheme to be introduced by EA in association with UKAS. It is widely recognised by all concerned that the current availability of traceable RMs, or even adequate QC materials, is totally out of proportion to the requirements set by the new scheme, the schedule for which embraces a wide range of both inorganic and organic analytes. It is clearly impossible for VAM to address all of these needs but it is proposed in the new programme to target key analytes identified by industry experts as of particular analytical concern. It is planned that this VAM work will be undertaken in full collaboration with the interested parties and also the CONTEST PT scheme which is operated by LGC. This approach will ensure that the work is well focussed and that the resource provided by VAM is augmented by substantial contributions from the interested parties. As

mentioned above, the emphasis will be on joint development of "total analytical packages", not merely production of reference materials.

LGC has produced a range of food reference materials for many years as part of the VAM programme, principally through the round robin approach. This will continue but discussions are being held with CSL with regard to their FAPAS scheme. Collaboration between the two activities should improve efficiency, enable production of CRMs carrying both definitive and round robin values, and allow provision of traceable reference values for relevant FAPAS PT schemes. The latter would facilitate validation of methodology for analyses recognised by the industry as having on-going problems. A similar collaboration has already been established in the clinical field with WEQAS and it is planned that this should continue in the new programme. Provided agreement on collaboration can be reached, it would be beneficial to extend the clinical activities to include the UKNEQAS schemes.

Main Activities

- Certification of calibration standard solutions
- Production and certification of matrix CRMs, RMs and QC materials
- Pilot UK and international comparisons providing certification data for the CRMs and RMs
- Publication of specific analytical methods, documented and validated through round robin collaborations
- Provision of reference values for related PT schemes

Project CM3.2 Traceable Measurement of Organic Analytes

Aims & Objectives

To provide UK field laboratories with the tools required to achieve valid and traceable measurements of organic analytes in key applications within the following areas:

- Industrial production and consumer safety
- Environment
- Food
- Health
- Forensic

To evaluate the application of new measurement technologies for characterising complex systems and demonstrate their potential to the following:

- the UK industrial (laboratory) community in general
- UK companies involved in clinical research and diagnosis and nutraceutical formulation and supply in particular

Deliverables

Deliverable	Description	Due
CM3.2/1	Ethanol standards and alcohol matrix CRMs certified in collaboration with UK laboratories and the provision of reference values for the DAPS PT scheme using GC-C-IRMS for low uncertainties	Sep 06
CM3.2/2	Validated and documented methods, QC materials, RMs and CRMs from two collaborative studies with environmental laboratories, UKAS and EA to support accreditation to the contaminated land MCERTS scheme for organic analytes	Sep 06
CM3.2/3	In collaboration with WEQAS and NEQAS provide reference values for PT schemes, and in collaboration with UK and European laboratories produce pure clinical standards (e.g. digoxin) and a herbal product CRM for organic analytes	Sep 06
CM3.2/4	Validated methods and matrix CRMs for organic toxins or nutrient in food developed through two collaborative studies involving FAPAS and food laboratories	Sep 06
CM 3.2/5	Acting as the pilot laboratory, complete and report on 1 or 2 CCQM/EUROMET studies; candidates include vitamins in a food matrix	Sep 06
CM3.2/6	In collaboration with industry through a user group, identify a target nutraceutical compound and produce a fully characterised standard	Sep 05
CM3.2/7	Prepare and characterise a matrix reference material for the chosen nutraceutical in an appropriate product	Sep 06
CM3.2/8	Development of guidelines and protocols for characterising nutraceuticals based on experimental work	Sep 06

Background

For a general background and rationale to the CM3 series of projects, see the 'Background' section of Project CM3.1.

LGC has long-standing expertise in preparation and certification of pure organic compound standards and, in some cases, certified calibration solution standards prepared from them. Re-certification of ethanol CRM's using GC-C-IRMS will provide a value with lower uncertainty than the titrimetric based method used previously. The same technique will allow certification of alcohol matrix CRM's such as wines, lagers etc. for ethanol content (currently certified for alcohol by volume using densitometry), giving added value to existing CRM's. It is also planned to collaborate with the DAPS PT scheme operated by LGC, particularly to provide reference values (of both ethanol and alcohol content) requested by the participants. This will facilitate collaborative improvement of the industry methodology.

The enhancement of the capability for purity determination will also facilitate the production of additional materials and/or calibration solution standards, ideally linked to CCQM international comparisons. Relevant studies in the CCQM timetable include CCQM-P31 (organic calibration solutions of PCB's, PAH's, pesticides) and CCQM-P20c (purity study of atrazine and an organo-phosphate).

The development of new measurement technologies such as 1-d and 2-d high resolution separation (e.g. CE, LC-LC, GC-GC), hyphenated/sensitive detection (i.e. MS, MSn, uv, Fluorescence, Rapid Scanning FTIR, Micro SpectroChemical Imaging, NMR, light scattering, fast GC-MS-MS) offers opportunities for complex matrix characterisation including trace detection in multi-component samples. Applications include the identification of specific compounds or determining differences in products or formulations, defining active ingredients in natural products, nutraceuticals or herbal remedies, or profiling metabolites or biomarkers in biological systems. Taken together these applications have economic, public health, regulatory, quality control and production significance.

Main Activities

- Certification of calibration standard solutions and pure calibration materials
- Production and certification of matrix CRMs, RMs and QC materials
- Pilot UK and international comparisons providing certification data for the CRMs and RMs
- Publication of specific analytical methods, documented and validated through round robin collaborations
- Provision of reference values for related PT schemes
- Evaluate the application of new measurement technologies for characterising complex systems.

Project CM3.3 Traceable Measurement of Chemical Species

Aims & Objectives

- To provide UK field laboratories with the tools required to achieve valid and traceable measurements of organo-metallic compounds and other chemical species in key applications within the following areas:
 - Industrial production and consumer safety
 - Environment
 - Food
 - Health
 - Forensic

Deliverables

Deliverable	Description	Due
CM3.3/1	A report providing an overview of the current suppliers of calibration standards for organo-metallic speciation which highlights the future UK needs	Sep 04
CM3.3/2	Pure 117Sn enriched TBT material and solution calibration standards for organo-metallic speciation produced with the help of external collaborators	Sep 05
CM3.3/3	CRMs for the speciation analysis of organometallics in products such as insoles or PVC toys undertaken in collaboration with UK laboratories and DTI's Consumer Safety Unit	Sep 06
CM3.3/4	Reference values and CRMs for organometallic speciation in clinical analysis (Sn, As and Hg) produced in collaboration with UK and European laboratories, WEQAS and NEQAS	Sep 06
CM3.3/5	Acting as pilot laboratory, complete and report on one or two CCQM/EUROMET studies involving organometallic species, such as DBT/TBT in a marine sediment, or a consumer product	Sep 06

Background

For a general background and rationale to the CM3 series of projects, see the 'Background' section of Project CM3.1.

In the area of organo-metallic speciation there is a need for a comparison of commercially available calibration standards and provision of additional isotopically labelled speciation standards to meet the current needs of analytical community. Some of this work will be undertaken in collaboration with Agilent Technologies and field laboratories. The aim will be collaboratively developed routine methods based on use of the calibration standards and isotopically labelled speciation spike materials certified by The Chemical Calibration Facility.

In addition it is essential to undertake production and certification of clinical reference materials for organometallic speciation analysis. Suitable matrices may be urine, serum or blood for species of Sn, As and Hg. Production and certification of

consumer safety reference materials for speciation analysis is also required, for example artificial/synthetic products such as trainer insoles and PVC toys. Development of selenium speciation started in the last programme and this will be continued collaboratively, if possible with additional support from an EU project. The aim will be to develop a CRM and a traceable routine method for dietary supplement analysis as the benefit from Se is now believed to be species dependant.

A GC-IR-MS capability is firmly established at LGC as a result of previous VAM projects. An extension of the development of compound specific isotope standards is needed for source of origin work such as drugs of abuse, explosives, and chemical warfare agents. Part of this work could be used to source material for a possible CCQM study (piloted by LGC) if sufficient NMI interest/capability is available, providing additional high-level input to the VAM work.

