National Measurement System

National Measurement System Programme for Chemical and Biological Metrology

Programme Document: Summary of live projects at June 2013

National Measurement Office

NPL National Physical Laboratory

LGC Setting standards in analytical science

National Measurement System Programme

for

Chemical and Biological Metrology

Programme Document: Summary of live projects at June 2013

Compiled June 2013

Prepared by:

LGC Limited

NPL

Approved by the NMO

Contents NPL projects

Contents LGC projects – for ease this contents page is repeated on page 78

IM2c	International and National Representation	2011	109
IM2d	International and National Representation	From 2012 contract but starts 2014	111
IM2e	International and National Representation	From 2013 contract but starts 2015	113
IS1	Absolute Carbon Isotope ratios	2009	115
IS11	Critical Water pollutants	2011	117
IS12	Elemental tissue imaging	2012	119
IS13	Characterisation of elemental standards	2012	121
IS14	Cr Speciation and RM	2013	123
IS15	A metrology platform for IRMS standards	2013	125
IS16	Production of a CRM for Toxic Metals in Blood	2013	127
KT1e	Increasing stakeholder awareness and engagement	2013	129
KT2	Improving measurement knowledge & skills	2009	131
KT2c	Improving measurement knowledge & skills	2011	133
KT2d	Improving knowledge & skills	2012	135
KT2e	Improving measurement knowledge & skills	2013	137
MD3e	Programme Management	2013	139
MD4d	Programme Formulation and Strategy	2012	141
MD4e	Programme Formulation and Strategy	2013	142
NB10	In vitro Nanotoxicology	2011	143
NB11	NanochOp	2012	145
OA7	Improved CRMs for Food Analysis	2010	147
OA12c	Reference material certification and support	From 2011 contract but started 2012	149
OA12d	Reference material certification and support	From 2012 contract but starts 2014	151
OA12e	Reference material certification and support	From 2013 contract but starts 2015	153
OA13	Direct analysis for organic purity assessment	2012	155
OA14	Ion Mobility Standards	2012	157
OA15	RMPs & CRMs for Therapeutic Drug Monitoring	2013	159

Executive Summary

The Chemical and Biological Metrology (CBM) Programme forms part of a larger portfolio of Programmes which contribute to the UK National Measurement System (NMS) operated by the National Measurement Office (NMO), an Executive Agency of the Department for Business, Innovation and Skills (BIS).

The CBM Programme is an NMS Knowledge Base Programme which underpins some of the most challenging chemical, physical and biological measurements being made in the UK that are important to the UK's industrial competitiveness and quality of life. The Programme is concerned with the realisation and maintenance of measurements and standards for the determination of the quantity of matter, for which the mole is the SI unit. In addition, the programme maintains and develops the UK primary measurement capability and calibration facilities. The programme is delivered by NPL and LGC.

This document represents the research contracts that are active as of June 2013.

Project No.	NS002GA2	**Price to NMO**	£103k
Project Title	Proficiency testing scheme for indoor air	**Co-funding target**	
Lead Scientist		**Stage Start Date**	April 2011
Scientist Team		**Stage End Date**	June 2013
		Est Final Stage End Date	2014+
Sector	Environmental Sustainability – Pollution and waste reduction	**Activity**	Development of Existing Capabilities

Summary
A traceable and validated measurement infrastructure for indoor emissions to address the growing concern about the quality of indoor air, ensuring that the meet regulatory needs, increase economic impact and quality of life improvements are met.

The Need
Millions of people suffer respiratory problems associated with indoor material emissions. The protection of human health and the natural environment depends strongly on the ability to measure harmful, toxic and carcinogenic substances cost-effectively, and with sufficient validity to be fit for purpose. At present there are no European mandatory standards for indoor air, but there is a convergence and tightening of various regulations in the chemicals arena (e.g. REACH) and future EU directives (e.g. European Construction Products Directive, the General Product Safety Directive and European Energy Performance of Buildings Directive). Higher levels of analytical control, more reliable methods of measurement that can be widely applied and appropriate reference gas mixtures to calibrate analytical systems are in demand to meet these current and future needs.

ISO standards methods for measuring indoor air have been developed. To obtain sufficient sensitivity, it is necessary to trap and concentrate the compounds of interest and then analyse using chromatographic techniques. Active methods, using air sampling pumps to draw through an absorber and diffusive methods that do not require pumps are available with sufficient sensitivity and accuracy for many, but not all, compounds. It is now recognised that the range of compounds in indoor air that should be monitored is much wider than originally believed – therefore new analytical techniques need to be developed. This project will maintain NPL's world-leading position in providing traceability to underpin measurement of indoor emissions.

The Solution
As new measurement techniques are introduced there is a need to check that different laboratories' capability in correctly carrying out and interpreting the results obtained. This project will focus on a proficiency-testing scheme involving the UK laboratories that will be involved with indoor air monitoring. Feedback of these results obtained will greatly assist in corroborating the general competency of the UK laboratories and highlight potential areas of improvement for specific laboratories.

Project Description (including summary of technical work)
The initial phase of the project will be to draw a definitive list of compounds to be included in the study. These are typically expected to be such compounds as n-hexane, methyl isobutyl ketone, toluene, cyclohexane, trimethylbenzene, butylated hydroxyl-toluene etc. Colleagues at NIST will also be consulted to ensure some uniformity of approach between the US and Europe.

- Once the compound list is identified the appropriate sorbent for the tubes can be selected.
- The second phase will be the loading of the sorbent tubes and their distribution to the participating laboratories.
- The final phase will be the analysis of the returns from the participants and issuing a report and disseminating the results.

Impact and Benefits
This project will have significant impact on indoor air quality monitoring required to protect public health. It is well documented that atmospheric air quality influences health and wellbeing; poor air quality has been linked to premature death, bronchitis, heart attack and other cardiovascular problems. The presence of pollutants in indoor air (e.g. oxides of nitrogen, ozone, airborne particulates, VOCs and carbon dioxide) that originate from various consumer goods, building materials and furnishings have similar consequences on human health (e.g. skin irritations, nausea, asthma and even cancer). According to U.S. Environmental Protection Agency, indoor air can be

2 to 5 times more polluted than outdoor air. Since people spend most of their time indoors, careful monitoring and the development of a traceable measurement infrastructure specific to indoor air is needed before any reduction programmes can be meaningfully implemented and their benefits assessed. The traceability delivered through this project will enable the UK to fulfil its commitment to indoor air and workplace air legislation.

Support for Programme Challenge, Roadmaps, Government Strategies

This work aligns with the ChemBio Gas Analysis theme and sub-themes of Gas Analysis and Environmental Technologies. Aligns with the UK's commitment to climate change, EU and EC air quality directives on monitoring of ambient pollutants and tropospheric ozone precursors, indoor air legislation and emissions trading. Aligns and supports TSB's and NMO's Environmental Sustainability Application Area and Draft Strategy, respectively.

Synergies with other projects / programmes

The output of the project will significantly underpin the confidence in the UK indoor air analysis capability. Future studies of health monitoring of people exposed to potential indoor air contaminants will benefit from a sound metrological base providing accurate measurement of the compounds concerned.

Risks

NPL has extensive experience in running proficiency testing schemes in general with specific skills and experience within the thermal desorption techniques. There is therefore only a low technical risk associated with this project.

Knowledge Transfer and Exploitation

The primary knowledge transfer route will be the distribution of the results to the participating laboratories. The results will clearly indicate to each participant their relative performance compared to the other participants. Proficiency testing schemes in general are a popular and recognised valuable tool in improving quality performance within organisations.

Further knowledge dissemination will be by presentation at conferences and workshops, publications in high impact journals. This project will continue to build on existing contacts with UK industry and external collaborations.

Co-funding and Collaborators

The essence of a proficiency-testing scheme ensures collaboration in that the participating laboratories have volunteered to participate.

Deliverables

1	**Start: 01/04/2011**	**End: 31/05/2011**	

Deliverable title: Select candidate compounds to include in the scheme and select appropriate sorbent for tubes.

Deliverables

2	**Start: 01/06/2011**	**End: 31/12/2011**	

Deliverable title: Develop loading technique and analytical method (GC-MS). Load appropriate tubes, distribute to participants.

Deliverables

3	**Start: 01/01/2012**	**End: 31/06/2012**	

Deliverable title: Analyse responses and issue report Publication of proficiency testing scheme

Project No.	NMS/CBM12017	**Price to NMO**	£57,689
Project Title	Co-funding for TSB EcoIsland Hydrogen Vehicle Refueller	**Co-funding target**	£36,730 from TSB
Lead Scientist		**Stage Start Date**	Nov 2012
Scientist Team		**Stage End Date**	Oct 2015
		Est Final Stage End Date	Oct 2015
Sector	Energy	**Activity**	Low carbon energy

Summary

To design, build, install and operate a grid-connected hydrogen refuelling platform on the Isle of Wight, with capacity to operate a fleet of 18 - 20 commercial vehicles and a hydrogen-powered boat. NPL will provide accurate and traceable measurements of the purity of the hydrogen supplied by the refuelling stations before, during and after commissioning. This is part of the TSB-funded EcoIsland project, of which NPL is one of 11 partners.

The Need

The project will address the challenges facing hydrogen technologies to move from development to providing practical low-carbon solutions in combination with other energy and transport products, by demonstrating a system that integrates hydrogen production and storage with key elements of the energy system and transport infrastructure. This project will bring together a multitude of partners, who are leaders in their respective technology and research fields, to design, build, operate and demonstrate a means of producing hydrogen at the point of use solely from renewable energy. This will demonstrate the benefits of hydrogen as a triple zero fuel (no CO2 produced from its generation, transportation or use) and demonstrate how an electrolyser and a hydrogen store can be effectively used as a demand side management load under the control of the local electricity operating company.

The Solution

The project will design, build, install and operate a grid-connected hydrogen refuelling platform on the Isle of Wight, with a capacity to produce, store and dispense 100 kg/day for the operation of a fleet of 18 - 20 commercial vehicles and a hydrogen-powered boat. The refueller will demonstrate the use of an electrolyser and hydrogen store operating as a demand side (DSM) load for maximising the utilization of excess renewable power generation as part of the EcoIsland intiative. In addition, the refueller will provided a means of showcasing hydrogen vehicle platforms on land and water, first in the form of HICE powered vehicles and boats and later as a mean of powering fuel cell powered vehicles. The project will optimise the system for full life costing and provide experience of the use of electrolytic hydrogen as a DSM load (operating under a variable load factor) and as a zero-carbon fuel for a variety of commercial hydrogen-powered vehicles and boats.

Project Description (including summary of technical work)

NPL will contribute to the technical workpackages related to building the refueller, commissioning of refuellers, and trial and data collection. NPL will provide accurate and traceable measurements of the purity of the hydrogen supplied by the refuelling stations before, during and after commissioning. These measurements will demonstrate whether the purity of the supplied hydrogen is in compliance with the robust specifications set out by ISO 14687-2. Analysis will be carried out off-line at NPL's laboratories, where the concentrations of selected key impurities will be measured using state-of-the-art analytical methods calibrated by NPL's suite of traceable primary reference gas mixtures. For pre-commissioning, two batches of five samples from each of the two refuellers during pre-commissioning at ITM Power's Sheffield facility will be measured; NPL will also provide quality assurance and technical support with sample collection. One set of 10 samples will be analysed in M9 and one set of 10 samples will be analysed in M15, giving 20 samples in total. During the initial Commissioning phase, three batches of two samples from each of the two refuellers during commissioning on the Isle of Wight in M18, will be measured (12 samples in total.) For the final commissioning and trials, five batches of two samples from each of the two refuellers during further trials on the Isle of Wight will be analysed during the second half of the project (20 samples in total.) The total requirement is therefore for the analysis of 52 samples during the course of the project.

Impact and Benefits

The current size of the UK market for grid balancing is estimated at £360million and the use of hydrogen as a means of DSM will demonstrate the wider benefit of the integrated system as a means of utilising intermittent and excess renewable energy that will permit continued expansion of renewables and produce a low or zero-carbon fuel having monetary and environmental value. Being in a position to offer proven, operable and scalable zero-carbon hydrogen refuelling technologies will provide the consortium, and the wider UK hydrogen energy supply chain, with considerable first-mover advantage and enable a significant early market share to be captured. Benefits will include establishing a comprehensive UK capability and a market for hydrogen refuelling systems, configured and optimised for use as demand side management technologies capable of maximising the benefits from excess renewable electricity generation. Proving the capability of hydrogen refueller systems such as those developed and used in the project to operate as a demand side management devices and the benefits that can accrue to network operators and electricity generators from using such devices will encourage their wider adoption thereby accelerating the creation and use of a hydrogen refuelling infrastructure in the UK. The wider adoption of the use of such technology will lead to increased revenues across the UK hydrogen and smart energy supply chains and wider benefits associated with increased employment. Social benefits will

include greater public awareness and real understanding of the environmental benefits of the use of zero-carbon fuel and the potential to fully utilise excess renewable electricity. Environmental benefits will include the reduction in carbon emissions from road and sea transport locally during the demonstration phase and more widespread with the future roll-out of the wider hydrogen infrastructure under the UKH2Mobility plan.

Support for Programme Challenge, Roadmaps, Government Strategies

The project builds on recent successful hydrogen on-site trials of hydrogen electrolyser refuellers funded by the TSB and aligns closely with the objectives of the UKH2Mobility iniative launched jointly by three UK Government Departments and 13 industrial participants in January 2012, to ensure that the UK is positioned for the commercial roll-out of hydrogen as a fuel for ultra-low carbon vehicles by 2014/15. The current size of the UK market for grid balancing is estimated to be worth £360million and the use of hydrogen as a means of DSM will demonstrate the wider benefits of the approach, so as to allow continued expansion of renewables necessary to meet the UK's current renewable generation targets.

Synergies with other projects / programmes

This project links to the NMS ChemBio project H1 Traceable measurements of hydrogen quality and storage capacity for fuel cells and the hydrogen economy.

Risks

Technical Risk: Electrolyser failure (H) a modular approach allows rapid electrolyser stack change over and minimises downtime; fluctuating electricity supply (M) will be managed by developing an appropriate control strategy; complexity of project supply chain and logistics (M) will be managed using project management processes; Commercial Risk: the benefits accrued from developing and demonstrating a DSM device capable of producing zero-carbon fuel for transport are insufficient (L) the results from other hydrogen on-site trials have proven the utility of hydrogen as a low-carbon transport fuel and utilising renewable power will ensure zero-carbon; failure to exploit effectively (L) the partners form a natural integrated value chain and are well placed within their industry sectors to exploit the core benefits of the project.

Knowledge Transfer and Exploitation

Outputs will include integrated system designs and operational control strategies demonstrated for the duration of the 12 month trial of a hydrogen refueller system integrating active electrolysers, hydrogen storage and end-user operable dispensing facilities that are configured to operate as demand side management devices under the control of the local electricity operating company as a means of utilising excess renewable capacity. In addition the refueller will support the operation of a fleet of 18 - 20 HICE powered commercial road vehicles and a boat to demonstrate the benefits and operability of hydrogen as a zero carbon transport fuel. Outputs in addition to full technical analysis and reporting will include education and public engagement programmes. In addition to the demonstration of HICE powered vehicles the refueller will provide showcase opportunities for Fuel Cell Electric Vehicles (FCEV).