Main Activities

- Certification of calibration standard solutions, pure calibration materials and isotope-labelled materials
- Production and certification of matrix CRMs, RMs and QC materials
- Pilot UK and international comparisons providing certification data for the CRMs and RMs
- Publication of specific analytical methods, documented and validated through round robin collaborations
- Provision of reference values for related PT schemes

Project CM4 Tools for Chemical Metrology

Aims & Objectives

- Remedy deficiencies in practical uncertainty estimation for multivariate problems
- Establish a practical methodology for handling correlation in analytical uncertainty estimation
- Develop methods for assessing uncertainties near detection limits
- Provide internationally acceptable assessments of purity-related uncertainties in pure reference materials

Deliverables

Deliverable	Description	Due
CM4/1	A paper on numerical estimates of uncertainty for multivariate calibration accepted for refereed publication. The paper will report the results of literature review and experimental studies of multivariate calibration, comparing published multivariate uncertainty estimates with numerical methods.	Mar-05
CM4/2	A method for treating uncertainty near natural limits (detection limit and 100%) published in a peer-reviewed and accepted as a Supplement (or replacement section) on the estimation of uncertainty near detection limits for the EURACHEM/CITAC guide	Mar-06
CM4/3	A paper on treatment of correlated uncertainties using numerical (especially spreadsheet) methods, accepted for publication and a software tool implementing the recommendations for correlation available for free download from the VAM website	Jun-04
CM4/4	An expert working group report on uncertainty treatment for purity statements, including review of prior literature, practical tests of alternatives, and consequent recommendations, accepted for publication in a peer-reviewed journal	Jun-05

Background

Achieving internationally accepted results from UK laboratories will require the UK to develop a complete metrology infrastructure for traceable chemical measurement. Among the most critical technical elements of traceability are the uncertainties associated with reference standards throughout the calibration chain. While the appropriate procedures are well established for the physical parts of the traceability chain, there are important gaps in assessing uncertainty in chemical measurements for higher metrology. Four principal areas need attention:

- No existing international guidance provides for the common and important problem of uncertainties near fundamental natural limits of concentration, that is, near zero and near 100% concentration. These are important regions for regulation at the low end and for reference standard certification at the upper end of the scale; measurement near detection limits is common, and assessment and reliable statements of purity are critical for high purity CRMs. Addressing this need will improve traceability to primary standards by promoting consistent treatment of

purity data, and will facilitate compliance with legislation through provision of consistent guidance on treatment of low-level results.

- While uncertainty estimation for routine analysis allows for correlation by studying method performance as a whole, this is not an adequate approach at international metrology level, and effective and practical correlation handling is becoming essential to support traceability to primary standards in chemistry.
- Multivariate methods have general applicability for a wide range of problems, but establishing traceability (including uncertainty) for the results is made difficult by the complexity of the calibration models in use. This in turn makes the methods hard to validate, reducing applicability in regulation and reference material applications. It is therefore important to establish practical methods for uncertainty assessment in multivariate analysis, facilitating uptake of leading edge multivariate measurement technology in practical applications.

Main Activities

The project is divided into five areas, covering the issues identified above:

- Uncertainties near detection limits will be addressed through a study of existing treatment of uncertainties near natural limits (with special attention to detection limits) in chemical and biological analysis, leading to recommendations for treatment of uncertainties near limits. This will be developed in collaboration with the NMS Software Support for Metrology programme, where the issue is to be addressed from a theoretical point of view; this VAM project will both contribute to that activity and transfer the resulting best practice guidance to the chemical measurement sector
- Uncertainties near 100% concentration will be addressed with specific reference to uncertainties for purity declarations. The activity will include consultation with a suitable international expert group, followed by production of agreed guidance and, if specific calculations are required, supporting software illustrating the principle
- Correlation will be addressed by developing a practical numerical approach to the problem, which will be published as a formal technical paper and also implemented as a general spreadsheet application which, though intended principally for metrology applications, will be available to the analytical community
- Uncertainty estimation for multivariate methods will be reviewed from a theoretical point of view to establish available theoretical approaches. Numerical treatments will be assessed against the best current theoretical models, in order to obtain approaches that can be applied with existing multivariate software

Project NM1.1 International Standards and Performance Indicators for Nucleic acid Measurements

Aims & Objectives

The overall aim of the project is to produce a set of plasmid-based reference standards, which can be used to check the performance of quantitative nucleic acid measurements. It has three main objectives:

- To improve the quantitation of DNA through the use of plasmid based reference standards which have been validated through international trials
- To establish the equivalence of DNA quantitation measurements produced by NMIs
- To develop the performance standards for potential uses and distribute them to users

Deliverables

Deliverable	Description	Due
NM1.1/1	A report and a paper submitted to a refereed journal on the international evaluation of the NIST/LGC plasmid standards, including an evaluation of the equivalence of the NMIs involved, and a detailed assessment of the potential of the plasmid standards as reference materials.	Oct 04
NM1.1/2	A redesigned protocol for use of plasmid system or a redesign of the plasmid (whichever is deemed appropriate), and an improved protocol for the quantitation of DNA based on the results of the first round international trial of the plasmid system.	Apr 05
NM1.1/3	A report on the second round international evaluation of the plasmid system in at least 10 NMIs or international laboratories presented at an international meeting	Oct 06
NM1.1/4	An optimised plasmid-based performance indicator and protocol for its use available for distribution to users and described in a paper submitted to refereed journal, with information on its development being described in five updates on the MfB website	Mar 07

Background

Quantitative genetic measurements are particularly important, for example in underpinning legislation (detection of GM ingredients in food) and in disease management (monitoring pathogenic load with respect to disease progression or efficiency of treatment). However such quantitative PCR-based measurements are not sufficiently robust. Factors such as different detection methodologies and ill defined or in house standards all contribute to variability in results between laboratories.

Both national and international regulatory bodies are growing in support for the concept of plasmid based standards for DNA quantitation Two studies using plasmid standards have been carried out ^{5,6}. Both these studies describe the successful use of

plasmid standards for the quantitation of GMO but do not compare the results to other commonly used GM quantitation reference materials.

In 2001 LGC and NIST jointly filed for a patent based on a 2-plasmid system for real time quantitative analysis such as GM, bacterial detection, and prenatal diagnostics. A pilot study to produce and carry out initial inter-laboratory trials between NMI's using the system designed by NIST and LGC will have been carried out in early 2003. The purpose of this study is to verify the ability of a laboratory to determine the relative ratios of specific DNA sequences.

A significant potential problem with the use of plasmids is a high chance of PCR contamination. The cloning process, as well as all PCR reactions produce millions of copies of the target that are very stable and can contaminate all reagents in a laboratory. The routine use of plasmids in a laboratory will require rigorous and strictly maintained levels of plasmid and PCR product control. It will require more rigorous controls than genomic DNA based standards. To this end we will produce guidelines on the handling of plasmid based reference materials for PCR.

It is anticipated that a second round evaluation of the ratio system and a refinement of the plasmid target will be needed before a satisfactory level of agreement in the results is reached. Detailed analysis of the data from both rounds will be needed to evaluate the potential of the system as a certified reference material.

The work will be undertaken in collaboration with NIST and it has been assumed that there will be a sharing of the costs of the design and production of the standards.

Main Activities

- An assessment of plasmid standards through the organisation and analysis of two rounds of international intercomparisons
- Redesign of the plasmid targets in order to optimise their utility
- Collaboration with NIST on the development and production of plasmid standards and reference material for wider dissemination

Project NM1.2 A Primary Method to Produce Standards for DNA Quantitation

Aims & Objectives

- To complete the development of an IDMS based method for DNA quantitation
- To produce a set of quantified reference standards for use with common methods
- To validate through international trials a reference measurement system for DNA quantification, based on real-time PCR

Deliverables

Deliverable	Description	Due
NM1.2/1	An improved IDMS methodology to enable quantitation of PCR products (length 100 base pairs) with an associated uncertainty of less than 15%. To be achieved by improvements to purification methodology applied to PCR products prior to LC-MS.	Mar 04
NM1.2/2	A report on an international/CCQM trial to establish the integrity of one oligonucleotide from the reference system.	Mar 05
NM1.2/3	A documented quantitative DNA Measurement System, based on real time PCR (incorporating the method and standards for primers and PCR product) capable of achieving an associated uncertainty of less than 10%.	Sep 05
NM1.2/4	A completed international/CCQM study of the quantitative PCR reference system, including a report on the findings	Sep 06
NM1.2/5	A report on an international/CCQM trial for the validation of the IDMS methodology as a primary method for DNA quantification, plus a paper submitted to a refereed journal	Mar 07
NM1.2/6	Certified reference materials with values assigned by the IDMS technique comprising two primers and a PCR product, which support the reference measurement system.	Mar 07
NM1.2/7	A documented, validated reference measurement system (reference method and reference materials) for the high accuracy quantification of DNA using IDMS with details of the work published in a refereed journal and five regular updates on the work posted on the MfB website.	Mar 07

Background

Analysis requiring DNA quantitation has grown exponentially over the past 2-3 years. Applications such as GM quantitation, analysis of minimal residual disease in cancer and the assessment of bacterial and viral infection are all areas that have benefited from increased use of quantitative technologies. However the inconsistency in the terms used to describe the quantitation of DNA, such as genome equivalents or copy number makes it very difficult to make genuine comparisons between methods and between different laboratories. The thrust of the project is to produce certified reference materials comprising purified and quantified primers and targets, which will improve the accuracy and comparability of the measurement. The value assignments of the materials will be carried out using IDMS.

Pioneering work at LGC under the 2000-2003 VAM programme has shown the potential of IDMS as a primary method for DNA quantitation. Further work is required to refine the method such that it can be applied to PCR products of greater than 100 base pairs in length. In particular this will involve the development of novel purification technologies such that fragments larger than 100 base pairs can be accurately identified by mass spectrometry. It will also be necessary to validate the method through an international trial involving NMIs and similar institutions.

The reference materials produced in the project will be used as part of a reference measurement system for quantitative DNA analysis, based on 'real-time' PCR. We have designed and produced a quantitation system based on two quantified primers and a quantified amount of target (the reference materials). The system should be more reproducible than simply supplying the target DNA and allowing in-house quantification of the primers for the PCR since this introduces an additional variable into an already highly variable process. It will enable users to calibrate their system, thus improving the accuracy of their measurements and underpinning the quantification. We aim to validate the procedures through two international studies that will initially confirm the integrity of the oligonucleotide primer and then the entire reference measurement system.

Main Activities

- To establish methods for purification of fragments greater than 100 base pairs
- Three international or CCQM inter-laboratory trials :firstly a trial to determine oligonucleotide integrity, secondly a trial of the quantified system in real-time PCR, and thirdly a trial of the IDMS methodology
- Evaluate the performance criteria of the DNA reference system including validation experiments
- Production of reference materials for wider distribution

Project NM1.3 Development of Standard Units to Measure Gene Expression

Aims & Objectives

- To engage relevant scientific, industrial and regulatory communities in the concept, benefits, approach and supporting technology for creating an internationally accepted unit of measure for gene expression
- To initiate, co-ordinate and facilitate efforts to produce a commonly accepted unit of measurement for gene expression with associated methodologies and standards for detection

Deliverables

Deliverable	Description	Due
NM1.3/1	A report documenting, rating and recommending approaches for creation of a standard unit of gene expression that has the full support and backing of at least 8 key experts in the field, plus 2 experts from the MfB WG, published on the MfB web site and submitted as a review article to a peer reviewed journal.	Dec 04
NM1.3/2	An experimental strategy agreed with the NMSD and 2 members of the MfB WG for the practical evaluation of 1 to 3 key approaches to developing a standard unit of gene expression.	Mar 05
NM 1.3/3	A report detailing the outcome of the practical assessment of the approaches to a standard unit published on the web site together with at least one peer-reviewed paper and presentation at a key international scientific meeting.	Nov 06
NM1.3/4	A functioning working group of at least 12 key industry and academic members which is working towards a unified development and promotion of the standard unit for gene expression on an international scale.	Mar 07

Background

Gene expression profiling using, for example, microarray technology has become an indispensable approach for gaining insights into cellular regulation on a global or “omics” level. As such, underpinning activity in this area has a significant impact on the economics of major areas of UK industry (e.g. pharmaceutical, healthcare and agrochemical) and on the understanding of disease states with longer-term benefits in human wellbeing.

To date, the extent to which genes are expressed is principally determined relatively by comparison of two samples or two genes in order to produce ratios of RNA which is indicative of differences in gene expression. These ratios give no indication of the actual amount of RNA transcripts that any one gene is producing. The ratios produced are also influenced by many experimental factors, which therefore also makes them an often-unreliable indicator of differential gene expression.

Development of technologies, reference standards and methodologies to allow determination of the amount of gene products present in absolute levels in terms of

number of transcripts present (or other defined units) is highly desirable, as it provides the only feasible mechanism for comparing data across experiments, platforms, samples and users. This is of particular importance when data from distinctly different techniques such as RT-QPCR, Northern Blotting and microarrays are to be compared. However, quantifying absolutely the extent to which genes are expressed remains a major hurdle that has yet to be overcome. This is partly due to the complexity of the process and partly due to the current lack of a co-ordinated effort by technology providers and users to develop such methodologies and approaches.

The development of an absolute measure of gene expression will be achievable and there are multiple publications describing potential approaches for developing such measures. There is an urgent requirement, however, to ensure that the appropriate approaches are adopted, and that up-take is swift and uniform and recognised in an international setting. In taking a lead in such activities, the UK will be best placed to ensure that standardisation is appropriate for the needs of its industries and that relevant companies will reap the benefits of early implementation.

Main Activities

- Establishing and leading an informed group of practitioners in the design of optimum approaches to the formation of a “standard unit” of gene expression.
- Demonstration of the desired approach through practical experimentation and third party evaluation.
- Widespread dissemination of the findings and co-ordination of efforts to promote and establish the outputs internationally and across industry.

Project NM1.4 Specificity standards and performance indicators for arrays

Aims & Objectives

- To provide the scientific community with a common set of specificity standards for use on DNA arrays
- To provide recommendations for use and applications of such standards
- To investigate the potential of emerging techniques for preparation of targets for array based genotyping analyses using whole genome amplification

Deliverables

Deliverable	Description	Due
NM1.4/1	A validated set of array standards (developed in the previous project to “proof of concept” stage) for use with SNP genotyping arrays. Achieved by establishing the reproducibility, robustness, accuracy, stability and overall “fitness for purpose” of standards as performance indicators for a model SNP assay through the generation of a statistically significant dataset.	Jul 04
NM1.4/2	A report published on the MfB website detailing the practical evaluation of applicability of standards for use in expression profiling. The fitness for purpose of the standards for data normalisation and comparability will have been investigated through the generation of a statistically significant dataset.	May 05
NM1.4/3	A report on the outcome of a full external evaluation of the performance of standards for use with both genotyping and expression arrays achieved through distribution of standards and instructions for use to laboratories for “round-robin” trials. A minimum of 3 and a maximum of 8 laboratories will be recruited for the trials. Benchmark measurement parameters will include assay specificity evaluation determined by generation of match/mismatch ratios and assay efficiency evaluation determined by overall fluorescence intensities generated using specified assay conditions.	Mar 06
NM1.4/4	Guidelines for use of standards for dissemination to the scientific community. Guidelines to be prepared in collaboration with at least two key players in the industry and published on the website. The scientific community to be alerted to their presence through notification in a minimum of 1 trade journal and publication in a peer reviewed scientific journal. Feedback on value of guidance notes sought by inclusion of feedback form on website.	Jan 07
NM1.4/5	A production batch of validated certified reference standards available for distribution to the scientific community.	Mar 07
NM1.4/6	A report published on the MfB website on the practical evaluation of suitability of WGA methodologies for use in target preparation. This will have been achieved by using the targets from a model SNP panel as the basis to compare WGA approaches to standard multiplex PCR in terms of sensitivity, specificity, reproducibility, robustness and amplification bias as assessed on the arrays.	Mar 07

Background

DNA array-based technologies offer enormous potential for performing multiplexed DNA analysis in a cost-effective high-throughput manner. However, such high levels of multiplexing can result in reduced individual assay performance unless careful assay design and appropriate standards and controls are used. The amount of starting material required and the amplification step needed to produce the targets for hybridisation is a further limiting factor. Multiplexing more than approx. 100 targets using locus specific PCR is problematic and genome-wide analyses requires the amplification of many thousands of targets.

A major success of the current VAM programme has been the development of a set of specificity standards, which can be used as performance indicators for array based analyses. They comprise seven pairs of oligonucleotides of varying melting temperatures, which are modified to allow covalent attachment to array surfaces. Within each pair, there is a single internal base difference.

In order to assess the array performance, the standards are attached to the array along with the target probe sequences. Fluorescently labelled complements to one of the pair of each of the standards (7 in total) are hybridised along with the target under investigation. By measuring the ratio of the signal between perfectly matched and single base mismatched standards a measure of specificity can be achieved. This will vary between each of the 7 pairs of standards depending on experimental conditions, and can therefore be used as an indicator of array performance and allow comparison between experiments and platforms.

In addition, measuring the overall signal intensity will provide an indication of hybridisation efficiency and again allow platform and experimental comparability and standardisation.

To fully exploit the potential of the standards further work is required (as proposed) to fully optimise and validate the standards such that they are in a format that can be distributed as reference materials, together with detailed notes on how they can be applied.

In addition, to overcome the problems associated with highly multiplexed target amplifications novel approaches are needed which do not depend upon the development of many complex multiplex PCR amplifications. Previous attempts to perform “whole genome amplification” (WGA) using random primers have been disappointing with amplification bias a major concern. Newer approaches have been developed which are intended to amplify the entire genome without such biases. This project will investigate the potential of such techniques for multi-target amplification.