Co-funding and Collaborators

Cofunding is from the TSB; the lead partner is ITM Power, ITM Power designs and manufactures Hydrogen energy systems for energy storage and clean fuel production and has grown from its original platform of novel polymeric electrolytes for electrolysis and fuel cells to that of a technology provider. There consortium is made up of 11 partners. The EcoIsland project will bring together within the Isle of Wight a critical mass of smart energy technologies to demonstrate sustainable ultra low carbon energy use. SSE is a leading electricity and gas company operating in the. IBM is a global IT and consulting services company and as a partner in the EcoIsland Partnership are developing innovative ways in which demand and supply can be managed and controlled to maximise the potential use of renewable sources. Cable & Wireless is a global telecommunications company providing a wide range of high-quality managed voice, data, hosting and IP-based services and applications. Cheetah Marine are leading designers and builders of power catamarans based on the Isle of Wight. The University of Glamorgan's Hydrogen Research Unit (HRC) provides expertise and undertakes scientific research in sustainable environmental technologies. Arcola Energy is a UK SME experienced in the delivery of innovative hydrogen and fuel cell public engagement and education programmes.

Deliverables

1	**Start: 01/04/13**	**End: 30/09/15**	
Deliverable title: Pre-commissioning sampling and measurement of 20 samples			
2	**Start: 01/12/13**	**End: 31/10/14**	
Deliverable title: Initial commissioning sampling and measurement of 12 samples from two refuellers			
3	**Start: 01/10/14**	**End: 31/10/15**	
Deliverable title: Further commissioning sampling and measurement of 20 samples from two refuellers			

Project No.	NMS/CBM13005	**Price to NMO**	£1,108k
Project Title	Gases maintenance	**Co-funding target**	£300k
Lead Scientist		**Stage Start Date**	1 April 2013
Scientist Team		**Stage End Date**	31 March 2016
		Est Final Stage End Date	
Sector	Low carbon energy & Climate change targets	**Activity**	Provision of standards and maintenance of capabilities

Summary
This project aims to maintain the core capabilities at NPL which underpin UK industry's requirements for traceable reference gas mixtures and accurate methods for the analysis of gases. It will ensure that the current flexible and cost-effective infrastructure for preparing and validating primary reference gas mixtures is maintained, thus enabling continued compliance with existing national and European legislation. The facilities will also be used to deliver underpinning work to support other projects within the ChemBio Programme.

The Need
It is essential that the UK maintains its capabilities for traceable gas analysis and the preparation of reference gas mixtures (by gravimetric and dynamic methods) in order to meet legislation in areas such as: emissions trading, air quality monitoring, indoor air, atmospheric monitoring, climate change, industrial emissions, breath alcohol monitoring, and vehicle emissions. Large sectors of the UK advanced manufacturing (such as the microelectronics industry), are also crucially dependent upon traceable gas analysis measurements. The project is therefore vital to ensure that the UK is fully compliant with current European legislation, such as the Emissions Trading Scheme and EU Directives which specify limit values for pollutants in ambient air and in emissions.. Amongst many other examples, the project also ensures that breath alcohol legislation is fully supported and that the testing of vehicle emissions in MOT test centres across the UK are reliable, stable and comparable.

In addition, the project will also enable NPL to maintain its current extensive UKAS scopes of ISO Guide 34 (Reference Materials) and ISO 17025 (Calibration) accreditation for gas analysis, which are used to disseminate traceability across a range of UK industrial sectors. NPL's ISO Guide 34 scope is strongly aligned to its Calibration and Measurement Capabilities (CMCs) in the CIPM MRA – these are the most extensive CMCs of any NMI and there is a continual and on-going need to demonstrate international comparability for gas analysis capability between NMIs worldwide. This project will therefore maintain NPL's position as a world-leading lab for gas analysis by supporting its unique position as the provider of high-level traceability.

The Solution
This project will address the above needs by maintaining the core facilities and infrastructure required to provide continued traceability in gas measurements in order to meet the needs of UK industry and ensure continued compliance with existing national and European legislation. Maintaining these facilities will provide industry with a source of accredited, traceable and accurate calibration gas mixtures, including standards of natural gas, refinery gas, trace water vapour, volatile organic compounds, process emissions gases, vehicle emission gases, breath alcohol, gases for ambient air quality measurements, atmospheric gases, greenhouse gases and zero gases. It will also maintain NPL's CMCs in the CIPM MRA by participating in strategic CCQM key comparisons.

Project Description (including summary of technical work)
This project will maintain the facilities required for delivering traceable standards and analytical methods for measurements of: fossil-fuel derived energy gases (*e.g.* natural gas, refinery gases and coal gases); hydrogen fuel quality; trace water vapour (including the measurement of water vapour transmission rate); volatile organic compounds (including ozone and particle precursor VOCs, and chlorinated hydrocarbons); industrial and process emissions; vehicle emissions; breath alcohol (including interfering substances); CO, CO_2, methane, NO, NO_2, SO_2 and ozone in ambient air quality and the atmosphere; greenhouse gases; and zero gases for purity analysis applications.

It will also maintain the critical software and databases that support NPL's quality system for preparing, analysing and archiving primary gas standards, and ensure that capability is available to maintain and underpin NPL's CMCs in the CIPM MRA by participating in strategic international comparisons, including CCQM key comparisons on O_2 in N_2 (Q2 2013), formaldehyde in N_2 (Q2 2014), water in N_2 (Q4 2014) and natural gas (2015).

Impact and Benefits
The maintenance of these key facilities will have a direct impact on a range a major UK industrial and environmental sectors including: natural gas trading, hydrocarbon fuel refining, hydrogen production, microelectronics, monitoring of atmospheric pollutants, air quality measurements, monitoring of stationary source emissions, breath alcohol legislation,

and vehicle emissions testing. These sectors will all benefit from maintenance activities which allow the continued provision of accurate and traceable gas standards and analytical methods to underpin measurements required for legislative purposes and to facilitate research.

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns strongly with the 'Energy' and 'Sustainability' challenges in the BIS NMS strategy for 2011-2015 and the 'Energy efficiency and diversification of supply' and 'Monitoring the state of the planet' challenges in NPL's Vision for Metrology in the 2020s. It also addresses key issues in numerous other published strategies and roadmaps.

Synergies with other projects / programmes

This project has synergies with all other proposed projects in the Gas Analysis theme.

Risks

The risks in this project are low due to the focus on existing facilities about which NPL has a depth of knowledge and a long-standing track record of successful delivery.

Knowledge Transfer and Exploitation

The facilities maintained by this project will be used to continue to support UK industry by offering UKAS accredited measurement services. Approx. 7000 calibrations are conducted p.a. and services are published on the NPL website. CMCs will be published on the CIPM MRA database. A peer-reviewed paper will be published from the results of an NPL-piloted CCQM comparison.

Co-funding and Collaborators

Co-funding will be obtained from the provision of standards and measurements to UK and international customers. Collaborators include a large number of UK industrial partners, academic research groups, European research institutes and other NMIs.

Deliverables

1	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of standards and facilities for energy gases (natural gas, odorants, refinery gases, liquid hydrocarbon mixtures and coal gases).			
2	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of standards and facilities for the analysis of trace-level impurities in hydrogen to meet the specifications in international standards.			
3	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of facilities to provide an infrastructure for measurements of trace water vapour and water vapour transmission rate of high performance barrier layers for encapsulation of organic electronic devices.			
4	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of standards and automated facilities for the accurate measurement of volatile organic compounds (including ozone and particle precursor VOCs, and chlorinated hydrocarbons).			
5	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of primary gas standards to underpin measurements of industrial and process emissions.			
6	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of high accuracy gas standards for the measurement of vehicle emissions and UK breath alcohol testing (including interfering substances).			
7	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of the UK national Standard Reference Photometer for ozone and dissemination of traceability to UK laboratories and field monitoring stations.			
8	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of standards of CO, CO_2, CH_4, NO, NO_2 and SO_2 for ambient air quality and atmospheric monitoring applications.			
9	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of facilities to provide and validate sources of ultra-pure zero gas for the preparation of ultra-trace level reference gas mixtures.			
10	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of critical software and databases that support NPL's quality system for preparing, analysing and archiving primary gas standards.			
11	Start: 01/04/2013	End: 31/03/2016	
Deliverable title: Maintenance of the capability required to underpin CMCs in the CIPM MRA (including participation in strategic CCQM key comparisons).			

Project No.	NMS/CBM13006	**Price to NMO**	£618k
Project Title	Greenhouse gases	**Co-funding target**	£250k
Lead Scientist		**Stage Start Date**	Apr 2013
Scientist Team		**Stage End Date**	Mar 2016
		Est Final Stage End Date	
Sector	Environmental sustainability	**Activity**	Methodology for new capabilities

Summary

This project aims to provide a validated and traceable measurement infrastructure to develop our understanding of the increasing influence of human activity on the global atmosphere and to provide the basis for stable and comparable measurements of key species required for global atmospheric monitoring.

The Need

Global climate change poses one of the greatest risks to society worldwide. Consequently, there is substantial demand from policy makers to improve our understanding of the global atmosphere and the mechanisms that control the levels of the gases involved in radiative forcing, control the increasing influence of human activity on it and address the effects of climate change and air quality. This requires long-term observations of the chemical composition of the atmosphere. Such measurements must be based on accurate and stable standards of the highest impact greenhouse gases and reactive and short-lived species required for global atmospheric monitoring in order to ensure that the data meets the requirements of environmental policy makers as well as academic and regulatory users. The Climate Change Act is a key driver and puts in place a framework to achieve a mandatory 80% cut in the UK's carbon emissions by 2050 (compared to 1990 levels), with an intermediate target of between 34% by 2020. Furthermore a large number of atmospheric compounds are specified in various European Directives (2008/50/EC, 2008/1/EC, 2002/3/EC, 2001/81/EC and 2000/76/EC) that make monitoring mandatory in member states.

The WMO's Global Atmospheric Watch (GAW) Programme plays a central role in coordinating global monitoring of atmospheric composition and addresses the main long-term objectives of the WMO Strategic Plan 2012-2015. Although significant progress has been made, the interpretation of data used to improve our understanding of the contribution of these key compounds to stratospheric and tropospheric chemistry is limited by a lack of traceable calibration resulting in poor comparability of measurement results. Research is required to develop traceable standards with long-term stability for the reactive and short-lived compounds identified by European Directives and the WMO as critical for global air quality monitoring. The measurement of greenhouse gases is also pivotal to understanding the changes in Earth's climate and needs to be carried out with a high degree of accuracy. The WMO data quality objectives for carbon dioxide and methane are 50 nmol/mol and 2 nmol/mol respectively. With the exception of water vapour, these compounds are the highest contributors to the greenhouse effect. Demonstrating comparability of reference standards with the required accuracy is a major challenge. Systematic biases are often introduced from instrumentation at monitoring stations when reference gases vary in isotopic composition from the measured environment. This significantly increases the challenge to disseminate high accuracy reference standards.

The Solution

NPL is currently the only NMI providing VOC ozone precursor gas standards to the Global Atmospheric Watch Programme of the WMO. NPL also holds a leading position in the preparation and analysis of multi-component VOC and greenhouse gas standards demonstrated by coordination and participation in key comparisons (EURAMET 886 in particular). NPL supplies these reference standards to monitoring stations, local authorities, universities and other NMIs. This project builds on current capability with research to develop primary reference standards of greenhouse gases, reactive and short-lived species with substantially improved uncertainties on current capabilities to meet the challenging requirements for underpinning atmospheric monitoring. These standards will be delivered by improving preparation methods and analytical techniques. The compounds addressed are typically present at parts-per-billion levels in the atmosphere and therefore present significant challenges to measurement and standards technology. This project will overcome a major obstacle to providing international comparability for greenhouse gas standards at the required stringent uncertainties by characterising systematic biases associated with varying isotopic composition for several analytical techniques. A diffusion device capable of delivering calibration gas flows for calibrating instruments at these levels will be developed. This offers the potential for accurate and accessible calibrations in a range of atmospheric monitoring applications.

Project Description

This project will develop an infrastructure for disseminating high accuracy standards of the highest impact greenhouse gases (e.g. carbon dioxide and methane) and reactive atmospheric species required for global monitoring (these will include terpenes and other short-lived species). This work will include research to characterise instrumental biases introduced from varying isotope effects in greenhouse gas standards, enabling the high accuracy requirements of GAW data quality objectives to be met. The project will also focus on dynamic methods for generating reactive reference mixtures and will involve the design, construction and validation of a new micro-scaled dynamic calibration source for low concentration calibrations to disseminate traceability to field monitoring sites.

Impact and Benefits This project will have a direct impact on the environment and quality of life in the UK as it will underpin global monitoring, provide a greater understanding of the increasing influence of human activity on the global atmosphere and inform decisions on policy. It will provide a much needed infrastructure that will directly answer the pressing need for traceable measurements of key greenhouse gases, reactive and short-lived compounds. It will allow the UK to comply with current national, European and international legislation requiring the measurement of compounds in ambient air which govern climate change and air quality. In particular, it will meet the target requirements specified for global monitoring of these compounds by the WMO expert group. This will form the basis for future data sets for these compounds, and improve our understanding of the family of chemical reactions that determine the oxidizing capacity of the atmosphere and influence the formation of tropospheric ozone and aerosols. Specific examples of high-impact benefits are:

- New high accuracy reference standards of key greenhouse gases (e.g. CO_2 and CH_4) to underpin global monitoring and data to fully characterise the influence of isotopic composition on analytical measurements.
- Reference standards of NO_2 with lower uncertainty and more sophisticated methods for their validation at levels required by EU directives.
- Development of a novel micro-scale diffusion device for disseminating traceability to field measurements.
- New reference standards to underpin measurements of terpenes and short-lived species in the atmosphere.

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns well with the "environmental sustainability" and the "measurement infrastructure" challenges in the BIS's NMS strategy and is a fundamental part of the CBKB gas analysis theme roadmap. It is an important part of underpinning the facilities required to deliver NPL's Metrology 2020 Vision, especially in the areas of 'Monitoring the State of the Planet' and 'A Healthy Population'. The project also addresses the Royal Society of Chemistry's Grand Challenges on 'Air Quality and Climate Change' as set out in their roadmap 'Chemistry for Tomorrow's World'.

Synergies with other projects / programmes

This project has a clear alignment with research strategy of the gas analysis theme as it supports global research, promises to meet EU directives for monitoring ambient air and contribute to the assessment of the UK's commitment to climate change. The development of a measurement infrastructure for high accuracy greenhouse gases and short-lived atmospheric species links to and succeeds work in the current programme (GA04, GA06, GA07 and GA08). The project has synergy with the current EMRP project "Metrology for Chemical Pollutants in Air".

Risks This research project will be delivered by research scientists with experience in the preparation and analysis of trace level standard gas mixtures. This will minimise the risk of technical failure in the project.

Knowledge Transfer and Exploitation

The outputs will be disseminated by high impact publication in the peer reviewed literature and presentations at relevant international fora (e.g. Gas 2013 symposium, meetings of the WMO GAW and CCQM). These will be of particular interest to the academic, air quality and global monitoring community. Input into relevant standardisation committees (PTI 15, ISO TC158 and CEN TC 264) will enable the work of the project to be transferred and used effectively to ensure the UK leads in terms of meeting and forming future requirements. There is potential IP associated with the micro-scale diffusion device. A route for its exploitation will be explored as the project progresses.

Co-funding and Collaborators A JRP which aligns with the work described here will be developed as part of the 2013 EMRP environment call (£250k, likelihood: high). Further co-funding will be received from provision of primary reference gas mixtures and calibrations to UK and international customers. Collaborators include academia (Universities of York, Leeds and Royal Holloway), members of the GAW monitoring network, UK industry and NMIs.