Main Activities

- Raise awareness of need for use of controls in array-based measurements
- Refine array standards developed under BQ1 and demonstrate applicability
- Extend use to expression arrays
- Promote uptake of standards by the scientific community and perform “round robin” trials

- Evaluate performance characteristics of WGA techniques compared to PCR in terms of sensitivity, specificity, reproducibility, robustness etc
- Disseminate by scientific papers, guidelines and protocols, presentation at conferences

Project NM2.1 Comparability and Consistency of Genetic Measurements

Aims & Objectives

- To promote appropriate use of molecular biology methods and technology
- To develop a truly generic PT scheme for DNA analysis, to provide the tools for cross-sectoral benchmarking of laboratory performance
- To facilitate introduction of quality systems, especially within start-up SMEs and academic laboratories

Deliverables

Deliverable	Description	Due
NM2.1/1	A chapter/section for the revised Analytical Molecular Biology, Quality and Validation book, describing routes to implementation of quality systems in the SME/academic laboratory	Mar 04
NM2.1/2	Establishment of a truly generic PT scheme for DNA analysis, including production of target analytes and liposome-based artificial matrices and promotion of the scheme.	Sep 05
NM2.1/3	The completion of two rounds of the PT scheme, involving a minimum of 15 participants. A VAM bulletin article on the overall findings plus a trouble-shooting guide covering the main problems encountered by participants disseminated through the MfB web site.	Mar 07
NM2.1/4	A workshop and training materials for a minimum of 5 core molecular biology skills, encompassing good practice guidelines. A minimum of 10 participants on the workshop, with feedback obtained on the training material and the usefulness of the course, and with appropriate training materials made available in the multi-media package.	Dec 04
NM2.1/5	A multimedia package to succeed the successful Analytical Molecular Biology, Quality and Validation book. It will comprise an updated version of the book and interactive/video material based on the training material developed for the workshop. The book will be totally revised with outdated material being replaced with information on updated techniques and more currently relevant material. It will contain an additional chapter on quantitative PCR and fluorescent labelling chemistry plus a chapter focussing on quantitative low level DNA analysis using material produced in other projects in the programme.	Mar 07

Background

The specificity, speed and sensitivity achievable using nucleic acid-based analyses make increasing reliance on such methods very likely. In the UK the impact of the increasing use of genetic measurements for diagnostic use is beginning to be considered by health economists, but little information on the economic impact of DNA based measurements is available. However, it is clear that DNA-based analyses will increasingly underpin medical diagnostics, as the technology becomes more accessible. Venture capitalists GeneVest have estimated that the current molecular diagnostics market is \$2 billion in the US, with nucleic acid-based diagnostics likely to increase its share of the \$40 billion in-vitro diagnostics market significantly in the

near future. In other areas such as food safety and public health, applications based on genetic measurement are also increasing in use. The increased uptake and wider application of molecular biological methods requires assurance of the accuracy, reliability and comparability of the techniques, to permit the technology to be taken up and used with confidence. The aims of this project are to provide the resources to build core molecular biology skills, tools to assess laboratory performance, and routes to establishing a well-structured environment for the performance of quality molecular biological analyses.

Results from the generic PT scheme in the current programme has highlighted the need for effective and accessible training materials, and appropriate external assessment schemes to foster continuous improvement of analytical performance. The focus here on production of truly generic analytes should widen the applicability of the PT scheme as a tool for assessing general laboratory competence cross-sectoral benchmarking. Laboratory quality systems are central to supporting consistent analytical performance. The acknowledged importance of accreditation in the eyes of potential customers further increases the need for smaller enterprises to possess relevant accreditation certification to remain competitive. However, introduction of quality systems can be burdensome, and development of accessible materials to facilitate introduction of quality systems into SME and academic laboratories will facilitate uptake and promote an environment appropriate for the performance of quality assured nucleic acid analysis.

Main Activities

- Production of one or more targets and artificial matrices for a truly generic PT scheme to assess laboratory performance in key DNA analytical methods. Development and launch of the generic PT scheme using the artificial analyte(s). Promotion of the scheme to accreditation and funding bodies, including request for formal recognition. Exploration of routes for independent/self-sufficient funding and wider launch of the scheme.
- Development of resources to promote appropriate use of existing technology, including construction of a framework for good DNA analytical practice. Organisation of a workshop to build core molecular biology skills, such as DNA extraction, PCR and sequencing. Production of accessible training materials encompassing good practice and core skills in DNA analysis for new staff/students.
- Revision and relaunch of the Analytical Molecular Biology; Quality and Validation book, removing outdated Chapters and including the new materials on low level DNA detection, real-time quantitation (microarrays) and the updated Accreditation Chapter.
- Production of clear guidelines on the introduction of accreditation in the small and medium sized laboratory, through revision and update of the accreditation Chapter in the Analytical Molecular Biology; Quality and Validation book.

Project NM2.2 Critical Data Analysis for Low Level DNA Measurements

Aims & Objectives

- To address the practical issues associated with low level genetic measurements, including increasing appropriate use of current technology for key applications, and developing a framework for critical data analysis.
- To identify or develop appropriate statistical tools to underpin realistic interpretation of low level measurement data, including methods to identifying and overcoming bias and contamination.
- To facilitate uptake of novel highly sensitive measurement technologies by providing the scientific community with information about the fitness for purpose of emerging techniques.

Deliverables

Deliverable	Description	Due
NM2.2/1	A technique to substantially reduce measurement uncertainty in low level analysis, which utilises bootstrapping techniques to model the limits of detection. The method will be published in a peer-reviewed journal and as a report on the MfB website. It will also be disseminated directly to three laboratories employing trace detection	Jun 04
NM2.2/2	A significantly improved method for the non-invasive prenatal diagnosis of inherited disorders, through the development of an internal positive control for the detection of foetal nucleic acid, which will pave the way for development of a wider variety of non-invasive antenatal screening programs in the UK.	Mar 06
NM2.2/3	Production of a chapter for the revised Analytical Molecular Biology, Quality and Validation book, focussing on best practice in quantitative low level analysis. The chapter will incorporate good practice, developed through practical investigations in the current and previous programmes.	Dec 06
NM2.2/4	Two update reports disseminated through the web site, reporting significant advances in techniques for highly sensitive genetic analysis.	Mar-07

Background

Currently available techniques provide sufficient analytical sensitivity for many applications, but problems still exist in realistic data interpretation through failure to appreciate analytical limitations. The development of physico-chemical techniques permitting highly sensitive genetic measurements is further increasing the need to understand both the potential and limitations of sensitive measurement techniques.

In developing applications such as non-invasive prenatal diagnosis, the challenge is not only to achieve sufficient analytical sensitivity but also to establish robust internal positive controls for the presence of foetal nucleic acid. Non-invasive molecular tests for Rhesus antigen status, dominant paternally inherited and sex-linked genetic disorders are being more widely used, but no effective positive controls exist. Current

practice is to screen for Y-chromosome linked sequences, but a universally applicable positive control assay is required to permit unequivocal interpretation of negative assays for specific disease-linked targets. The most widely used antenatal screening methods employ invasive collection of foetal material by amniocentesis, which is a technically demanding procedure with a risk of miscarriage. Improving the robustness and applicability of non-invasive testing of the foetal nucleic acid freely circulating in maternal blood would improve antenatal screening capabilities in the UK, and also potentially reduce the costs of testing significantly. In addition, utilising practically determined data on achievable analytical sensitivity may allow the design of robust clinical assays by building on work in the current programme utilising bootstrapping techniques to determine the probability of detecting an analyte at a known low level.

The drive to develop integrated measurement devices facilitating highly sensitive on-site testing will pose even greater challenges to ensuring correct interpretation of trace measurement data. In addition, work in the current programme has the need to control uncertainties from sampling bias and reduce potential sample contamination, which may be detected using such sensitive techniques. To answer these needs a practical approach to adopting robust systems for low level DNA analysis will be developed, and will be disseminated through a new chapter in the revised Analytical Molecular Biology, Quality and Validation book.

Main Activities

- Investigation of approaches to avoiding sampling bias and potential contamination in analysis of low concentration samples, focusing on a current significant problem, e.g. healthcare/diagnostics, forensic analysis, with input from potential end-users of improved methodology.
- Evaluation of the fitness-for-purpose of various statistical techniques, and determination of appropriate routes for analysis of quantitative and qualitative trace measurement data.
- Assessment of emerging techniques for low level DNA analysis, and critical review of their fitness-for-purpose.
- Production of a chapter focussing on best practice in low level DNA analysis for the revised Analytical Molecular Biology, Quality and Validation book.

Project KT1 Publicity and Promotion

Aims & Objectives

- To increase the number of organisations benefiting from the VAM programme
- To raise awareness of the importance of valid analytical measurement
- To improve understanding of what constitutes a valid analytical measurement

Deliverables

Deliverable	Description	Due
KT1/1	A VAM Helpdesk that provides a central contact point through which individuals and organisations can access technical advice and obtain VAM products. The services provided by the VAM Helpdesk will be reviewed annually and summarised in the VAM Annual Report.	Sep 04 Sep 05 Sep 06
KT1/2	A VAM Website that contains up-to-date information on VAM and related topics. Research and update the VAM Website monthly with information (news, events, publications) relevant to UK analysts. Prepare and issue monthly email alerts to registered users to update them on new material added to the VAM Website. Increase the number of registered users of the website by 800 per year. Maintain the proportion of registered users that have visited the site more than once. Issue quarterly updates of the VAM Database to other VAM contractors (e.g. NPL). Manage the VAM Database in accordance with the requirements of the Data Protection Act, providing facilities for contacts to update their details and opt-in/out of receiving email and other information.	Sep 04 Sep 05 Sep 06
KT1/3	Publish four issues (2pa in years one & two) of the VAM Bulletin: The Bulletin will be published in hard copy and electronic format; hard copies will be distributed to contacts on the VAM database; electronic copies will be published for download via the VAM website. A report on results of a VAM Bulletin readership survey with recommendations to improve the format and content of the Bulletin and options for generating cofunding to offset production costs will be produced by the end of the 1 st Year of the programme.	Sep 04 Sep 05
KT1/4	A VAM Brochure which explains the economic and quality of life benefits of the programme. The VAM Brochure will be produced in collaboration with NPL.	Sep 04
KT1/5	Three case studies, researched and developed in conjunction with external organisations, to illustrate how the adoption of VAM and the use of traceable results can bring business benefits. Each of the case studies will be published in the VAM Bulletin.	Sep 04 Sep 05
KT1/6	Two sector guides to VAM, developed in conjunction with sector-based organisations, to raise awareness of VAM in specific sectors, and to complement NMS KT Programme awareness material. The guides will be distributed at VAM promotional events. They will be made available to other NMS contractors for dissemination via their unit programme activities and in conjunction with the regional metrology advisory centres being developed under the NMS KT Programme.	Sep 05

KT1/7	At least 10 promotional activities per year (displays at conferences and events, presentations, promotional articles), delivered in conjunction with intermediaries (trade associations, supply chain) to promote the benefits of valid analytical measurement and the outputs of the programme. At least one promotional activity per year to be organised in conjunction with another NMS unit programme.	Sep 04 Sep 05 Sep 06
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Background

This project will continue to support day-to-day activities associated with disseminating the outputs of the programme. It provides the communication channels (e.g. the Helpdesk and website) through which UK business can access expert advice and products to help diagnose and solve measurement-related problems.

The project will continue to provide leadership in the transfer of knowledge developed by the programme. The VAM Bulletin is widely accepted as a focus for disseminating information on project outputs and for exchanging information on analytical measurement-related topics. As the internet develops further, the VAM website will become an increasingly important forum through which all stakeholders can keep abreast of developments and obtain information on VAM and related topics.

In order to increase the outreach of the programme, the project will also contain an enhanced promotional activity aimed at increasing the number of organisations engaged in the 'chemical' programme. This will be a focused activity, which utilises proven promotional tools, and is co-ordinated with the overarching NMS Knowledge Transfer Programme. Key to increasing engagement in VAM will be the use of intermediaries and development of case studies to promote the business benefits of VAM.

Main Activities

- Maintain the VAM Helpdesk as a central contact point through which individuals and organisations can obtain information on VAM. Provide UK companies with a limited amount of technical advice on analytical quality related issues. Route enquiries received by telephone, email and via the VAM website to technical experts, where appropriate. Process orders for VAM products (excluding reference materials). Edit and produce the VAM Brochure and VAM Bulletin. Review opportunities for generating cofunding for the VAM Bulletin through advertising, sponsorship and charging for non-UK distribution.
- Design, create and maintain an up-to-date set of web pages that promote VAM products and services, support VAM networks and disseminate outputs of the VAM technical project work in the chemical and biochemical themes of the Programme. Research and publish more general information on VAM and VAM-related topics relevant to the UK analytical community (e.g. news, events, publications, international developments)
- Maintain a central database that can be used by all contractors to the VAM Programme to facilitate dissemination and marketing campaigns, both generically and by targeting specific sectors of the database population. Update the database with details of new individuals and organisations recruited to VAM

- Research, develop and publish case studies, in collaboration with external organisations, to illustrate the business and quality of life benefits of VAM. Design, edit and produce introductory guides to VAM for specific sectors. Arrange for VAM presentations at selected meetings and for awareness articles for publication in scientific and technical press. Work with intermediaries to increase gearing of promotional activities

Project KT2.1 Support for Schools and Colleges

Aims & Objectives

The aims of the sub-projects in this area are to continue to enhance the teaching of the concepts of valid analytical measurement at the GCSE and post-16 level. The primary objective is to improve the skills base of students going on to further education in scientific disciplines, or gaining employment with organisations involved in making chemical analytical measurements. This gains leverage through the knowledge gained by the teachers which will impact on more students than the 1200 or so who take part in the competitions each year. In addition students who do not follow a scientific route will have the basis on which they should judge the quality of analytical results.

Deliverables

Deliverable	Description	Due
KT2.1/1	Three Proficiency Testing (PT) competitions for A-level students, or equivalent, focusing on chemical measurements, each will involve at least 80 centres and will raise awareness of good measurement practices for both students and teachers. A report of the results of each competition, including key learning points based on feedback from students and teachers will be published annually.	Sep 06
KT2.1/2	At least two collaborative events per year: An educationally significant event for teachers and curriculum developers (e.g., ASE annual conference) An event for students that promotes effectively the importance of good measurement practice (e.g., RSC "Chemistry at Work" events or SETNET activity)	Sep 06
KT2.1/3	Three 'hands-on' workshops for teachers which will give practical experience of modern analytical techniques and disseminate material for use at GCSE and A-level. Their success will be measured by means of a delegate questionnaire at the end of each event.	Sep 06
KT2.1/4	At least three (one per year) new or revised items of material produced in collaboration with, and endorsed by key stakeholders, which will allow teachers to effectively disseminate the principles and concepts of VAM at the school/college level. The material produced will be influenced by the outcome of a review of existing material.	Sep 06

Background

If the future workforce is to have the analytical skills required by UK businesses, it is essential that the concepts of measurement and its key role in everyday life are introduced to students as early as possible. There is a continuing need to introduce students to the concepts of chemical and biochemical analytical measurements and the importance of quality in such measurements. This is as important for students who intend to follow a scientific career as it is for those who specialise in another areas, for example, lawyers also need a better understanding of the measurement process.

This can be achieved by working with those involved with developing and delivering curricula, to influence the content of courses taught at the GCSE and post-16 level.

Ideally, such courses should cover the concepts of measurement and analysis, the ideas behind valid analytical measurement and introduce students to the basic analytical laboratory skills. The teaching of these key concepts will only be effective if teachers have access to support which will enable them to cover the topics in a way that engages the interest of their students. The Proficiency Testing competitions have certainly both informed the teachers and increased the knowledge of the students.

Main Activities

The proposed main areas of activity are:

- Organisation and delivery of events for teachers and curriculum developers which effectively promote the importance of good analytical practice
- Organisation of Proficiency Testing competitions in chemical measurements for post-16 students.
- Development of materials which will allow teachers to introduce effectively the concepts of good measurement practice and the VAM principles to their students. This will include completing the review of existing successful VAM material, to assess the level of revision required to ensure that the material remains relevant and accessible. The new and revised products will be promoted at the ASE Conferences.

Project KT2.2 Support for Tertiary Education

Aims & Objectives

The primary aim of the sub-projects in this area is to engage in a dialogue with teachers in the tertiary sector, not just in departments of analytical science, to get them more involved in quality assurance concepts. Following an acceptance, relevant materials and activities will be produced to enhance the teaching of the concepts of valid analytical measurement at this level. The overall objective is to improve the skill base of students entering employment as scientists after postgraduate study.