Deliverables

1	**Start: 01/04/13**	**End: 31/03/16**	
Deliverable title: Development of a capability for high accuracy standards to support new and emerging greenhouse gases and meet GAW data quality objectives.			
2	**Start: 01/04/13**	**End: 31/12/14**	
Deliverable title: Research to address analytical challenges for greenhouse gas reference standards with varying isotopic composition.			
3	**Start: 01/04/13**	**End: 01/04/15**	
Deliverable title: New dynamic micro-scaled diffusion sources at trace amount fractions to provide calibration for field monitoring sites.			
4	**Start: 01/04/13**	**End: 01/04/15**	
Deliverable title: Stable standards for atmospheric background levels (ppb) of short-lived atmospheric species (terpenes and oxygenated VOCs).			
5	**Start: 01/04/13**	**End: 01/04/14**	
Deliverable title: An improved infrastructure (reference standards with novel dilution methods and an analytical capability based on highly sensitivity spectroscopy) to underpin measurements of ambient levels of NO_2.			
6	**Start: 01/04/13**	**End: 31/03/16**	
Deliverable title: Investigation of the stability of reactive gases in new commercial storage technologies			

Project No.	NMS/CBM13007	**Price to NMO**	£574k
Project Title	Emerging energy gases (GA12)	**Co-funding target**	£250k
Lead Scientist		**Stage Start Date**	1 April 2013
Scientist Team		**Stage End Date**	31 March 2016
		Est Final Stage End Date	
Sector	Low carbon energy	**Activity**	Methodology for New Capabilities

Summary

This project aims to provide:

- Novel capabilities for the accurate and traceable measurement of a diverse range of emerging low-carbon ('non-conventional') energy gases.
- Support for the UK natural gas and refining industries through the provision of improved and extended standards for composition analysis, and an infrastructure to ensure measurement comparability.
- Traceable measurements of hydrogen fuel quality and robust methods for hydrogen sampling to support the UK's rapidly expanding hydrogen vehicle fleet and refuelling infrastructure.
- Traceability for the measurement of trace-level contaminants in carbon dioxide from carbon capture and storage processes.

The Need

The ultimate success of Europe's aim to become a zero-carbon economy relies on achieving challenging emissions targets, such as the UK's commitment to reduce CO_2 emissions by 34% by 2020, 50% by 2027 and 80% by 2050. To achieve this, traceable measurements of a wide range of less carbon-intense energy gases are urgently required to underpin the on-going diversification of the energy supply. For example, EC Mandate M/475 instructs CEN TC408 to develop a specification for the chemical composition of biogas for injection into natural gas networks. The potential injection of other non-conventional gases (*e.g.* shale gas) into the UK gas network also crucially relies upon traceable composition measurements to ensure than the physical properties of the gas are within specified ranges. Whilst the UK remains heavily reliant on natural gas, LPG & LNG, traceable measurements of the composition of these fuels are also essential to underpin measurements for compliance with fiscal trading and transport legislation.

Using hydrogen as an energy vector has the major benefit of being a genuinely zero-carbon fuel if it is produced at the point-of-use by electrolysis powered by renewable energy. As even trace-level impurities in hydrogen may cause irreversible damage to fuel cells vehicles, novel traceable measurements of hydrogen fuel quality are required to ensure that industry meets the highly challenging impurity specifications set by the ISO 14687 series of standards.

The carbon capture and storage industry requires knowledge of the nature and concentration of any components within captured CO_2 in order to ensure its safe transport from plant to storage facility. Carbon dioxide is typically captured by absorption in an amine solution or chilled ammonia which may introduce contaminants into the gas.

The Solution

The project will develop a range of novel, traceable and accurate standards and methods, which will address a broad array of needs of the energy gas sector. These include standards and methods for the analysis of: trace-level impurities in biogas; the chemical composition of shale gas, expanded ranges of natural gas, LPG & LNG; impurities in hydrogen and trace-level contaminants in CO_2. These standards and methods, and the scientific knowledge gained during the project, will be disseminated to industry and other key stakeholders. The project will also provide a route for ensuing the comparability of refinery gas measurements in the UK through the operation of a PT scheme.

Project Description (including summary of technical work)

This project will achieve its and meet the needs stated above by:

- Developing novel methods and standards for the accurate and traceable measurement of trace-level toxic impurities in biogases, particularly a new traceable method for measuring total silicon (as an indicator of siloxane concentration) by ICP-MS.
- Developing new, traceable multi-detector GC measurements for the composition of shale gas, biogas and emerging non-conventional gases with lower uncertainties than those currently available.
- Expanding the range of components in reference gas mixtures for the measurement of natural gas and refinery gas composition, and improving the accuracy and stability of standards for odorisation.
- Successfully operating a refinery gas proficiency testing scheme for accredited UK gas analysis laboratories.
- Developing an extended range of traceable standards of LPG & LNG in constant pressure cylinders. Improving the accuracy and stability of such mixtures by a study of the transition of the mixtures from the liquid to the vapor phases and developing a novel sampling device to improve the repeatability of GC analysis.
- Delivering step-wise improvements in methods for measuring the most challenging trace-level impurities in hydrogen (*e.g.* total sulphur compounds, ammonia), and development and validation of a robust sampling method to take representative samples of hydrogen from 350 bar refuelling stations into vessels suitable for lab analysis no reactive contaminants are lost.
- Developing novel standards and analytical methods for the traceable analysis of amines in a CO_2 matrix.

Impact and Benefits

This project will have substantial and direct impact on the UK energy industry by reducing barriers to innovation and trade. The energy industry underpins the entire UK economy – in 2011 it directly employed 171,800 people and contributed 4.4 % of UK GDP and 51 % of industrial investment. Specific examples of high-impact benefits are:

- A novel method for biogas analysis to support the rapidly-expanding UK biogas industry.
- More accurate methods for gas composition analysis to underpin fiscal trading.
- Novel, more stable standards of LPG & LNG for improved measurements of this key imported fuel.
- Traceable QA measurements of hydrogen fuel for gas suppliers and fuel cell and vehicle manufacturers.
- Traceable measurements to support the nascent UK shale gas industry, which is expected to expand significant following the publication of the Energy Bill in late 2011.
- Ensuring comparability of UK refinery gas measurement and support of UKAS through a PT scheme.

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns strongly with the 'Energy' and 'Sustainability' challenges in the BIS NMS strategy for 2011-2015 and the 'Energy efficiency and diversification of supply' challenge in NPL's Vision for Metrology in the 2020s. It also addresses key issues in a large number of published strategies and roadmaps including: The EC Energy 2020 strategy, the EC Energy Roadmap 2050, the DECC UK Renewable Energy Roadmap, the UK Government's Carbon Plan, the 2011 Energy Bill, RSC's 'Chemistry for Tomorrow's World' roadmap, and the JRC Technology Roadmap.

Synergies with other projects / programmes

This project has synergies with all other proposed projects in the Gas Analysis theme, proposed projects TA1 & TA3 in the Trace Analysis Theme, and the following on-going projects: EMRP ENG01, H2FC (EC FP7), HyQ (EC JTI) & EcoIsland (TSB). It is also expected to align with a number of projects developed during the 2013 EMRP Energy call.

Risks

The risks in this project are related to the complexity of the technical work. These risks are mitigated by the depth of experience available to NPL and amongst key collaborators.

Knowledge Transfer and Exploitation

Outputs will be disseminated by the provision of the new standards, methods and sampling technologies to partners, and the operation of a proficiency-testing scheme. The scientific advances made in this project will be published in high-impact peer-reviewed, journals, presented at an international gas analysis conference and disseminated by supporting the UK's interests in ISO TC193, ISO TC158 & CEN TC408.

Co-funding and Collaborators

Co-funding will be obtained from projects in the 2013 EMRP Energy call (£250k; very high likelihood), and the will be provision of standards and measurements to UK and international customers. Collaborators include specialty gas companies, major oil and gas companies, UK SMEs, calibration and testing laboratories, academic research groups, European research institutes and other NMIs.

Deliverables

1	**Start: 01/04/2013**	**End: 31/03/2016**	
Deliverable title: Novel methods and standards for the accurate and traceable measurement of trace-level toxic impurities (*e.g.* silicon-containing compounds) in biogases.			
2	**Start: 01/04/2013**	**End: 31/03/2016**	
Deliverable title: Primary reference gas mixtures with increased number of components and wider concentration ranges for the measurement of natural gas composition, natural gas odorisation and refinery gas composition.			
3	**Start: 01/01/2014**	**End: 30/06/2015**	
Deliverable title: An increased range of traceable standards of liquid hydrocarbon mixtures (*e.g.* LPG & LNG), with improved accuracy and stability.			
4	**Start: 01/04/2013**	**End: 31/03/2016**	
Deliverable title: Improved hydrogen sampling and analysis methods to underpin fuel quality measurements at hydrogen refuelling stations.			
5	**Start: 01/08/2014**	**End: 31/03/2016**	
Deliverable title: A strategic suite of standards to underpin measurements of new non-conventional gases such as shale gas.			
6	**Start: 01/01/2014**	**End: 31/12/2015**	
Deliverable title: New standards of amines and other compounds in a carbon dioxide matrix to support the carbon capture and storage industry.			
7	**Start: 01/07/2014**	**End: 30/06/2015**	
Deliverable title: Completion of a refinery gas proficiency testing scheme in conjunction with UKAS to support UK calibration and testing laboratories.			

Project No.	NMS/CBM13008	**Price to NMO**	£279k
Project Title	Primary standards for process gases (GA13)	**Co-funding**	£125k has been removed to co-fund EMRP i17 which sits in the IRD programme
Lead Scientist		**Stage Start Date**	Apr 2013
Scientist Team		**Stage End Date**	Mar 2016
		Est Final Stage End Date	
Sector	Advanced Manufacturing and Services	**Activity**	Methodology for new capabilities

Summary
This project aims to provide a traceable and validated measurement infrastructure to support the development of advanced manufacturing and sustain UK leadership in the high technology micro-manufacturing sector.

The Need
The microelectronics industry has advanced significantly over recent decades. Control of Airborne Molecular Contamination (AMC) is essential for the optimization of industrial micro-fabrication processes in order to guarantee the performance of products which rely on ultra-clean manufacturing environments such as semiconductor-, photovoltaic- and LEDs. AMCs are typically present at low parts per billion to parts per trillion amount fractions, making detection very challenging. Sensitive on-line monitoring techniques for these compounds are required to inform the operator of their presence and ensure corrective action is taken to minimise impact on the production process. Reference standards of these challenging compounds at trace amount fractions are required to provide traceability and validate these developments. However these reference standards are unavailable due to their limited stability in high pressure cylinders.

The Solution
Dynamic methods have the potential to overcome the difficulties in generating reference standards of challenging reactive gases at trace amount fractions. As standards are generated continuously, losses due to absorption on the walls of the system are negligible after equilibrium has been achieved. NPL will conduct a detailed investigation to assess the feasibility of existing methods for generating dynamic standards of key contaminants in process gases and manufacturing environments. This will provide an assessment of the feasibility of various approaches and inform the development of a NPL capability to deliver accurate and traceable reference standards of these challenging compounds. This will require a novel approach which considers a strategy for minimising equilibrium times and delivering a high dynamic range. Stable static standards of the target compounds will be developed at higher amount fractions (ppm). These will provide the infrastructure and will be used to generate reference standards by dilution at trace amount fractions either for direct use or to validate dynamic facilities. This will be a significant step in providing traceability for the measurement of AMCs.

Project Description (including summary of technical work)
The project will develop an infrastructure to support measurements of several key AMCs in manufacturing environments at trace amount fractions (e.g. NH_3, HCl and HCHO). Initial work will review the application of existing dynamic methods to generating reference standards of the compounds of interest. This work will inform the development of a capability at NPL to deliver dynamic reference standards of key compounds at trace amount fractions. The project will then focus on the development of stable static reference standards of the target compounds at higher concentrations (ppm levels). Producing accurate and stable mixtures at these concentrations is a major challenge and will require close work with speciality gas companies to test and validate the performance of new cylinder passivation technologies and assess their suitability for use with the compounds described here. Measurements to determine the stability of mixtures prepared will be conducted at regular intervals. This is an essential part of the project as these measurements will provide useful information on the compatibility of different passivation chemistries with the compounds under study and will provide evidence to guarantee the stability of the mixtures. Novel preparation methods will be required to minimise sources of uncertainty introduced from transferring the pure material to the cylinder. Protocols will need to be developed to ensure the safe handling of materials.

Impact and Benefits
In 2009, manufacturing was the third largest sector in the UK economy in terms of share of UK GDP and generated some £140bn in gross value added, representing just over 11% of the UK economy. The UK is currently among the world's leading players in advanced manufacturing (plastic electronics in particular) with a market value that is forecast to rise from $2 billion today to $120 billion in 2020. This project will have a direct and significant impact on the UK economy by removing barriers to innovation and trade within the advanced manufacturing industry. It will also have a substantial impact on the environment and quality of life by underpinning the development of high efficiency, low cost

photovoltaic devices. Specific examples of high-impact benefits from this project are:

- An infrastructure to support measurements of key contaminants in process gases and manufacturing environments which will lead to higher product performance and inform the preparation of legislation relating to occupational health and safety.
- Disseminate traceability to support the development of new state-of-the art techniques based on optical spectroscopy to meet the need for detection of AMCs at challengingly low concentrations demanded by industry.

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns well with the "global competitiveness" and "measurement infrastructure" challenges in the BIS's NMS strategy and is a fundamental part of the CBKB Gas Analysis Theme Roadmap. It is essential work to deliver NPL's Metrology 2020 vision, particularly in the areas of "energy efficiency and diversity of supply" and "the big factory". This project also addresses the 2011 International Technology Roadmap for Semiconductors and the Royal Society of Chemistry's Grand Challenges on 'energy' as set out in their roadmap 'Chemistry for Tomorrow's World'.

Synergies with other projects / programmes

This project strongly aligns with the analytical chemistry and measurement science research currently in the gas analysis theme. The development of a dynamic capability to generate reference standards of reactive compounds has synergy with the core activities in the current programme (GA06, GA07, GA08) aimed at developing an infrastructure to underpin measurements of environmental gases, energy gases and advanced manufacturing.

Risks

This project is focused on the development of new methods to underpin measurements of reactive compounds at trace amount fractions. Therefore the main risk is whether application of new measurement techniques will be successful. This risk has been reduced by preliminary calculations. Access to methods and protocols used in industry will be required for the development of static reference standards at NPL. These risks could be mitigated by strong collaboration with industry.

Knowledge Transfer and Exploitation

The outputs of this project will be disseminated by high impact publication in peer-reviewed literature, presentations at relevant international fora and via the provision of reference standards developed. These will be of particular relevance to the academic and industrial community in the micro fabrication arena. Additional routes of exploitation will be strongly pursued, mainly within standardisation organizations and through IP-Protection. The outputs from this project will be disseminated with presentations and good practice guides.

Co-funding and Collaborators

A deliverable to the original project "A fully validated facility consisting of dynamic reference standards (e.g. ammonia and acid gases) and high precision analytical techniques to underpin measurements of key airborne molecular contaminants in manufacturing environments at trace amount fractions" has been removed and is being used to co-fund the EMRP i17 project which sits in the IRD programme (). Further co-funding will be received from provision of reference standards to UK and international customers Collaborators for this work will include academia (Oxford and Newcastle universities), UK industry (e.g. BOC, Honeywell Analytics, Centre for Process Innovation, VG Scienta and Plasma Quest Ltd), and several NMIs (VSL, MIKES, PTB and INRiM).