Deliverables

Deliverable	Description	Due
KT2.2/1	Six lectures and/or workshops per year promoting valid analytical measurement to post graduate students. The lectures will target areas where there is a need to demonstrate proven competence before professional registration, e.g., forensic and clinical areas. Materials produced for these activities will be made available to lecturers via the VAM website. Existing VAM web based tertiary resource material will be reviewed and revised if necessary.	Sep 06
KT2.2/2	Two workshops, in collaboration with industry and professional bodies, for postgraduate students which introduce effectively the key concepts of good measurement practice and demonstrate how they are implemented in commercial laboratories.	Sep 06

Background

It is only by introducing and reinforcing the principles of good measurement practice at all levels in the educational system that the future workforce will have the necessary analytical skills required by industry. It is therefore important that students studying graduate and postgraduate courses in the chemical and biological sciences are exposed to the key concepts of analytical measurement. In previous programmes, it has proved more difficult to engage tertiary education than schools and colleges. However, a number of successful activities have been undertaken such as the delivery of lectures on QA to undergraduate and postgraduate courses. The gaps in the skills of new graduates reported by industry indicate that there is a need to persevere with this sector and increase the knowledge of students. This audience contains the future end users of analytical results.

Main Activities

- Explore the possibility of working with the Research Councils, Faculty staff responsible for Key Skills training for postgraduate students and the QAA for universities to increase uptake of quality assurance within the university sector. We will target specific modules in degree courses, paying particular attention to those modules that will meet part of the requirement for a professional qualification, e.g. medical biochemistry, clinical biochemistry and industrial chemistry. Organisations such as the Association of Clinical Biochemists, the

RSC and representatives from clinical departments of teaching hospitals will be used to gain leverage

- Organisation and delivery of workshops to introduce postgraduate students to the key concepts of good measurement practice and demonstrate how they are applied in commercial analytical laboratories and research institutes.
- Delivery of lectures to students studying courses with an analytical component and arrange visits to laboratories for such students. Material supporting the lectures will be made available to lecturers via the VAM website.

Project KT2.3 Support for Professional Analysts

Aims and Objectives

The aim of the sub-projects in this area is to enable UK businesses, particularly SMEs, to implement the principles of good analytical practice more effectively by providing them with training and a range of support material and tools.

Deliverables

Deliverable	Description	Due
KT2.3/1	<p>The provision of coaching and expert advice for the four sectoral “user group” networks established under CM1.4/5. Each network will be supported by a “knowledge transfer” club area on the VAM website. Deliverables provided with the support of the networks will include:</p> <p>A report, based on information from network participants in each network and agreed by network representatives, which identifies the general causes of error in their areas and recommends three additional coaching/training materials to improve performance. The findings on general sources of error will be made available to support deliverable KT2.4/3</p> <p>Three items of material (one per year) to support training needs highlighted by the networks.</p> <p>A document, produced in conjunction with and endorsed by at least one of the networks, which explains to users of analytical results the significance of implementing the VAM principles.</p> <p>Two sector specific seminars bringing together users and producers of analytical results which will promote the need for valid analytical measurements and highlight the consequences of unreliable results.</p>	Sep 06
KT2.3/2	Report, agreed by a suitable expert committee, including a specified framework for single-use software applications (that is, structure, distribution method, internal consistency of features, target operating system and application environment, error trapping, help facility and documentation requirements etc), together with recommendations for four applications.	Mar 04
	Four consistently presented software applications (at least one per year) including online help and documentation, fully tested and reviewed by an appropriate expert group and available for general use. The possible incorporation of relevant packages into instrumental software will also have been explored.	Mar 06
KT2.3/3	A web-based tool to help plan method validation, and capable of providing a downloadable validation protocol or validation plan suitable for use with mVAL, tested, operational and published on the VAM website.	Sep-06
KT2.3/4	<p>Revision of two VAM products which have proved useful but are no longer available:</p> <p>“Quality in the Analytical Chemistry Laboratory”, revised to reflect recent changes to accreditation requirements for laboratories and the new format of open learning textbooks.</p> <p>“Practical Statistics for the Analytical Scientist”, updated to include more worked examples and an introduction to measurement uncertainty calculations.</p>	Sep 06
KT2.3/5	Guidance on uncertainty estimation for sampling drafted via a suitable international expert group and submitted for international voting.	Sep 06

KT2.3/6	Two collaborative events or projects, with e.g. Eurachem, UKAP, RSC, DEFRA, FSA, UKAS to support the production of materials to help organisations introduce procedures to improve the quality of measurement in research and testing.	Sep 06
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Background

Under the 2000-2003 programme, three successful sectoral networks were developed and supported. The areas covered were environmental analysis (Environmental Measurements Training Network, EMTN), clinical measurements in primary care (Point of Care Testing network, POCT) and specialist organic chemicals (SOCSA Analytical Networking Group, SANG). The networks provided the support needed for the coaching and training required for the effective implementation of the VAM principles, and organised benchmarking exercises to evaluate the core competencies required for analytical measurement.

The network meetings have confirmed the need for coaching and support in the implementation of the principles of valid analytical measurement. The need for such support is particularly strong for SMEs and in the clinical testing area. The network meetings have also highlighted a number of areas where additional training material is required. For example, easily understood guidance on validation and measurement uncertainty, further guides on specific techniques such as spectroscopy, and exercises to demonstrate competence.

Four sectoral networks are being established and operated under project CM1.4. The aim of the networks is to bring together users of reference materials to provide them with a better understanding of the benefits of traceable measurements. To maximise the effectiveness of the networks in improving the quality of results produced by UK laboratories, there is a need for activities which focus specifically on the implementation of good measurement practice. Project KT2.3 will directly support the networks by providing coaching and expert advice, organising events and producing material which will allow laboratories to implement the principles of good analytical practice more effectively. Customers of analytical results have not received much attention in KT activities to date. This will be addressed through one of the sectoral networks by organising seminars and producing material which highlight the importance of the implementation of VAM to the end users of analytical results.

Many statistical recommendations remain dormant or cause difficulty because users have no ready access to software for their implementation. This lack in key applications will be remedied by providing simple, sound, single-function tools for specific purposes, available through a variety of channels including web download. It will be important to fill existing gaps which the market does not currently address. Specific examples where there are known gaps in availability for routine labs are:

- Numerical methods of uncertainty evaluation: Supported by commercial software for simple numerical differentiation, but simulation approaches showing distribution and accurate confidence levels currently require expensive and often complex simulation software;
- Uncertainty estimation using reproducibility information: Not currently supported by available packages;

- Detection limit calculation from linear calibration (an ISO recommendation): No current software supports the requisite algorithms, which have to be hand coded by the analyst or replaced with additional experiments;
- Implementation of extended QC chart interpretation rules: Supported in high-end QA packages, but unavailable at a 'learning' level;
- Uncertainty from linear calibration: No software tools currently provide this in isolation; few statistical tools provide prediction uncertainty and no spreadsheet applications do so;
- Uncertainty calculations for simple sampling plans: No low-cost software currently available.

In addition, planning validation studies remains a difficult topic, especially for ad-hoc requirements and where fitness-for-purpose is the principal issue. While the previous programme delivered software to assist in very flexible implementation of many validation protocols, this is not intended to advise on the requirement, only to implement it. To maximise the usefulness of the mVal software, support in planning validation protocols is therefore required.

Some of the materials on aspects of good measurement practice that are already available, are perceived by field laboratories to be too complicated. In some areas there is a need to produce materials that are more user friendly and possibly sector specific. To ensure that such material is disseminated as widely as possible, it is essential that key organisations such as UKAP, RSC, DEFRA, FSA and UKAS support its production. UKAS are in a good position to both assess the need and disseminate knowledge about available products. Since UKAS are happy to be involved in such activities, this will achieve better leverage in accredited laboratories and in companies seeking accreditation.

Sampling is critical for analysis; without representative sampling, measurement results have little meaning. Sampling uncertainty is a critical and often dominant source of uncertainty, and few analysts are in a position to estimate this component. However, there is no international consensus on whether sampling uncertainty should, or should not, be treated as part of measurement uncertainty, and where it should, views on appropriate methods of assessment and control vary from relatively simple and practical observation of variability to attempts to develop detailed 'uncertainty budgets'. The project is intended to promote international consensus in this area and to ensure that recommendations for routine laboratories are practical.

Main Activities

- Support four sectoral networks (established under project CM1.4) through the provision of coaching and expert advice on good measurement practices.
- Preparation of a report based on information from network participants which identifies the general sources of error and identifies areas where additional training material is required.
- Production of suitable training material to support training needs identified by the networks.
- Production of material for the end-users of analytical results, explaining the importance of the implementation of the VAM principles.