Deliverables

1	**Start: 01/04/13**	**End: 01/04/15**	
Deliverable title: Develop new, fully validated and stable primary static standards to underpin measurements of ammonia, formaldehyde and acid gases. Conduct long-term stability trails to assess the performance of a variety of passivation chemistries.			
2	**Start: 01/04/13**	**End: 01/12/13**	
Deliverable title: Review the feasibility of applying several candidate dynamic methods to the development of a facility for generating reference standards of reactive gases at trace amount fractions.			

Project No.	NS0022011P06	**Price to NMO**	£252k
Project Title	Metrology for chemical pollutants in air	**Co-funding target**	£135k
Lead Scientist		**Stage Start Date**	01/07/2011
Scientist Team		**Stage End Date**	30/06/2014
		Est Final Stage End Date	2017
Sector	Environmental Sustainability; Underpinning Metrology	**Activity**	Development of Existing Capabilities

Summary
The measurement of gaseous pollutants in air is a priority issue as it has large impact on human health and the environment. The work proposed in this project contributes to a wider body of research in the European Metrology Research Programme (EMRP) Joint Research Project 14e (JRP14e) "Metrology for Chemical Pollutants in Air". This JRP addresses metrological issues in monitoring both ambient and indoor air, so that standardization committees, regulatory bodies, environmental monitoring networks and testing laboratories will benefit.

The Need
EU directives list ambient atmospheric pollutants—resulting from human activities, industrial emissions or natural processes—that must be monitored by member states, including the UK. For example, the concentration levels of the primary gas pollutants (sulphur dioxides, nitrogen oxides, carbon monoxide, benzene and ozone) are regulated by the European Directive 2008/50/EC "Ambient air quality and cleaner air for Europe", which sets limit values and data quality objectives for the measurement of air pollutants in ambient air. However, the existing metrological infrastructure is fragmented and does not meet the requirements set in regulations and documentary standards (such as EN standards prEN14211, prEN14212, prEN14625, prEN14626). These standards set stringent specifications for the impurity levels of traceable zero gases used in type approval testing and QA/QC. Nitrogen and pure air, used for zeroing gas analysers and for dilution purposes, should be free of contaminants that may interfere with the measurements. Zero gases should not contain more than 1 ppb of the pollutant measured (except for carbon monoxide). Certifying such low levels is not within the capability of most EU air quality monitoring networks.

Although no European mandatory standards exist for indoor air, higher levels of analytical control, more reliable methods of measurement that can be widely applied and appropriate reference gas mixtures to calibrate analytical systems are in demand. Regulation and assessment of high-priority gas indoor pollutants (including various volatile organic compounds [VOCs], formaldehyde, carbon monoxide, nitrogen dioxide and ozone) is very difficult, due to the infiltration of polluted outdoor air and to emissions from countless sources, such as building materials, furniture. The ISO 16000-6:2004 standard describes procedures for measuring semi-volatile organic compounds (SVOCs) using thermal-desorption measurement methods. However, these methods do not provide accurate measurement results for long-chained (C16 to C22) SVOC molecules with higher boiling points.

The Solution
To meet the requirements of measurement uncertainty as stated in the EU Air Quality Directive (2008/50/EC), the quality of zero gas should be analysed against given specifications. This project will contribute to the development of a reliable "zero gas" for gas standards used in air quality monitoring and improved measurement methods to lower uncertainties in the measurement of nitrogen oxides (NO and NO_2). Specifically, the development of a new approach for the single and simultaneous assessment of impurities in zero gas by traceable novel optical techniques, such as Cavity Ring Down Spectroscopy (CRDS). In addition, this project will contribute to the development of new reference methods and traceable reference materials for the measurement of SVOCs in indoor air. Specifically, the study of the feasibility of using sorbent tubes as an alternative method for preparing traceable and accurate reference standards for traceability or quality control purposes.

Project Description (including summary of technical work)
Working with the other JRP consortium members, NPL activity will contribute to:
Zero gas standards: Optical analytical techniques, e.g. CDRS, will be used to measure NO and NO_2 impurities in zero gas at ppb and sub-ppb level. Such optical systems, if validated, may be used as absolute methods and solve the "zero" point calibration problem. Measurement strategies will be developed for the simultaneous detection of impurities. Once fully traceable, these measurement approaches will be used to test cleaning devices, filters and

scrubbers for the supply of zero gas standards.
Traceability for the measurement of SVOC in indoor air: 1) Selection of specific VOCs and SVOCs for investigation, 2) Specific analytical requirements, such as concentration levels and relative uncertainties will be assigned to the selected compounds, 3) Gas standard mixtures will be prepared and used for calibration and measurement purposes, 4) Suitable sampling techniques and measurement methods will be developed for SVOC and preparing SVOC calibrants using sorbent tubes.

Impact and Benefits
This project will have significant impact on atmospheric and indoor air quality monitoring required to protect public health and to address climate change. The project will reduce the risks of exceeding the maximum allowable data quality objectives of the EU and the UK, optimise procedures and methods for calibration and monitoring, reduce the uncertainty associated with the measurement of gaseous air pollutants, and improve the services offered by calibration laboratories to end-users by the exploitation of new calibration and comparison methods.

Support for Programme Challenge, Roadmaps, Government Strategies
This project will support the UK's activity in a European-wide metrology research project, focussing on ambient and indoor air pollutants and is closely linked to the EU Air Quality policy (Directive 50/2008/EC). Specifically, the outputs of this work will support the UK Government's strategies relating to air quality through improvements in the quality of data for policy-making and regulation and underpinning other environmental research initiatives. It also aligns with and supports TSB's and NMO's Environmental Sustainability Application Area and Draft Strategy, respectively.

Synergies with other projects / programmes
This project builds on NPL's world-leading research activity in gas metrology and environmental monitoring. Through previous, and current, Chemical and Biological Metrology Programme projects, NPL has developed state of the art facilities and leading capabilities in the provision of gas standards and measurement methods.

Risks
1) *Risk*: Detection technique(s) not suitable for (sub) ppb levels of the impurities in zero gas. *Mitigation*. The measurement of trace level impurities in zero gas will use, and compare, classic and novel detection techniques. 2) *Risk*: Problem of generating a gaseous mixture of a SVOC. *Mitigation*. To generate gas standards with traceable concentrations, the surface in contact with the generated gas should be inert and heated, the heating temperature must be above the chosen vaporization temperature and, surfaces may be specially treated.

Knowledge Transfer and Exploitation
The knowledge developed in this project, as part of the EMRP JRP14e, will be transferred via publications (reports and scientific papers) and presentations at leading conferences; input and information exchange with stakeholders and end-users through brochures, presentations and a workshop; input and information exchange with ISO (ISO/TC146 Air Quality/SC6 Indoor Air and ISO/TC158 Gas Analysis), CEN (CEN/TC264 Air Quality/WG12 Reference measurement methods) and national standardization committees; and an one-day technical training event will be developed for end-users and stakeholders in air quality.

Co-funding and Collaborators
This project comprises NPL's input into EMRP JRP14e. The consortium, led by VSL (Netherlands) comprises: BAM (Germany), EJPD (METAS, Switzerland), IL (FMI, Finland), INRIM (Italy), JRC (Institute for Environment and Sustainability, EC), LNE (France), MIKES (Finland), NPL (UK), PTB (Germany), SMU (Slovakia) and UBA (Germany).

Deliverables

1	**Start: 01/07/11**	**End: 30/06/2013**	

Deliverable title: Cofunding for EMRP project "Metrology for chemical pollutants in air"

Project No.	NS0022011P07	**Price to NMO**	£237k
Project Title	Metrology for automotive exhaust emissions	**Co-funding won**	£207k
Lead Scientist		**Stage Start Date**	01/10/2011
Scientist Team		**Stage End Date**	30/09/2014
		Est Final Stage End Date	2016
Sector	Environmental Sustainability; Underpinning Metrology	**Activity**	Pollution and Waste Reduction; Traceability and Uncertainty

Summary

The work proposed contributes to a European Metrology Research Programme (EMRP) Joint Research Project 6e (JRP6e) "Emerging requirements for measuring pollutants from automotive exhaust emissions", now designated ENV02. As part of ENV02, NPL will develop the innovative underpinning metrology required to better understand, measure and control two of the main constituents of automotive exhaust emissions, soot particles and mercury (Hg).

The Need

Automotive vehicles are a major source of environmental pollution, particularly primary atmospheric contaminants (CO, NO_X, and hydrocarbons), Hg (via petrol combustion), and sub-micron particles (present in exhausts especially from diesel combustion). The pollution by particles is of particular significance, as modern engines with high-pressure injection emit many ultrafine particles (below 0.1µm in size), which are dangerous to people's health. To ensure that emissions of ultrafine particulate pollutants can be controlled, the European Commission needs the evidence base necessary to adopt a new number-based approach of measuring emissions of particulate pollutants, in addition to the current mass-based approach. European emissions standards (EURO 5 and 6 and the EURO VI standards) define exhaust emission limits for new vehicles sold in EU member states. The vehicle emissions regulation (ECE R83, R49) defines the requirements for particulate measurement instruments (such as condensation particle counters [CPCs]) and is applicable for type approval according to EURO 5b for diesel vehicles (starting September 2011) and later for direct injection gasoline vehicles as part of EURO 6. The definition for the calibration procedure of the equipment in use today allows a high degree of freedom for the calibration laboratories, which can result in different calibrations and test results. This procedure is being elaborated in ISO WD 28971, but the metrological underpinning is lacking. European Legislation (the Fourth Air Quality Daughter Directive) requires the measurement of Hg vapour in ambient air in all Member States to ensure the measured concentrations as a result of emission from combustion sources, such as automobiles, remain within acceptable levels. The majority of current measurements of Hg vapour are traceable to the vapour pressure of Hg. A static headspace generator (bell-jar apparatus) allows a saturated concentration of Hg to develop in air, from which a known amount of mass of Hg can be removed for calibration purposes. Several empirical equations are available to describe the vapour pressure of Hg at a given temperature, but agreement between them is not good as data sometimes can differ by 5% or even more. To remove the dependency of Hg vapour measurement on these empirical equations, and to provide stability, comparability and coherence, traceability to SI units needs to be developed.

The Solution

The establishment of a new metrological base for particle emissions in exhaust gases of diesel vehicles in UK and Europe, including a particle number concentration standard for soot particles for the calibration of measuring instruments for the type approval of Euro 5 and Euro 6 diesel vehicles. Further, this project will enable the validation of novel instrument types that can measure the soot particle concentrations in exhaust gases from diesel vehicles and be used for the regulatory periodic emission control of vehicles. The project will also produce SI traceable Hg vapour sources, at much lower concentration levels than have previously been achieved, suitable for the direct calibration of measurements of Hg vapour in vehicle exhaust.

Project Description (including summary of technical work)

Working with the other ENV02 consortium members, NPL activity will contribute to:

Soot particles: 1) Coordinated installation and characterisation of a system for traceable number concentration measurement of combustion particles. Reduction of the uncertainty for CPC calibration, e.g. by better multiple charge treatment, improved aerosol flow control, high-level aerosol electrometer calibration. 2) Definition of a protocol for comparison of national particle number concentration standards and experimental validation of the protocol. 3) Definition of a common calibration protocol for calibration services for the automotive industry fulfilling

the requirements of ECE R83.

Hg vapour measurement: 1) Validated and traceable Hg vapour standards suitable for calibrating directly measurements of Hg in automotive emissions and in ambient air. 2) SI traceability of Hg vapour measurements using ID-ICP-MS technology to measure the content of the a priori standard (the saturated concentration of Hg vapour in the static bell-jar apparatus). 3) Demonstration of accurate and traceable Hg measurements in exhaust emissions and in ambient air with lower uncertainties.

Impact and Benefits

Dissemination of the results to regulation bodies will allow further reductions in emissions from diesel vehicles and these results could also be conveyed in the future for use by the transportation sector (and other emission sources), to meet EU and specific UK air quality targets and objectives. Reliable traceability for the particle number concentration measurement and for the calibration of CPCs will lead to reduced effort in costs and time for manufacturers, research institutes, NMIs and the automotive industry. The development of a metrological infrastructure for Hg measurements will provide the high accuracy link between the vapour pressure of Hg and the SI that will allow accurate and traceable measurements to be made with greater certainty around the world, thereby allowing tighter future regulation on Hg emissions to be proposed and enforced with confidence.

Support for Programme Challenge, Roadmaps, Government Strategies

This project will support the UK's activity in EMRP ENV02 for improving the metrological infrastructure around automotive exhaust emission pollutants. The outputs of this work will support the UK Government's requirements on pollution control and climate change, EU air quality directives on monitoring of ambient pollutants and link to DEFRA's air quality monitoring networks. Finally, this work aligns with the TSB's and NMO's Environmental Sustainability Application Area and Draft Strategy, respectively.

Synergies with other projects / programmes

Through the Chemical & Biological Metrology Programme (ChemBio), NPL has pioneered (along with EJPD and NMIJ) the inclusion of airborne particles within the metrological framework, and has built up extensive laboratory experience of soot nanoparticle generation, and CPC and SMPS operation. In addition, NPL has ISO/IEC 17025 accreditation for the calibration of CPCs, and has contributed to the work of the UNECE's Particle Measurement Programme (PMP) for diesel emission measurements. Also, NPL has extensive experience of Hg vapour measurement in ambient air as part of the UK Heavy Metals Monitoring Network, which NPL runs on behalf of the UK government. Through a ChemBio project, NPL has been active in working towards establishing the SI traceability of Hg vapour measurements, benchmarking the accuracy of the Dumarey equation for Hg vapour in air, validating and calibrating Hg vapour generators, producing and validating standard methods for Hg vapour measurement in CEN TC264 WG25, and researching into Hg particulate to Hg vapour ratios in ambient air.

Risks

In the Hg vapour activity; there is risk of failure to deliver improved SI traceability or low-level calibration standards. The consortium members are highly experience in the area and have a strong track record of delivery in this area.

Knowledge Transfer and Exploitation

The outputs form this work will be primarily disseminated through reports, scientific publications in peer-reviewed journals and presentations at conferences or workshops. NPL and the EMRP ENV02 consortium are well represented on appropriate bodies that will enable results to be disseminated directly. For example, through the following technical standards committees: ISO TC 24 SC4 WG 12 (Particle characterisation), CEN TC 264 WG32 Air quality – Determination of the particle number concentration and CEN TC264 WG25 Hg in ambient air, and vehicle committees such as PMP (UNECE) and BTC Emissions Testing Group (UK).

Co-funding and Collaborators

This is a ring-fenced project that comprises NPL's input into EMRP ENV02. The following institutes, led by PTB (Germany), form the consortium: BAM (Germany), JRC (EU), LNE (France), EJPD (Switzerland), MIKES (Finland), NPL (UK), IJS (Slovenia), VSL (Netherlands) and DFM (Denmark).

Deliverables

1	**Start: 01/10/11**	**End: 30/09/14**	

Deliverable title: Cofunding for EMRP project "Emerging requirements for measuring pollutants from automotive exhaust emissions"

Project No.	CB/2011/CF13	**Price to NMO**	£62k
Project Title	Metrology for ocean salinity and composition	**Co-funding target**	£51k already won from EMRP
Lead Scientist		**Stage Start Date**	01/10/2011
Scientist Team		**Stage End Date**	30/09/2014
		Est Final Stage End Date	2016+
Sector	Environmental Sustainability – Climate change targets; pollution and waste reduction	**Activity**	Development of existing capabilities

Summary
The work proposed in this project contributes to a wider body of research in the European Metrology Research Programme project "Metrology for Ocean Salinity and Acidity". The project aims at the development of methods, standards, and tools to improve the databases used as input for climate change and oceanography models. It aims to provide metrological traceability to the SI system for the measurement of the key oceanic variables such as salinity, acidification, composition, and dissolved oxygen content where such traceability is currently lacking.

The Need
The world's oceans and seas play a major role in influencing changes in the world's climate and weather because they have a large storage capacity for CO_2. At present, it is estimated that the total inorganic carbon in the ocean increases at a rate of about 0.05 % per year, causing the ocean's pH to decrease by 0.002-0.003 pH units per year [*Journal of Marine Systems*, 30, 67-87, (2001)]. Changes in ocean chemistry and composition can have severe consequences for marine organisms. Therefore, the measurement of many oceanic parameters is key to assessing the health of the ocean, the long-term sustainability of aquatic biosystems, pollution levels (especially from deposition from air, and run-off from land) and informing climate change studies – all of which are currently grand challenges for governments around the world. Because of the size of the ocean, many of these parameters show very small absolute changes even though the ocean is under continual assault from a variety of chemical vectors. Many apparent state-of-the-art techniques only provide measurement uncertainties that are larger than the trends in question, and therefore are not useful for long-term monitoring. For example, traceability to standard seawater (not an invariant parameter) via the use of a secondary conductivity cell for salinity, and ion chromatography and or ICP-OES without proper correction of physical and chemical matrix effects for composition. In this context, a further problem is the changing analytical methods used over time and the lack of traceability for many of these parameters. The main parameters of interest in this project are salinity and minor chemical components in the ocean.

The Solution
The solution to these problems is to put in place a measurement infrastructure providing traceability for measurements of salinity and ocean composition. This will provide the framework to ensure that these measurements made around the world have comparability and stability over time and location, and are coherent across measurement methods, thus making the assessment of long-term trends possible. Furthermore, the development of ultra-trace analytical methods for ocean composition will ensure that the uncertainty of these measurements is reduced to the extent that long-term trends in these parameters become observable. This is a mandatory requirement to enable a common international basis for co-operation over ocean observation.

Project Description (including summary of technical work)
The work will be carried out as part of EMRP Environment project "Metrology for ocean salinity and acidity" which will be coordinated by PTB. NPL will lead tasks in a work package on "Primary and reference methods for acidity, salinity and composition". The aims of these tasks are the development of accurate and traceable methods for the determination of seawater composition and salinity. The focus will be put on those components (macronutrients, strontium) for which a need for improved measurements has been identified and demonstrated by interlaboratory comparison studies such as CCQM P-111, and on trace elements having an important role as micronutrient, such as iron. In particular NPL will develop capability to determine ionic concentration using microelectrode arrays, and will assess the ability of these devices to provide quantitative measurements of salinity based on a scale of chloride concentrations.

Impact and Benefits
Immediate impacts will be the delivery of traceability and improved accuracy methods for the key oceanic parameters mentioned above. This will in turn allow robust assessment of the state of the ocean over time, and will enable a more accurate assessment of the effect of pollution and climate change on the aquatic ecosystem. The major impact of the project in the longer term will be to help authorities to implement, enforce and assess appropriate strategies and legislation in order to protect and preserve marine environments around the world with an increasing variable climate and higher CO_2 levels. This will have many economic and quality of life issues

associated with areas as diverse as the fishing industry, shipping, marine emissions, ocean science and tourism.

Support for Programme Challenge, Roadmaps, Government Strategies

This project will support the UK's activity in a Europe-wide project to better understand and provide the metrology infrastructure to gauge the effects of climate change on the world's oceans. The project is co-linear with the current Chemical and Biological Metrology Programme roadmaps in the Particles and Trace Analysis strategic priority theme – in particular the sections on providing traceability from miniaturised devices and sensors arrays. The work also helps to deliver on key UK Government strategies associated with understanding and mitigating climate change and provides supporting information for the UK Air Quality Strategy.

Synergies with other projects / programmes

The project has some synergies with ChemBio project TA1 where there is some work in the area of primary pH measurement, which is looking at macroscopic sensor devices. The future plan would be to develop and take this work forward under successors to the current TA1 project to develop miniaturised devices for multiplexed sensing of a range of relevant solution parameters. There is some synergy with the NMS Physical Programme, which is also collaborating on making density measurements of seawater under this EMRP project.

Risks

This work builds on previous experience in related areas, and involves partnership with very experienced international experts in the field; therefore, very few problems or risks are expected.

Knowledge Transfer and Exploitation

The outputs of this project will be primarily disseminated through:

- Scientific papers: the novel and cutting-edge nature of the science to be delivered throughout the work package will lend itself to a number of publications in high-impact peer-reviewed scientific journals (e.g. Ocean Science, Deep Sea Research, and Marine Chemistry).
- Presentations at leading international conferences. Transfer of relevant information to instrument manufactures and suppliers of standards, manufacturers of instruments with face-to-face meetings to explain and promote the relevance of the research to encourage take-up.
- Input to IAPSO, IAPWS, IUPAC working groups developing new documentary standards and guidelines in this area. Input will take place by leading the development of appropriate new documentary standards, and providing other technical input and expertise in order to disseminate the project outputs.

Co-funding and Collaborators

This project comprises NPL's input into an EMRP Environment project, led by PTB. £51k of co-funding has already been won from the EMRP, and there is likely to be approximately £15-20k of in-kind co-funding from equipment loans. Collaborators include: LNE, JRC (IRMM), INRIM, SMU, PTB, IPQ, NPL, and University of Plymouth.

Deliverables

1	**Start: 01/10/11**	**End: 30/09/14**	

Deliverable title: Reference procedures for the determination of anion mass fractions

Project No.	NMS/CBM/12011	**Price to NMO**	£324k
Project Title	P10: Facilities for airborne particle measurements (NPL)	**Co-funding target**	
Lead Scientist		**Stage Start Date**	01/04/2012
Scientist Team		**Stage End Date**	31/03/2015
		Est Final Stage End Date	2018+
Sector		**Activity**	Provision of standards and maintenance of capabilities

Summary

The UK, through the NMS, has a leading presence in the area of airborne particle measurements. This ring fenced project will maintain NMS facilities covering particle mass concentration, size and number concentration, and Elemental Carbon / Organic Carbon analysis This will allow calibration and analysis services, necessary to meet the UK's legislative and regulatory requirements, to be continued.

The Need

It is estimated that the health impact of man-made particulate air pollution costs between £8.5 billion and £20.2 billion in the UK each year (House of Commons Environmental Audit Committee Report, Nov 2011). Airborne particles also have significant radiative forcing effects (typically net cooling) in the context of climate change. These particles are a complex and rapidly changing mixture of primary and secondary material, whose origins and behaviour are not well understood. Problematic regulations for air quality, based on mass concentration (PM_{10} and $PM_{2.5}$), and for vehicle particle number emissions are being extended. The lack of consistent, accurate measurement techniques is a major obstacle in the enforcement of these regulations and in understanding the relevant atmospheric chemical processes, and this is starting to be addressed by recent initiatives within EURAMET, ISO and CEN, as well as the UNECE's Particle Measurement Programme for vehicle emissions. Underpinning metrological work funded by UK government is necessary as part of international efforts to bring rigour and international traceability to these measurements.

The Solution

The solution to meeting the identified needs can be divided into three main areas of maintenance:

- Facilities to cover measurements of airborne nanoparticles, specifically the Combustion Aerosol Standard (CAST) and other nanoparticle generators; the suite of nanoparticle detectors including the reference aerosol electrometer; and the mixing chamber for multi-instrument calibration and comparison
- The chamber with highly controlled temperature and humidity housing a high accuracy automated filter weigher, as used in the reference method for PM_{10} and $PM_{2.5}$
- The Elemental Carbon/Organic Carbon thermal-optical analyser.

Project Description (including summary of technical work)

In all areas the project will involve the maintenance, calibration, testing and training necessary to allow capabilities to be continued at current levels. Specifically, these are the ability to calibrate Condensation Particle Counters and Scanning Mobility Particle Sizers according to ISO 15900 and ISO 27891 (when published), using the range of materials and sizes currently offered; the ability to make measurements of PM_{10} and $PM_{2.5}$ according to the reference methods (EN 12341 and EN 14907); and the ability to analyse samples of particulate matter on filters for Elemental Carbon and Organic Carbon according to CEN TR 16243.

Impact and Benefits

The project will have substantial impact on the implementation of various UK air quality monitoring networks, and institutes dealing with air pollution assessment by enabling UK compliance with air quality legislation through provision of the traceability and harmonisation of particulate matter measurement methods, and also on the implementation of engine emissions legislation. Ultimately this will benefit the public through improved air quality and subsequent reduction in air-quality-related health issues, while avoiding unnecessary cost burdens on industry due to inaccurate monitoring data. In addition, this work will provide the necessary metrology platform to enable innovations in the monitoring of particulate air pollutants (relevant to both instrument manufacturers and monitoring network operators), and in underpinning our scientific understanding. Within Europe, NPL and METAS (Switzerland) have been early participants in the area of airborne particle metrology; PTB (Germany) and LNE (France) are among a group of NMIs rapidly developing similar facilities. Therefore, NMS measurement capabilities need to be at least maintained for the UK to hold its current position at the forefront of this important field.

Support for Programme Challenge, Roadmaps, Government Strategies

The project links directly onto themes within the NMS Strategy 2011-2015 document, specifically the "continuing need to measure pollutants in air" within the Sustainability Challenge, and the priority science area of "quantitative environmental monitoring" within Investing in Excellent Science. The project links directly onto the Particles Theme Roadmap within the ChemBio NMS Programme Strategy. It also aligns with BIS's UK Nanotechnologies Strategy published in March 2010, in the area of Environmental Health and Safety Research, and of course is directly relevant to implementing Defra's Air Quality Strategy for England, Scotland, Wales and Northern Ireland (most recent version: July 2007).

Synergies with other projects / programmes

The project extends the maintenance aspects from the ChemBio project P9. It will be vital for the EMRP-co-funded project ENV02 (Automotive particulate emissions), in which NPL work is focussed on harmonising soot-based CPC calibration, and ChemBio project proposal P11 within the ChemBio Particles theme. The work will also feed in to the current FP7-co-funded project AirMonTech (ChemBio project CF11), which is assessing future possibilities for revising Air Quality legislation. Regarding external projects, there will be direct synergy with two current contracts with Defra, operating the Particle Counting and Black Carbon Networks, and also a contract on aeroengine particle emissions, as part of the European Aviation Safety Agency-funded SAMPLE III project.

Risks

As the project is concerned with the maintenance of facilities, the associated risks are low.

Knowledge Transfer and Exploitation

As a maintenance project, most active dissemination will take place via the associated projects mentioned above. International comparisons, participation in standardisation committees, and presentations to conferences are not covered by this proposal. Dissemination directly from this project will take place mainly through the calibrations and analyses made possible by the work. The customers for these will include: Defra, through NPL's contracts to operate UK monitoring networks, with additional input into the European group of monitoring networks through NPL's role in the Reference Laboratory group AQUILA; other air quality network operators requiring, for example, PM and EC/OC measurements; and vehicle engine manufacturers and test houses, requiring CPC calibration.

Co-funding and Collaborators

As a maintenance project, cash co-funding is primarily envisaged to come from calibration and analysis work, and this is anticipated at an average level of £25k per year. There is synergy of far greater value with the other projects mentioned above. NPL has many regular collaborators in this area, notably King's College London, Birmingham University, Reading University, Bureau Veritas and AEA Technology in the UK, and organisations such as JRC Ispra and IUTA in Europe, whose expertise will be sought when necessary. There will be direct links to the FP7 projects AirMonTech and ACTRIS (successor to EUSAAR).

Deliverables

1	**Start: 01/04/12**	**End: 31/03/15**	
Maintenance, calibration, testing and training relating to: the Combustion Aerosol Standard (CAST) and other nanoparticle generators.			
2	**Start: 01/04/12**	**End: 31/03/15**	
Maintenance of Particulate Matter (PM_{10} and $PM_{2.5}$) facilities			
3	**Start: 01/04/12**	**End: 31/03/15**	
Maintenance of EC/OC facilities			

Project No.	NMS/CBM13009	**Price to NMO**	£270k
Project Title	Core Metrology Capabilities for Particle Analysis (Chemical) (P14)	**Co-funding target**	£125k
Lead Scientist		**Stage Start Date**	April 2013
Scientist Team		**Stage End Date**	March 2016
		Est Final Stage End Date	
Sector	Underpinning Metrology	**Activity**	Provision of Standards and Maintenance of Capabilities

Summary

This project aims to sustain core metrology capabilities for providing traceable measurement results in the environmental analytical and electroanalytical areas at current levels, allowing current legislation to be met and also underpinning work on other NMS projects. In particular the project aims to ensure the infrastructure remains in place at NPL to provide:

- Traceability for the sampling and analysis of metals in ambient particulate matter and mercury vapour
- Traceability for the sampling and analysis of ambient polycyclic aromatic hydrocarbons (PAH) in the vapour and particulate phases
- Traceability for the sampling and analysis of the ionic content of particulate matter in ambient air

Furthermore the project will realize, maintain and provide traceability for SI units at existing scope and levels of uncertainty by:

- Underpinning reference electrode production, validation and measurement capability for primary pH measurements.

The Need

This project is needed to ensure the UK maintains:

- The capability required to meet existing European regulatory and legislative requirements for ambient air analysis and monitoring of particulate-bound polycyclic aromatic hydrocarbons, particulate-bound metals and mercury vapour in ambient air – Directive 2004/107/EC.
- The capability to meet existing European regulatory and legislative requirements for the monitoring of particulate-bound anions and cations in both the PM_{10} and $PM_{2.5}$ phase of ambient particulate – Directive 2008/50/EC.

Without this there would be lack of full traceability for these measurements and the UK would be in danger of failing to demonstrate robust compliance with these legislative and regulatory requirements. Lack of maintenance of these facilities would also affect the delivery of other NMS projects.

In addition the project is needed to ensure the UK, together with international partners at the BIPM level, continues to realize and maintain the primary scale of pH at existing scope and levels of uncertainty. This also will sustain a core metrology capability at current levels. This requirement would also include providing UK representation at CCQM Electrochemical Analysis Working Group (costs associated with M3). Without this input the UK's direct link to the primary scale of pH would not maintained at current levels, and there may be increased cost for UK end users and higher uncertainties as a result. The delivery of other NMS and related projects would also be affected.

The Solution

The project will maintain the facilities, equipment and analytical methods required to provide accurate and traceable measurements for these key parameters. It will also include the work required to perform the ongoing calibration, validation, quality assurance and quality control activities required to ensure the continued accuracy and traceability of the measurements performed on the facilities in question.

The project will additionally maintain the facilities and equipment required to prepare, test, validate and compare reference electrode used in measurements of primary pH.

Project Description (including summary of technical work)

The project will involve activities to maintain facilities, equipment and analytical methods for:

- Sampling, digestion and analysis of metals in the PM_{10} phase of ambient air using inductively coupled plasma mass spectrometry
- Sampling, extraction and analysis of PAHs in the vapour phase and in the PM_{10} phase of ambient air using gas chromatography mass spectrometry
- Sampling, thermal desorption and analysis of mercury vapour in ambient air using cold vapour atomic fluorescence spectrometry
- Sampling, liquid extraction and analysis of the ionic content of particulate matter in ambient air using anionic and cationic ion chromatography
- The preparation, validation, testing and comparison of silver/silver chloride reference electrodes without liquid

junctions for use in the primary measurement of pH using the Harned Cell.