- Agree a framework for implementation of software tools (specification of operating environment, general user interface requirement, general documentation requirements and 'help' system requirements).
- Provide software implementations for priority cases (as agreed by a suitable expert working group). Priorities will be set based on availability of adequate alternative software as well as on analytical user needs as identified through current and future networks.
- Specification and content development (that is, textual content and structure definition) of a web-based tool for planning method validation.
- Implementation of the validation tool as a web application (possibly via third party developer).
- Revised editions of two successful existing VAM products ("Practical Statistics for the Analytical Chemist, A Bench Guide" and "Quality in the Analytical Chemistry Laboratory").
- Participate in two collaborative projects to support the production of materials to help organisations improve the quality of analytical measurements.
- Form (or contribute to) an international working group on sampling uncertainties.
- Prepare, with others, appropriate internationally agreed guidance on the assessment and control of uncertainty associated with sampling.

Project KT2.4 Evaluating the Technical Performance of UK Laboratories

Aims and Objectives

The aims of the sub-projects in this area are to assess the technical performance of UK laboratories, identify the mechanisms used by laboratories to improve the reliability of their results, provide guidance on the use of PT data in assessing measurement uncertainty and improve practice in customer-run PT activities.

Deliverables

Deliverable	Description	Due
KT2.4/1	A paper on PT data for uncertainty estimation, based on literature review, and incorporating results of experimental assessment of actual PT and uncertainty estimation in at least two interlaboratory exercises, accepted for publication in a refereed journal.	Mar 05
KT2.4/2	Guidance for laboratories and accreditation bodies on the use of PT data for uncertainty estimation, agreed by a suitable International working group including accreditation body representatives.	Sep 06
KT2.4/3	Delivery of a benchmark report on UK analytical performance assessed from PT schemes in food, environment and health sectors and supported by literature study, which includes comparisons with performance of other countries and identifies specific technical causes of poor performance in interlaboratory studies.	Sep 06
KT2.4/4	Publication of a short best practice guide, agreed by UK experts in PT, for laboratory customers wishing to set up a scheme to monitor their supplier laboratory performance.	Mar 05
KT2.4/5	A short publication summarising PT interpretation, for distribution to laboratory customers (including the legal profession) and agreed in consultation with a suitable expert working group.	Sep 04
KT2.4/6	Publication of a revised international protocol for PT in analytical chemistry (in collaboration with other agencies).	Sep 05

Background

A clear understanding of the actual performance of laboratories is essential in setting regulation based on analytical results and in identifying priorities for improvement. Comparison of actual performance with calculated measurement uncertainties is an important check on uncertainty estimates and measurement 'models', and interlaboratory dispersion is accepted under certain conditions as a legitimate basis for uncertainty estimation in testing. Traditionally, these uses have relied most heavily on data from planned collaborative studies of specific analytical methods as part of method validation. In principle, however, proficiency testing data can provide similar information. Because participation in PT is required, where possible, in accredited and many regulated laboratories, there is a large and growing body of data on laboratory performance in PT schemes, held by PT scheme operators world-wide. As well as its traditional use in educating and assessing individual laboratories, wider use of this data can help inform regulation, assist with implementation of uncertainty

requirements in laboratories, and identify improvement priorities. This project accordingly seeks to improve the acquisition and use of PT data in all these contexts.

There are four activities of high priority. For the testing laboratory community, the use of PT data for estimation of uncertainty is a key issue. Current guidance permits the practice, but because of a lack of technical data on the validity of the data, this guidance is extremely restrictive and few schemes comply. Recent guidance issued in other fields of testing suggests that these restrictions should be eased, but this cannot be done in chemical analysis without convincing technical data on the relationship between PT data and measurement uncertainty. This requires a study across a range of schemes to identify the reliability of assigned values and the effect of varying analytical methods on both assigned value and dispersion. The result will be clearer guidance on the validity of PT data as a basis for uncertainty estimation, with significant benefits in reduced load on laboratories. This will facilitate compliance with regulation by providing additional means of uncertainty estimation and thereby simplifying compliance.

For regulation and UK analytical capability development, a review of the performance of the main parameters in proficiency testing schemes over a period of time, and brought together in a single report will:

- Enable regulators to set realistic performance targets;
- Better identify areas of poor performance in which methods are not fit for purpose and identify parameters for which adequate methods are not in use or available to meet proposed targets;
- Identify and evaluate the effectiveness of the mechanisms used by laboratories to improve the reliability of their results;
- Enable a comparison of UK performance with other countries and assessment of the implications to UK trade and industry;
- Encourage inter-sector exchange of techniques and technologies to improve methods of analysis;
- Assist in identifying the need for reference materials and measurements;
- Assist manufacturers to identify areas in which design and develop of instrumentation could improve performance.

Increasingly, PT is used to qualify laboratories for activities, not just to educate, and the importance of interpretation of results has risen substantially as a result. This is particularly true when a laboratory's reliability is in question during legal proceedings in which they have provided evidence. Further, larger customers are using 'blind' samples to check their supplier laboratories. There is accordingly a need for guidance on customer-run PT, and for customer-directed guidance on the interpretation of PT for qualification of laboratories, benefiting laboratories and customers through technology transfer.

Finally, international guidance is now relatively old and IUPAC in particular are looking to review their existing guidance. There is therefore a need for international activity by the UK to ensure that VAM principles and UK views are properly represented.

Main Activities

- Undertake a study of PT scheme results to assess the validity of PT data as a basis for estimating uncertainty in testing laboratories.
- Based on the above study, prepare guidance on the conditions under which PT data can be applied for uncertainty estimation.
- Undertake a study of UK PT scheme performance in food, environmental and health sectors, assessing trends in performance, comparing UK and overseas laboratory performance and identifying priorities for technical development in the UK. This study will include an assessment of the principal causes of poor performance in laboratories and an evaluation of the effectiveness of the steps taken by participants in PT to improve the reliability of their results using a combination of literature study and information from PT providers and participants.
- Prepare guidance for customer-run PT in consultation with a suitable expert working group; publish guidance in VAM report or RSC leaflet/monograph format, together with a short 'flyer' on interpretation of PT results from laboratories, for distribution by laboratories to customers.
- Contribute to revision of IUPAC harmonising documents on proficiency testing.

Project KT3 National & International Harmonisation

Aims and Objectives

- To develop and maintain the UK's international credibility and influence on policy and strategic analytical measurement issues through proactive participation in key European and international organisations
- To provide the UK with increased value for money through fostering collaboration and facilitating co-ordination and harmonisation with other countries and regions
- To communicate to UK stakeholders regular information on representational activities undertaken and provide feedback on the significance and consequence of developments
- To harmonise general requirements for uncertainty and method validation in qualitative testing in accredited chemical testing laboratories
- To harmonise requirements for managing transfer of analytical methods between customer and supplier

Deliverables

Deliverable	Description	Due
KT3/1	Representation of UK VAM-Chemical interests at European and International committees and organisations in the field of chemical analytical measurement. Attend at least nine meetings per year. Produce written summary of representation undertaken and key international developments for inclusion in progress reports to NMSD (Quarterly Reports) and the VAM Bulletin (6 articles in total).	Sep 06
KT3/2	Organise or participate in at least four national networking meetings per year on generic topics which cross technical project areas. Such meetings will provide a framework to help formulate UK input to international bodies and support dissemination of international developments within the UK. Establish a national 'EURACHEM-UK' group, in conjunction with the RSC, to provide a transparent and representative UK input to EURACHEM. Produce written summary of networking undertaken inclusion in Annual Progress Reports to NMSD.	Sep 06
KT3/3	Deliver at least four collaborative projects that result in an improvement in the harmonisation of chemical measurement and analytical quality assurance practices. Each project will be delivered in partnership with at least four other organisations and result in a tangible measurable output, such as the publication of a harmonising protocol, or the organisation of a major conference or event.	Sep 06

Background

The overall aim of the VAM programme is not only to improve the quality of analytical measurement, but also to realise the economic benefits of such improvement. To this end, it is vital that progress continues to be made on achieving international harmonisation. The benefits to this approach are not only the direct ones concerned with international trade, but also less visible ones such as the value of sharing costs between countries and harnessing a wider pool of expertise through collaboration.

International recognition of national products is essential if they are to benefit the UK fully, and collaboration through organisations such as EURACHEM and CITAC provide an important means of gaining acceptance and endorsement of VAM outputs at the European and international levels. A proactive UK input to such organisations is essential if the UK is to maintain a position of influence, particularly in relation to achieving pragmatic approaches on key topics such as measurement uncertainty and traceability.

Input to international committees and organisations ensures that NMS knowledge and expertise is transferred into outputs that benefit business through harmonising approaches and practises, thus underpinning the mutual recognition of chemical measurements. National networking provides an effective means of disseminating information on international developments and ensures a firm basis for formulating UK stakeholder input to international committees and organisations. Qualitative tests such as presence/absence, identity checks and species identity form a large and important class of analyses in chemical and biological measurement. However, there are no widely accepted guides on performance assessment or IQC of the relevant procedures. There is therefore a need for widely agreed guidance on how to control and assess the performance of qualitative test methods.