Impact and Benefits

The impact of maintaining these key facilities will be to ensure that the underpinning infrastructure is in place to allow the UK to comply with current national, European and international legislation requiring the measurement of pollutants in ambient air, thereby having an immediate impact. This will also allow the UK to assess accurately the exposure of the population at large to these pollutants, thereby helping to safeguard quality of life. Continuation of the UK's direct link to the primary scale of pH ensures there is no increased cost of traceability for UK end users and low uncertainties for this measurement at an end user level are maintained.

Support for Programme Challenge, Roadmaps, Government Strategies

The measurement capability provided by these facilities aligns well with the 'Sustainability' and 'Health' Challenges in BIS's NMS strategy, is a fundamental part of the CBKB Particle Theme Roadmap, and is an important part of underpinning the facilities required to deliver NPL's Metrology 2020 Vision, especially in the areas of 'Monitoring the State of the Planet' and 'A Healthy Population'. The project also addresses the Royal Society of Chemistry's Grand Challenges on 'Future Cities' and 'Air Quality and Climate Change' in their roadmap 'Chemistry for Tomorrow's World'. Work in the pH and pHe area is also supported by the aims of the UK bioenergy strategy.

Synergies with other projects / programmes

This project underpins the (non-core) NMS projects in the Trace Analysis and Particles Themes and has significant synergy with the Gas Theme and Environmental Technologies Theme. It also provides ad-hoc analytical capability for a wide range of other NPL NMS projects both within and outside the CBKB Programme, especially in the EMRP domain.

Risks

Very low as this is a maintenance project for existing facilities where NPL has substantial experience and a track record of delivery.

Knowledge Transfer and Exploitation

Where interesting science is generated through the process of maintaining these facilities, this will of course be disseminated in the form of peer-reviewed publications. Otherwise for a maintenance project these activities will be limited to ensuring that the user community both in NPL and outside is aware of the facilities and measurement services supported by the project and are encouraged to make use of them as appropriate.

Co-funding and Collaborators

Co-funding will come mainly from measurement services income from third party users of the facilities maintained. Collaborators will include other NMIs and European air quality reference laboratories. We will work with these key organizations to ensure NPL's facilities are maintained to a high level and that comparability is maintained across the relevant measurement areas.

Deliverables			
1	**Start: 01/04/13**	**End: 31/03/16**	
Deliverable title: Underpinning reference electrode production, validation, measurement and comparison capability for primary pH measurements			
2	**Start: 01/04/13**	**End: 31/03/16**	
Deliverable title: Maintenance of facilities to provide traceability for ambient metals and mercury vapour analysis			
3	**Start: 01/04/13**	**End: 31/03/16**	
Deliverable title: Maintenance of facilities to provide traceability for ambient PAH analysis			
4	**Start: 01/04/13**	**End: 31/03/16**	
Deliverable title: Maintenance of facilities to provide traceability for ion analysis in ambient air			

Project No.	NMS/CBM13010	**Price to NMO**	£464k
Project Title	Novel sampling and measurement techniques for emerging pollutants in air (P16)	**Co-funding target**	£250k
Lead Scientist		**Stage Start Date**	01/04/2013
Scientist Team		**Stage End Date**	31/03/2016
		Est Final Stage End Date	
Sector	Underpinning metrology	**Activity**	Standards and regulation (future)

Summary
This project will:
- develop novel sampling and extraction techniques for key emerging ambient pollutants
- provide underpinning traceability for the measurement of mercury species in complex gaseous matrices

The Need
The list of air pollutants considered dangerous to human health and environmental sustainability continues to grow. Legislation, such as Air Quality Directive 2004/107/EC and 2008/50/EC, requires the presence of these species in ambient air and in emissions to be measured so that human and environmental exposure may be quantified and the effect of abatement strategies assessed. Current revisions of these Directives are recognizing the requirement to monitor for an expanded suite of pollutants. Furthermore, it is now recognized that rather than simple elemental composition, analytical techniques that provide information on the oxidation state and chemical form of the element in question provide much more helpful information when gauging the likely effects on human health. Therefore novel sampling and extraction techniques need to be developed so that the presence of these important emerging pollutants in ambient air may be accurately and traceably assessed. In particular mercury is increasingly recognized as an important global pollutant whose combined properties of toxicity and bioaccumulation make it a threat to human health and environmental sustainability. As a result monitoring of its presence in a number of environmental matrices is required by legislation to protect human health. Traceability for mercury vapour measurements in a number of complex environmental matrices where it occurs is also now required urgently.

The Solution
The project will develop, test and validate new sampling and extraction methodologies for the measurement of emerging pollutants in ambient air. For particulate-bound pollutants where on-filter degradation is not a concern, new digestion methods for species of interest (for instance total beryllium digested using sulfuric acid mixes) will be developed. For species where avoiding degradation during digestion is essential (for instance transition metal speciation) liquid based impinger sampling techniques will be trialed. This project will also aim to develop novel sampling and dynamic calibration systems using real sample matrices to assess the method biases caused to determination of gaseous mercury species in complex matrices, and then apply this understanding to provide SI traceability for these determinations by using an appropriated matrix-matched calibration arrangement.

Project Description (including summary of technical work)
The project will aim to test a number of options to determine the most successful strategy for the accurate measurement of these analytes in ambient particulate matter. In brief, the aims will be to:
- Develop and test an impinger sampling approach to simultaneously sample and extract target species, such as metallic or organic PM components.
- Benchmark the impinger approach against the traditional filter-based sampling approach to gauge the improvement obtained and the likely bias imposed by the traditional sampling mechanisms.
- Assess whether variations in the sampling time or filter type used have any effect in reducing the on-filter degradation observed during sampling.
- Develop sequential extraction methods to selectively remove target species from PM material collected using traditional filter based approaches and benchmark these against other emerging approaches such as non-destructive on-filter techniques
- Perform a field comparison of traditional methods against the most successful candidate methods and provide a validated set of these measurements in the field to provided novel concentration data for these species
- Developing a dynamic calibration system for use in the determination of gaseous mercury species. This system will use a variety of relevant gases to replicate real sample matrices
- A methodology will then be developed to fully describe the measurement and calibration procedure using the novel dynamic generator and determine and a full uncertainty budget for this procedure
- Following this these procedures will be implemented to provide a fully SI traceable measurement for the measurement of gaseous mercury species in a number of complex matrices

Impact and Benefits

The UK will benefit from valid and traceable measurements of priority emerging pollutants in UK air which will help to inform future policy and provide a better understanding of the exposure of the general population to enable improved quality of life. A UK lead in this area will advance air quality science and will help shape emerging European policy in this area, giving the UK a head start in defining relevant new measurands for air quality Directives and in implementing these requirements. These methods, especially the impinger-based techniques, will also provide improved and cheaper methods for direct measurement of emissions from stationary sources – where many of these emerging pollutants in ambient air are already limited – reducing the cost burden of compliance for UK industry and giving them increased confidence with more robust and defensible measurement results.

Support for Programme Challenge, Roadmaps, Government Strategies

The work in this project aligns well with the 'Sustainability' and 'Health' Challenges in BIS's NMS strategy, and is a fundamental part of the CBKB Particles Theme Roadmap. The project also addresses the Royal Society of Chemistry's Grand Challenges on 'Future Cities' and 'Air Quality and Climate Change' as set out in their roadmap 'Chemistry for Tomorrow's World'. NPL's Metrology 2020 Vision sets out goals, especially in the areas of 'Monitoring the State of the Planet' and 'A Healthy Population', which are consistent with the aims of this project. The project is directly relevant to the Defra EPAQS Report on Metals and Metalloids in Ambient Air and the recent AQUILA recommendation for revisions to the European air quality Directives.

Synergies with other projects / programmes

This project has synergies with the rest of the Particles theme and the Gas Analysis Theme. The project also has strong links with the UK PAH & Heavy Metals Monitoring Networks –air quality networks which NPL currently operates on behalf of Defra. We would also expect this to have significant synergy with the 2013 EMRP Environment Theme.

Risks Risks are low since the project is being delivered by an experienced team who has a track record in the area.

Knowledge Transfer and Exploitation

The outputs of this project will be disseminated by high impact publication in the peer-reviewed literature and presentations at relevant international fora: these will be of particular relevance to the academic and industrial community in the environmental, air quality and emissions arenas. Input into relevant national and European standardization committees will also enable the work of the project to be transferred and used effectively to ensure the UK is in the lead in terms of meeting the requirements of legislation and formulating future requirements. The new measurement capabilities developed will be offered as measurement services to the user community.

Co-funding and Collaborators

Co-funding will come from relevant EMRP projects in the 2013 Environment Call (high likelihood) and from third party income for calibration and validation work as a result of the new measurement services developed (high likelihood). Collaborators for this work will include the Centre for Ecology and Hydrology, Imperial College, Surrey University and the Environmental Research Group at Kings College London. A number of members of the European group of air quality reference laboratories (AQUILA) and other NMIs (PTB, NIST, LNE JRC-IES) and are also likely to contribute.

Deliverables

1	**Start: 01/04/2013**	**End: 30/09/2013**	
Deliverable title: Review available techniques for the sampling and measurement of labile or reactive species in ambient air and identify the most effective candidates which might also be appropriate for routine use in a field environment.			
2	**Start: 01/08/2013**	**End: 31/10/2015**	
Deliverable title: Develop and test impinger sampling approach to simultaneously sample and extract target species and sequential extraction procedures to selectively remove metallic or organic PM components, and compare this with traditional approaches.			
3	**Start: 01/11/2014**	**End: 31/10/2015**	
Deliverable title: Perform a field comparison of traditional methods against the most successful candidate methods and provide a validated set of these measurements in the field to provided novel concentration data for these species in the UK.			
4	**Start: 01/04/2013**	**End: 31/12/2015**	
Deliverable title: Development of dynamic calibration system for use in the determination of gaseous mercury species in complex matrices			
5	**Start: 01/01/2014**	**End: 31/12/2014**	
Deliverable title: Determination of bias for mercury vapour measurement in real sample matrices using currently available calibration strategies			
6	**Start: 01/01/2015**	**End: 31/12/2015**	
Deliverable title: Development of validated and SI traceable method for the measurement of gaseous mercury species in complex matrices and validation in the field			
7	**Start: 01/04/2014**	**End: 31/03/2016**	
Deliverable title: Dissemination of outcomes via at least six peer reviewed papers, presentations at relevant fora and input into relevant standardization committees			

Project No.	NMS/CBM12001	**Price to NMO**	£347k
Project Title	ET1: Providing Metrology for key Climate Change Uncertainties (NPL)	**Co-funding target**	£150k
Lead Scientist		**Stage Start Date**	01/04/2012
Scientist Team		**Stage End Date**	31/03/2015
		Est Final Stage End Date	2020 (next ECCP target for GHG reduction)
Sector	Environmental Sustainability: Climate change targets	**Activity**	Development of existing capabilities; statutory and policy obligations

Summary

The project will address three areas of the UK's response to climate change where underpinning metrology is critical:

- Evaluation of uncertainties associated with emission factors for industries such as waste management, forestry and agriculture.
- Evaluation of the uncertainties associated with differing methodologies used in determining carbon emissions in international trading and calculation of the consequential financial impact.
- Uncertainty work on measurements that underpin long-term trend data of the atmosphere's composition, critical in assessing the effectiveness of emission reduction strategies under the Kyoto Protocol and other UK/EU commitments.

The Need

Tackling climate change is a long-term process and hence the UK has made long-term commitments to reduce its emissions of carbon dioxide (CO_2), nitrous oxide (N_2O) and methane to atmosphere. At a national level, the 2008 Climate Change Act commits the UK to reduce greenhouse gas (GHG) emissions by 80% by 2050 compared to 1990 levels, whilst at the European level the UK has signed up to the European Climate Change Programme (ECCP) which is targeting limiting the global temperature rise to 2°C. If this target is not met the IPCC Fourth Assessment Report: The Physical Science Basics predicts a, "40% ecosystem extinction rate, 30% of global coastland lost, changes in disease vectors and increased mortality rate due to heat waves and floods". Measurement is key to the UK's response to climate change since coupled with well characterised uncertainties it is critical to know: the amount currently being emitted; the amount that emissions have decreased by as a result of reduction strategies; and how the composition of the atmosphere is changing as a result of the anthropogenic influence. It follows that the issues with the greatest need for metrology to underpin the UK's response are:

- Emission factors used in the agricultural, forestry and waste management industries are poorly defined. For example, in agriculture the accuracy of methane emission factors is currently ±30-50%.
- The uncertainty of methodologies used by different countries to estimate carbon emissions are not well characterised, hence there are consequences both in terms of accuracy emission reporting and for carbon trading.
- Uncertainties associated with measurements of atmospheric profiles are in many cases not yet fully characterised hindering conclusions and consequently the basis for policy decisions. For example, over the Mauna Loa atmospheric station in Hawaii a 2.2% increase in N_2O (298-times more potent a GHG than CO_2) has been monitored since 2000. However, investigative work has suggested that measurement of this species is subject to an uncertainty of 6.4%.

The Solution

This project will build on the expertise within the proposed team gained in the NERC/EPSRC-funded Continuum Absorption in the Visible and Infrared and its Atmospheric Relevance project (as part of a consortium that included University of Reading, Imperial College and the Met Office), work on measurements of emissions factors and current projects on assessing uncertainties in reporting for emissions trading.

- Field measurements of GHG (e.g. CO_2/methane/N_2O) emissions from key sources in the agricultural and waste management fields using optical sensing techniques will be used to improve the uncertainties in their emissions factors. The impact of the improved uncertainty in emissions factors on UK reported emissions will be calculated.
- Evaluation of the different approaches to determining carbon emissions applicable to trading under the EU emissions trading scheme (EU ETS) with assessment of the financial impact on UK trading.
- Assessment of uncertainties associated with measurements underpinning long-term trend data from monitoring stations that are part of global networks such as the Network of Detection of Atmospheric Composition Change (NDACC) and GCOS (Global Climate Observing System) Reference Upper Air Network (GRUAN).

Project Description (including summary of technical work)

- Review of existing emission factors in agriculture and waste management sectors to identify areas where improved uncertainty in emission factors is required (impact assessment). Carry out a series of targeted

measurements to assess emission factors, using optical sensing technologies to determine traceable uncertainties and determine the impact on UK emissions.

- Critique of available methodologies for carbon emission determination (*e.g.* the top tier of determination in the EU is calculation whereas in the US it is direct measurement). Evaluation of uncertainty sources to allow assessment of interoperability between different reporting systems. Work with stakeholders to assess financial impact of uncertainties.
- Develop methodology to determine uncertainties in trends in atmospheric profile data series (e.g. determine effect of different averaging kernels). Collaboration with NDACC and GRUAN monitoring stations in provision of raw datasets, consultation over error sources and propagation through complex analysis algorithms.

Impact and Benefits - The project outputs will influence policy decisions and help ensure the UK has more accurate knowledge of its emissions and better understands how to target future reduction strategies without unduly burdening UK industry. The project will enable UK influence on international bodies such as NDACC and GRUAN helping direct climate change science for the good of the UK and wider global interests. Also, the project will help protect the UK's financial position with regard to carbon trading through determining biases that trading partners may possess due to the preferred methodology for estimating CO_2 emissions. For example, for a typical power station emitting 20M tonnes of CO_2 equivalent *p.a.* there is a ~£5M exposure for every 1% uncertainty, this project will therefore support UK industry in reducing financial risks from climate change mitigation e.g. EU-ETS.

Support for Programme Challenge, Roadmaps, Government Strategies

The project aligns with NERC Strategy 2007-2012, DECC's Carbon Plan 2011 and the UK's Climate Change Act 2008, which commits the UK to a significant reduction in GHG emissions. The project aligns with the NMS Strategy Document 2011-2015 which states that the NMS will support, "national and international efforts to understand and mitigate the effects of climate change by providing confidence and reducing uncertainties in climate data" and, "carbon reduction targets to address climate changes". Furthermore, the ChemBio Programme Strategy lists a key area for future focus as, "underpinning metrology for technologies required to mitigate the effects of climate change (including carbon trading)". The project aligns with the Environmental Technologies roadmap which highlights the importance of *analysis of atmospheric speciation* which feeds into *global monitoring networks*. In addition, the project is consistent with BIPM's Resolution 11 of the 23rd CGPM (2007) which emphasises the need for SI traceable measurement to monitor climate change, a view supported by the World Meteorological Organisation (WMO).

Synergies with other projects / programmes

The project has synergy with an existing contract with DEFRA providing validation of sensors for testing methane emissions from cows and sheep. Existing partners would collaborate on this project and provide data for uncertainty evaluation work. The work will also link to the Global Climate Observing System through NPL's role in GRUAN.

Risks - Not engaging with the correct stakeholders due to broadness of community. This is mitigated by NPL's long involvement in this field and knowledge of researchers and policy makers.

Knowledge Transfer and Exploitation

NPL is a member of the NDACC and GRUAN global networks and so has direct interaction with the international community. In addition dissemination to stakeholders will also be through the International Emissions Trading Association (IETA), the International Carbon Action Partnership (ICAP), Carbon Disclosure Project (CDP), and the European CCS Demonstrator Network Project (www.ccsnetwork.eu). Knowledge acquired from the project would also facilitate future work in determining emission factors for emission sources where currently none exist (*e.g.* currently there is only one emission factor for all cows, different factors are needed for different breeds, summer *vs.* winter feeds, age, *etc.*).

Co-funding and Collaborators

NPL is currently the only NMI with a field measurement capability for compositional measurement across the various layers of the atmosphere. Cofunding will be sought from the EMRP Environment call in 2013. Also, in-kind funding will be available from collaboration with global networks NDACC and GRUAN, and the CDP (who will provide links to financial market information).

Deliverables

1	**Start: 01/04/2012**	**End: 31/03/2015**	
Metrological evaluation of UK emission factors as evidenced by a peer review publication (*e.g.* Journal of Environmental Monitoring).			
2	**Start: 01/04/2012**	**End: 31/04/2014**	
Impact of calculation methodology & associated uncertainties on UK carbon trading as evidenced by a NPL Public Report and peer reviewed publication.			
3	**Start: 01/04/2012**	**End: 30/11/2014**	
Impact of uncertainty on long term atmospheric composition trends as evidenced by 2 peer review publications and presentation at NDACC and GRUAN annual conferences.			

Project No.	NMS/CBM/12002	**Price to NMO**	£367k
Project Title	ET2: Metrology to Underpin Future Emission Monitoring Requirements (NPL)	**Co-funding target**	£100k
Lead Scientist		**Stage Start Date**	01/04/2012
Scientist Team		**Stage End Date**	31/03/2015
		Est. Final Stage End Date	2020
Sector	Environmental Sustainability: Pollution & waste reduction; climate change targets. Underpinning metrology: standards & regulation	**Activity**	Development of existing capabilities

Summary

The project aims are geared towards a capability to monitor reduced UK gas and particulate emissions from industrial processes.

- To provide the stack testing community with the metrology necessary to move to real-time, improved accuracy instrumental techniques for testing/calibration of in-situ continuous emissions monitors (CEMs).
- To evaluate uncertainties associated with cross-stack instruments.
- To provide a unique NMS capability allowing expansion of UK proficiency testing to include particulate sampling.

The Need - The effect on public health of air pollution is estimated to cost the UK £10.7 billion per annum (Air Quality Management Resource Centre). DEFRA has stated that if the European Commission rejects the UK's application for an extension regarding NOx and particulate exceeds that, then fines could reach £300 million. It is a requirement of regulation that stack gas emissions and in-situ CEMs are monitored and calibrated, respectively, by accredited reference methods. Many of the standard reference methods (SRMs) for gases are based on wet chemistry and so results are not available in real-time. Consequently if the CEM is failing to meet the requirements of EN 14181, UK Industry can waste significant time and money before this is discovered. Furthermore, with decreasing emissions due to improved abatement and cleaner feedstocks, there is an issue over accuracy. For example, in a recent study sponsored by the Environment Agency it was found that two UKAS accredited laboratories analysing the same wet chemistry sample for SO_2 deviated by 20 $mg.m^{-3}$, the required uncertainty for monitoring at gas fired power stations under the Industrial Emissions Directive is $\pm$7 $mg.m^{-3}$ (~2 ppm). With regard to instrumental techniques a key area where metrology is needed is with optical cross-stack analysers. Due to their cross-stack nature such systems use synthetic elements in their analysis algorithms, such as zero / background modelling (as it is not possible to make the plant produce zero gas). The uncertainties associated with these synthetic spectroscopic inputs are poorly characterised and work is needed so that the overall uncertainties and particularly the ability to monitor low concentrations are determined. Monitoring of low concentrations is also an issue with regard to particulate emissions. In a recent round of UK proficiency testing it was found that some stack testing teams failed to detect > 50% of the particulate in the supplied sample. Moreover, this only tested the recovery element of particulate measurement, so despite the importance of particulate emissions with regard to respiratory health issues having been known for some time, the UK's proficiency for the collection of samples from stacks remains unknown.

The Solution - This project will build upon experience in the team of over 20 years of stack monitoring and method development, including the development of FTIR methods and validation of testing methods such as the assessment of instrumental SO_2 instruments. Specifically, this project will address the stated needs through:

An intercomparison of SRMs and instrumental techniques under real stack conditions providing a definitive description of the performance of methods (e.g. uncertainty, limit of detection), particularly at low concentrations and data to support standardisation

A comprehensive study of the uncertainties associated with spectroscopic based cross-stack optical techniques.

Development of a new UK particulate generation capability simulating real stack conditions allowing assessment and development of stack testing team's proficiency for particulate sampling as well as recovery.

Project Description (including summary of technical work)

Collaborative experiments with stack testing companies, Environment Agency (EA) and Stack Testing Association (STA) utilising the NPL Stack Simulator Facility to assess the performance of instruments used with a range of monitoring methods alongside wet chemistry techniques. Metrological characterisation of techniques against sample matrices found on a range of common industrial processes. Comparison of performance against not only allowable uncertainties specified in applicable EU directives but also within the context of typical industrial process emission profiles.

Develop instrument modelling techniques to determine uncertainties in spectroscopic cross duct techniques, including the uncertainty contribution from the use of reference spectra, baseline fitting algorithms and other instrumental parameters.

Design, development and validation of expanded proficiency testing capability for controlled generation of particulates in a stack gas matrix. Determination of dependency of in-stack results to different synthetic dust feedstocks, gas

matrices and stack physical conditions, including determination of overall uncertainty.

Impact and Benefits - In 2010 the Environmental Audit Committee reported that in the UK there are 50,000 premature deaths per annum due to air pollution and that the lifespan of vulnerable individuals living in cities such as London is being cut short by up to 9 years. Asthma UK estimates that the annual cost of asthma to society is £2.3 billion. Consequently, the social and financial benefits of reducing UK emissions are clear. This project will provide the underpinning metrology necessary for further reduction in emission limits being driven by the Industrial Emissions Directive (being passed into UK legislation in 2013) and support UK industry in meeting its obligations in a cost effective way. Also, this project will provide a unique particulate capability putting the UK in a leading position to react to new legislation and adapt proficiency testing accordingly. There is a strong desire at both the EU and national level (the Environment Agency) to introduce the requirement to size distribute stack particulate emissions instead of only measuring total mass. Further research is needed before such measurements are possible on a stack and this project would underpin such future research.

Support for Programme Challenge, Roadmaps, Government Strategies

The project aligns well with the NMS 2011-2015 Strategy Document which under Investing in Excellent Science lists, ”Quantitative environmental monitoring”, as a priority area for investment. Further, this project aligns with NERC Strategy 2007-2012 and the ChemBio Programme Gas Metrology and Environmental Technologies priority theme, which highlights the importance of NMS support to enable UK compliance with, “EC directives that limit the emissions of industrial sources to the environment……..the Industrial Emissions Directive”. The project aligns with the Environmental Technologies roadmap in delivering *calibration and instrument test facilities* that feed into *regulation and control*. Also, the project is consistent with the UK Air Quality Strategy 2007, which acknowledges that measurement uncertainty is important in determining compliance with lower emission limits.

Synergies with other projects / programmes

The work will underpin NPL’s role in the UK’s Source Testing Association (STA) where NPL leads a number of task groups including one dedicated to the successful regulation of emissions monitoring using Fourier transform infrared (FTIR) spectroscopy. A standard produced by this task group has been nominated for adoption into a full CEN standard (protecting the practises of UK stack testing companies) and if successful NPL support will be critical. Also, taking a forward look this work will position the UK for future programmes regarding validation of new CEN standards for emissions monitoring.

Risks - Availability of stack testing teams for technique intercomparisons. Mitigated by timescale of project.

Knowledge Transfer and Exploitation

NPL is ideally placed to disseminate the project outputs holding both the chair of the STA and operating the UK’s proficiency testing scheme for stack testing companies. NPL’s representation on various CEN working groups—including WG3 (HCl emissions), WG33 (GHG emission reporting), WG9 (QA of CEMs), WG16 (methods for NOx, SO_2, CO, O_2 and H_2O emissions)—will also prove useful for dissemination to the relevant stakeholders.

Co-funding and Collaborators

NPL has been elected convenor of CEN TC/264 FTIR ad-hoc working group (facilitating contact with the two leading manufacturers of FTIR instrumentation for stack emissions, Gasmet & Protea) and due to having been on the cutting edge of FTIR monitoring for some time is ideally positioned to be commissioned for validation work. For standardisation to take place it is a requirement that validation work is funded, so the chances of co-funding are very high (90%). Significant in-kind funding will also be available from collaborators; EA, STA, and stack testing companies such as CES, AES.

Deliverables

1	**Start: 01/04/2012**	**End: 31/08/2014**	
Metrology evaluation of gas monitoring instrumental techniques as evidenced by: Publication of guidance document that will provide the definitive reference for stack testing companies, regulators and plant operators of the most applicable technique(s) for a given application and publication in peer review journal, and standardisation activities through CEN TC/264 WG3, WG16 and WG3 and Convenorship of CEN TC/264 WG9.			
2	**Start: 01/04/2012**	**End: 31/03/2015**	
Expansion of UK proficiency testing to particulate sampling as evidenced by: Validated key facility characteristics including temporal number density, spatial distribution, *etc.* Workshop at the Environmental Monitoring and Certification conference highlighting facility capabilities.			
3	**Start: 01/04/2012**	**End: 31/03/2015**	
Uncertainty evaluation of spectroscopically based error sources as evidenced by a peer reviewed publication (Vibrational Spectroscopy)			

Project No.	NMS/CB12003	**Price to NMO**	£341k
Project Title	ET3: Remote Sensing of Area Source Emissions (NPL)	**Co-funding target**	£100k
Lead Scientist		**Stage Start Date**	01/04/2012
Scientist Team		**Stage End Date**	31/03/2015
		Est Final Stage End Date	2020
Sector	Environmental Sustainability: Pollution and waste reduction	**Activity**	Development of existing capabilities; maintenance of capabilities

Summary

This project will develop metrology and techniques to meet future remote sensing requirements for monitoring emissions of greenhouse gases (GHGs) from area sources across many industrial sectors including petrochemical, waste management, agricultural. The project will provide novel test facilities to facilitate stakeholder development and validation of new instrumentation whilst also determining traceable uncertainties and developing improved interpretation algorithms to enhance existing remote sensing techniques.

The Need

There is an increasing drive under UK commitments to the Kyoto Protocol and Clean Development Mechanisms towards evidence-based determination of emission factors. Many of the UK's GHG (CO_2, Methane) emitting sectors are non-uniform sources, *i.e.* area emissions from sources such as landfill and agriculture rather than point emissions such as stacks on chemical plants. Remote sensing techniques offer advantages in accuracy and cost-saving in comparison to alternative means of measuring concentration and particularly the use of point measurement techniques to map area sources. Modelling techniques are needed to convert concentrations into pollutant flux and identify emission location(s) that recognise the limitations of short-term campaigns and the spatial / temporal variability of both the emission source and wind field. Until there are robust protocols for the use of remote sensing measurements there will be questions over the accuracy of emission magnitudes. For example, in the study of fugitive VOC emissions there have been differences of up to a factor of 6 in estimates of emissions made using traditional Leak Detection and Repair approaches and by remote sensing. Such large differences are of commercial, regulatory and policy significance. Uncertainty determination and validation data for area source measurements are underdeveloped and metrological work is required to facilitate the drive towards requirements, including, evidence based emission factors, more accurate direct monitoring of area emissions and the monitoring of leaks from carbon capture and storage (CCS). The Department for Energy and Climate Change have determined that meeting the European Climate Change Programme (ECCP) target to keep global warming to 2°C will be 70% more costly if CCS is not used. Hence, there is a cross-industry need for remote sensing monitoring for sectors including, petrochemical, waste management, agriculture, CCS.

The Solution

This work will build on NPL's experience of over 20 years in developing the methodology for area source emissions measurements and focuses on three main areas:

- Novel facilities able to validate a broad range of remote sensing techniques to provide validation for future work determining new UK emission factors and monitoring leaks from carbon storage sites.
- Metrological evaluation of uncertainties associated with modelling open path spectroscopic techniques such as Fourier transform infrared used in monitoring complex gas emissions.
- Definitive assessment of mathematical spatial analysis methods if applied to remote sensing techniques such as differential absorption Lidar (DIAL), including determination of uncertainties and ultimately provision of optimised analysis algorithms.

Project Description (including summary of technical work)

- Develop configurable area-source test facilities able to deliver traceable gas matrices containing GHGs (e.g. CO_2 or methane) or VOCs with different spatial and temporal distributions to simulate different real world emission scenarios (e.g. landfill), which will challenge the performance of optical techniques. Validate area source test facilities using both open-path and point measurements.
- Carry out a series of field measurements using open-path Fourier transform infrared (OP-FTIR) instruments to assess technique sensitivity and the capability of the technique to provide speciation data. Use system modelling approaches commonly employed in interpreting spectra (*e.g.* spectroscopic interference modelling, synthetic background fitting, *etc.*) determine technique sensitivity to key model input parameters.
- Evaluation of mathematics in the academic literature for spatially extrapolating DIAL data. Determination of uncertainties with specific focus on error sources from meteorological data used in determining emission fluxes. Development of optimised algorithms for flux calculation with traceable, overall uncertainty budgets.