National networking also provides the UK analytical community and industry with channels through which to access expert advice and products to help diagnose and solve measurement-related problems. It facilitates knowledge transfer of new measurement technologies and leading edge metrology originating overseas to UK stakeholders; thus providing analysts with better tools and services with which to improve the validity of their analytical measurements. Analytical method transfer (“Technology transfer” in the pharmaceutical industry) is a key activity in contracting for analytical services. In regulated industries, a range of responsibilities fall on contractor and customer to ensure that methods are effective and properly validated prior to transfer, that supplier staff are competent, and that the results remain consistent. However, practice varies from one customer to another, and there is no common agreement with regulators on the level of activity required, leading to duplication and over-engineering.

Main Activities

International committees and organisations

Prepare for and participate in meetings of key European and international committees and organisations that enable the UK to influence policy making and to harmonise standards and practices. Particular emphasis will be given to those organisations which foster international collaboration on VAM-related tasks and activities, to

explore areas of mutual interest, to increase the profile of UK activities and to help gain wider acceptance and uptake of VAM outputs.

Examples of representation undertaken:

- EURACHEM Committee meetings
- EURACHEM Executive Committee meetings
- EURACHEM Proficiency Testing Working Group meetings
- EURACHEM Education & Training Working Group meetings
- EURACHEM Measurement Uncertainty Working Group meetings
- EUROLAB / EA Permanent Liaison Group
- EURACHEM/EUROLAB/EA Joint WG on Proficiency Testing
- EA Expert Group on Uncertainty
- CITAC Working Group
- EPTIS

(Note international representation related to participation in CCQM, its working groups and on matters related to reference materials is covered within the Chemical Metrology projects.)

National networking

Develop and maintain national networks through which UK views and interests can be discussed and then represented internationally. Support participation of VAM experts into relevant national committees and organisations, for example, UKAP, BSI & RSC committees.

Specific consideration will be given to developing and piloting a national framework for EURACHEM-UK in conjunction with the RSC AMC to improve UK representation on EURACHEM and its related committees and working groups.

Collaborative Projects

Contribute to the organisation and delivery of international collaborations aimed at developing and harmonising approaches and practices in chemical measurement and analytical quality assurance, for example, the drafting and production of harmonised protocols, best practice guides and international conferences and workshops.

Examples of recent collaborations:

- Organisation of the EURACHEM/CITAC workshop ‘Workshop on Measurement Traceability and Uncertainty in Analytical Chemistry: Meeting the Requirements of ISO/IEC 17025’
- Drafting of ISO/DTS 21748 ‘Guide to the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation’
- Revision of CITAC Guide 1 ‘International Guide to Quality in Analytical Chemistry: An Aid to Accreditation’

Examples of possible future collaborations include:

- The development (via EURACHEM) of harmonised international guidance on general requirements for qualitative testing
- The production of guidance on analytical method transfer (“technology transfer”)
- The preparation of protocol for analytical system / software qualification

Project MD1 Programme Management

Aims & Objectives

- To provide co-ordinated management and delivery of all VAM projects contracted to LGC and to ensure the delivery of this work to quality, time and budget
- To ensure that the ‘Chemical’ VAM Programme projects are co-ordinated with other National Measurement System (NMS) programmes and initiatives
- To provide effective co-ordination and collaboration with other VAM contractors with the aim of delivering a seamless VAM (Chemical & Physical) programme

Deliverables

Deliverable	Description	Due
MD1/1	<p>Delivery of VAM projects contracted to LGC to quality, time and budget. Monthly Invoices to NMSD.</p> <p>Regular meetings of LGC and NMSD Programme Managers to discuss progress and direction of work. Ad-hoc liaison and meetings of LGC project managers with VAM WG trackers to review progress.</p> <p>Provision of ad-hoc financial and delivery information to NMSD, e.g. delivery projections, cashflow forecasts, estimates of cofunding and SME involvement in projects.</p> <p>Participation of LGC managers and experts in NMS policy and improvement initiatives (e.g. portfolio balancing, decision conferencing).</p>	Quarterly
MD1/2	Regular meetings of VAM-C (LGC) and VAM-P (NPL) Programme Managers and technical project managers to co-ordinate delivery and exchange information on topics that cross programme themes.	Quarterly
MD1/4	Attendance of LGC VAM project staff and experts in NMS KT and International programme co-ordination meetings.	
MD1/5	Quarterly Reports (9 in total), which provide an overview of progress on all VAM projects contracted to LGC, as well as supplementary detailed information (e.g. invoice reconciliation, progress towards milestones) as required by NMSD.	Quarterly
MD1/6	Annual Reports (years 1 & year 2), which provide an overview of progress on all VAM projects contracted to LGC, as well as supplementary detailed information (e.g. invoice reconciliation, progress towards milestones) as required by NMSD.	Nov 04 Nov 05
MD1/7	Final Report (years 1 to 3 inclusive), which provides an overview of progress on all VAM projects contracted to LGC, as well as supplementary detailed information (e.g. invoice reconciliation, progress towards milestones) as required by NMSD.	Nov 06
MD1/8	Annual Reviews (year 1 & year 2) which provide NMSD and VAM WG with the opportunity to discuss LGC-based VAM work with project managers and staff delivering projects.	Nov 04 Nov 05
MD1/3	Customer-Contractor Workshops on topics that cross programme themes to improve awareness and facilitate knowledge transfer between VAM contractors, the NMSD and VAM WG.	Jun 04 Jun 05
MD1/9	Report on study to assess uptake and impact of VAM-C outputs. The study will consult users of a cross-section of VAM-C products and services with the aim of identifying qualitative and semi-quantitative information on the impact of the programme.	Nov 05

Background

The VAM Programme is complex, comprising a variety of projects that are managed and delivered by more than one contractor. This project supports the management and co-ordination activities which are necessary to ensure that projects are delivered seamlessly, provide best value for money and that technical knowledge and know-how is actively transferred between contractors.

The VAM Programme is one of a portfolio of programmes within the National Measurement System. Effective liaison with NMSD and other NMS contractors is essential to ensure that the VAM Programme is co-ordinated with other NMS initiatives and programmes.

Main Activities

Preparation of written quarterly and annual progress reports on all VAM projects contracted to LGC. General liaison with NMSD (e.g. quarterly contract review meetings) and the VAM WG (e.g. meetings with project trackers). Organisation of Annual Progress Reviews for NMSD and the VAM WG. Participation of LGC project managers and staff in liaison meetings and progress reviews.

Organisation of meetings of LGC & NPL programme managers to provide top-level co-ordination on programme-wide issues, and to plan and manage co-ordination between contractors at the project level. Regular meetings of project staff to facilitate technical exchanges on topics that cross programme themes (e.g. knowledge transfer; measurement uncertainty; chemical metrology and mass spectrometry).

Participation of LGC VAM project experts in other NMS programme co-ordination activities (e.g. International Programme and Knowledge Transfer Programme) and NMSD initiatives (e.g. development of decision conferencing and development of programme formulation guidelines.)

Development of tools and measures to evaluate impact of VAM outputs. Undertaking studies to assess and report on the impact of VAM outputs.

This project does not cover 'project' management, which is an integral part of each project. It only supports 'programme' management activities, including 'internal' knowledge transfer activities to ensure synergy and sharing of knowledge between contractors.

Project MD2 Programme Development

Aims & Objectives

- To assist the DTI in the development of the 2006-2009 Chemical VAM Programme, specifically in the identification and procurement of the most effective programme of work for the available budget, consistent with DTI's NMS objectives.

Deliverables

Deliverable	Description	Due
MD2/1	Specification covering the 2006-2009 Chemical VAM Programme. The specification will be developed in close consultation with the NMSD and VAM WG and involve consultation with stakeholders and interested parties in the UK and overseas.	May 06

Background

This project covers the formulation of the next Chemical VAM Programme, which will run from October 2006 to September 2009. Formulation of the programme is expected to start in Spring 2005.

Programme development requires close liaison with the NMSD and the VAM WG to ensure that the technical specification for the programme is prepared in accordance with NMSD policy and procedures.

The programme specification is based on extensive consultation on requirements, e.g. through technical focus group meetings, one-to-one discussions and the collection and review of information on market needs and requirements.

Main Activities

The main task during programme formulation is the iterative production and revision of a series of programme documents (specifications) which evolve during the course of the programme development cycle (orientation – consultation – prioritisation – approval).