Impact and Benefits

In addition to the clear environmental benefits, there are financial benefits facilitated by this project due to the ability to identify the locations of emission sources using scanning remote sensing techniques. There is considerable

environmental concern over the potential consequences of leaks from proposed carbon storage facilities (hence the decision by the Netherlands to halt work on Europe's largest CCS plant at Alkmaar). In the event of a local environmental change where a leak is proposed as the cause there would be inevitable litigation on a scale that would cause considerable financial difficulty to individual companies involved in the CCS project. Remote sensing will also provide a key tool to provide hard data so that companies can exonerate themselves and avoid paying out against expensive compensation claims. The development of remote sensing validation tools and methodologies will support UK technology companies in exploiting the emerging clean technology market.

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns with the NMS Strategy Document 2011-2015 which states under Investing in Excellent Science that, "NMS laboratories will be supported in the priority science areas of: Quantitative environmental monitoring (including remote sensing)" and under the Overarching Challenge that, "…advanced instrumentation are examples of areas where the UK is a world leader and where advances in measurement science can support that strong position". It also aligns with NERC strategy 2007-2012 and the ChemBio Programme Strategy, which states, "Strategic areas for future focus include: Evaluation and extension of current environmental monitoring technologies for remote sensing". Further, the Environmental Technologies roadmap highlights DIAL and FTIR as key technologies feeding into future deliverables of *diffuse GHG emission mapping* and *next generation remote sensing methods*.

Synergies with other projects / programmes

This project will build upon the current ChemBio project RS1, concerned with work developing DIAL using next generation optical detectors of increased sensitivity and extending the technique to CO_2 measurements. The project will link with current work with the Conservation of clean air and water in Europe (Concawe; established by leading oil companies) to assess the performance of remote sensing emission flux algorithms in complex environments – which will provide data sets and wind tunnel experimental data to input into the proposed work.

Risks

A key risk is that, because of the strong need for this capability in different applications, the test facility will suffer from specification creep leading to a too complex system. This will be mitigated by a staged modular design enabling a core system to be built within this project with the potential to extension to meet different test configurations in the future (i.e. complex plant, storage tank simulation etc.).

Knowledge Transfer and Exploitation

NPL already maintains relationships with most of the key stakeholders in the area of remote sensing, which will greatly facilitate knowledge transfer. The project will be disseminated to the Concawe organisation ensuring the petrochemical industry benefits from the outputs in addition to DEFRA and the Environment Agency, facilitating landfill and other area source emissions monitoring policy going forward. KT will include standardisation through CEN/ISO including the currently proposed CEN standard on DIAL, an activity that NPL will lead providing a further dissemination conduit.

Co-funding and Collaborators

We will collaborate with existing partners including Concawe and DEFRA. Also our links with other industrialists and NMIs means we are well positioned to respond to EMRP (Environment 2013), TSB and FP7 calls where there are likely to be opportunities for co-funding, particularly with respect to CCS projects.

Deliverables

1	**Start: 01/04/2012**	**End: 31/04/2014**	
Operational facilities to simulate area source emissions as evidenced by a peer reviewed article on validation of facilities and trade journal article on capabilities (*e.g.* International Environmental Technology).			
2	**Start: 01/04/2012**	**End: 31/03/2015**	
Metrological evaluation of multi-species area source emission measurement with OP-FTIR as evidenced by a peer review publication (*e.g.* Vibrational Spectroscopy) and a paper at an international conference (*e.g.* PITTCON).			
3	**Start: 01/04/2012**	**End: 30/11/2015**	
Improved DIAL interpretation algorithms as evidenced by a peer review publication (*e.g.* Journal of Environmental Monitoring) and presentation of 2 papers at appropriate conferences (*e.g.* International Laser Radar Conference)			

Project No.	NMS/CBM/12004	**Price to NMO**	£310k
Project Title	ET4: Calibration and test facility for emerging nanotechnology applications for gas sensing (NPL)	**Co-funding target**	£90k
Lead Scientist		**Stage Start Date**	01/04/2012
Scientist Team		**Stage End Date**	31/03/2015
		Est Final Stage End Date	2016+
Sector	Environmental Sustainability: Pollution and Waste Reduction	**Activity**	Development of existing capabilities

Summary

This project aims to support greater innovation in gas sensor design and its application by UK industry through next-generation technology developments, particularly in the area of environmental monitoring for pollution control, which will also provide cross- sector impact in public safety, quality of life applications, industrial safety and homeland security applications. This will be accomplished by developing (and promoting through collaboration with end users) a novel, fast-response exposure chamber, available for testing future novel low-cost sensor devices (e.g. nanotechnology-based sensors and innovative diffusive samplers) by making use of the best design principles and expertise already established in the development of NPL's current Controlled Atmosphere Test Facility (CATFAC), and will provide a unique facility for UK industry to take the lead in the nanosensors area. A stakeholder consultation carried out indicates that a requirement for the proposed facility and that no other group is satisfying UK requirements.

The Need

Despite many advances in gas sensor technology in recent years, the tightening of environmental legislation and the emergence of new and demanding applications still represent significant hurdles for developers to overcome, at price levels that are acceptable to end users. Certain specific challenges that need addressing include: Lack of validation and availability of reliable published sampling rates for new NO_2 low cost sensors being developed by UK SMEs, as identified by Defra's WG on NO_2; VOC characterisation against complex backgrounds; improved selectivity and stability of gas sensors; combinatorial methodologies for optimising sensors; integrated MEMS using sensing arrays with widespread applicability. Validated test methods are also required to compare different gas sensor technologies targeting the same measurement application. Typically for each market sector there may be several measurands for a range of applications, each with different requirements for sensitivity, reliability, selectivity and cost. Advanced material and microfabrication technologies (e.g. emerging use of nanomaterials such as graphene) are being exploited to meet the performance, cost, ease-of-use and portability requirements of gas sensors employed in environmental and occupational health applications (e.g. acetone, formaldehyde and hydrogen sulphide in the case of lowering of limits by the American Conference of Governmental Industrial Hygienists and other regulators). Advanced sensors are an important area of work and a number of stakeholders have already expressed strong interest in collaborating with NPL.

The Solution

This work will employ NPL's expertise (e.g. *Langmuir*, 2011, 27(3), 1241), in measuring various devices under controlled atmosphere environments coupled with NPL's activity in nanotechnology-based gas sensors, to provide gas sensor technologies and calibration protocols for emerging monitoring applications that require specific gas species present in extremely low concentrations in complex environments. The development of this facility will enable NPL researchers and stakeholders to characterise a wide range of next-generation (including nanotechnology based) gas sensors that are capable of finding use in complex environments. In cases where these devices are not yet fully developed, it will help identify the main sources of measurement uncertainty for sensor developers and manufacturers, which do not have access to such environmental exposure chamber technology.

Project Description (including summary of technical work)

Controlled atmospheres will be generated in the CATFAC to characterise the performance of new NO_2 diffusive samplers fitted with meshes to minimise problems due to wind effects. The 28-day sampling rate will be determined under a wide range of known concentrations and environmental parameters that are applicable to UK background and urban roadside conditions. This will provide traceability in measurements and reduce the measurement uncertainty of samplers through improved repeatability. A new low volume test facility will be developed to operate under a wide range of environmental conditions to enable a number of priority test parameters to be determined including response times, repeatability, lack-of-fit, drift, influence of ambient temperature, influence of the sample gas flow, and most importantly the influence of a number of likely interferents which may compromise accuracy. Novel nanosensors based on, for example, metal nanoparticles, which are being developed to detect low concentration gases (e.g., hydrogen, water vapour, oxides of nitrogen and hydrocarbons) will be exposed to single and multi-component controlled atmospheres of volatile organic compounds including acetone (of environmental importance and present in human breath). This phase of the project will be used to demonstrate that complex atmospheres can be generated in the chamber and, in particular, that it can measure the effects of cross interfering gas species. Finally, the new capability will be extended to incorporate the measurement requirements of hydrogen sulphide sensors, which are gaining prominence in industrial safety applications, work well in the laboratory, but can demonstrate poor performance in the field even at the HSE limits of 10 ppm (15 minutes) and 5 ppm (8 hours). The work would also establish their effectiveness in accommodating changes to the proposed threshold limit value for this species for personal monitors in

the US. Indeed the annual American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) have been revised down in 2010 for H_2S to 1 ppm (8 hr-TWA) and 5 ppm (STEL). This limit has been matched in the Netherlands and is also anticipated to be adopted across Europe, which for many applications, challenges the industry's current detection capabilities with existing sensors but shows the direction of future trends based on health requirements.

Impact and Benefits - Although major sensor manufacturers have sensor test facilities these are usually exclusively reserved for production rather than for extending sensor research and development. Therefore, NPL's leading position in the area of gas analysis and metrology ideally places it to address several issues surrounding gas sensor innovation, while providing access to testing facilities for SMEs and other research groups across the UK. The ability to test and calibrate new sensor technologies under a variety of complex conditions—using a test facility that allows for changes in target and background concentrations, humidity, temperature, flow rates—would help stakeholders to innovate and accelerate technology development to meet end-user requirements. New applications are emerging that require higher-performance gas sensors, particularly in environmental (air quality), industrial, transportation, and homeland security sectors, where high sensitivity, specificity and selectivity of gas species against complex backgrounds are of increasing importance. For many of these emerging applications, the implementation of advanced materials and micro-fabrication technologies are needed to meet the performance, cost, ease-of-use and portability requirements of gas sensor systems (including detectors and analysers).

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns with the NMS Strategy for 2011 – 2015 in addressing the National Challenges of Sustainability and Growth and aligns with the ChemBio Programme Gas Analysis and Environmental Technologies priority theme and roadmaps (e.g. delivering nanoscaled gas sensing technologies, microscale analytical instruments). It is also directly relevant to implementing DEFRA's Air Quality Strategy for England, Wales and Northern Ireland and supports Defra's Local Air Quality Management (LAQM) Support activity for local authorities and practitioners of local air quality management in the UK.

Synergies with other projects / programmes - This work has synergies with environmental monitoring and gas sensor development and characterisation carried out previously as part of the Measurement for Innovators Programme, the EU funded "Exairdec" FP7 project that is concerned with dealing with air decontamination in the food processing industry, NPL activity in a DEFRA LAQM contract covering a QA/QC programme for NO_2 diffusion tubes, and activities as part of CEN TC264 WG 11 (diffusive sampling) and WG13.

Risks - The main risk is time delays in equipment delivery or collaborations with external partners. The project schedule is structured to accommodate certain delays, and there is a wide pool of organisations available to select as collaborators. Appropriate safety considerations and infrastructure will be necessary for the use of toxic gases.

Knowledge Transfer and Exploitation

The knowledge generated within the project, will be disseminated through a number of routes: presentation at workshops and conferences and publication in high-impact journals. Data will be made available to CEN TC264 WG11 and end-users, and as additional input to DEFRA's LAQM contract and DEFRA's Working Group on NO_2, the Gas Analysis and Sensing Group and the TSB's Electronics, Sensors and Photonics KTN. In the provision of controlled atmosphere measurement science capability for gas-sensor innovation and calibration we will look to test the facility in collaboration with a range of stakeholders, including gas sensor developers and producers, science researchers and end users. Future work would look to extend the capability for breath analysis applications.

Co-funding and Collaborators

Cofunding will be sought from companies seeking testing services. We have previously collaborated with Uni. of Surrey (Physics Department and Advanced Technology Institute) and provided research support for SMEs (e.g. Gradko and others) in gas sensor development and metrology. We will build on these partnerships as part of this project proposal with collaborators actively supplying NPL with appropriate samples to evaluate; this will be a useful metric for the market requirement of this work. Future funding opportunities include EMRP Environment call 2013.

Deliverables

1	**Start: 01/04/12**	**End: 31/03/13**	
Characterisation of the performance of NO_2 diffusive samplers as evidenced by a peer-reviewed publication of NO_2 Sampling Rate measured in CATFAC for modified samplers containing meshes			
2	**Start: 01/04/12**	**End: 31/06/14**	
An operational low volume, fast exposure chamber capable of generating single and multicomponent VOC atmospheres			
3	**Start: /01/07/14**	**End: 31/03/15**	
Extension of capability of exposure chamber and the ability to characterise the performance of H_2S sensors			

Project No.	CB/2011/CF15	**Price to NMO**	£331k
Project Title	Nano-characterisation of nanoscale soft emulsion structures	**Co-funding target**	£210k already won from TSB (£160k) and Syngenta £50k)
Lead Scientist		**Stage Start Date**	01/07/2011
Scientist Team		**Stage End Date**	31/05/2014
		Est Final Stage End Date	2016+
Sector	Advanced Manufacturing & Services – High-value manufacturing & bioproducts	**Activity**	Methodology for New Capabilities

Summary
This project comprises NPL's contribution to a TSB-funded project (smart emulsion technologies for novel approaches to crop protection) that aims to develop valid methods and tools to enable a fundamental characterisation of individual micro- to nano-scale soft structures including emulsion droplets using high resolution, low force atomic force microscopy (AFM) techniques. The methods developed in this project will determine the size of the structures, physical and mechanical properties of the nano-objects at the nanoscale and investigate the role of the interfacial layer on these properties. The development of this metrology is essential for validation of properties and underpinning new product development in a wide range of high value added industries ranging from healthcare, crop protection, food industry, pharmaceutical, drug delivery to personal care.

The Need
Over the past few years, there has been an increase in the use of very soft nano-objects and structures, including emulsions, in various industrial high value added applications and products. These nano-objects and structures can often exhibit improved or unique chemical, physical or biological properties due to their small size. As a result, there is a need for fundamental studies and the development of measurement techniques to characterise such soft materials in terms of their nanomechanical properties, their interfacial properties (including for emulsions the oil/water interface), and their size and shape. Current measurement techniques in use typically focus only on hard particles and surfaces primarily in air rather than in liquids. In addition, current methods are also valid only at larger length scales (micron scale).

The Solution
This project will develop the measurement capability for characterising individual soft nano-objects using AFM techniques for fundamental studies and validation of properties. AFM offers the possibility of very high resolution, low force imaging and spectroscopy combined with physical and chemical property measurements of individual emulsion structures in a liquid or air environment. This project will develop the required metrology and capability to do this and will be used to partially validate other complementary analytical techniques based on, for example, optical tweezers and ultrasound. Methods to image the nano-objects with high curvature will be developed and will build upon work currently under development in ChemBio project SA3, focussing on high resolution and low force images. This will prevent damage to the soft structures and provide valid measurement. In addition, AFM nanomechanical methods will be developed to characterise nanomechanical properties of the soft nano-objects. These will be tested and partially validated using computational and analytical models. Both the imaging and the nanomechanical measurements will enable a better understanding of the role of the interfacial properties of emulsion structures and characterise a range of structures from the micron scale to the nanoscale.

Project Description (including summary of technical work)
The project will be split into 3 deliverables
1. Imaging of individual emulsions structures – develop valid methods using AFM to image at low forces and high resolutions using appropriate tips, tip chemistry, cantilevers and imaging modes.
2. Nanoindentation of emulsion structures – develop protocols for sample mounting and handling, develop valid techniques using appropriate forces and probes. Investigate the role of the interfacial layer of emulsions on the results.
3. Nanomechanical modelling – develop models (finite element analysis and analytical equation) to help validate nanomechanical measurements of nano-objects, ranging from simple soft nano-objects through to individual complex emulsions structures.
Techniques will be developed with the larger micron to sub-micron structures first before moving to the nano-scale. Results will be correlated with, and help validate, other complementary techniques such as photonic force and ultrasound techniques.

Impact and Benefits
AFM and SPM metrology will be significantly advanced by extension of these techniques to classes of materials, soft nano-objects and emulsions, which are extremely challenging to measure. Development of these imaging tools

will enable a broad community of R&D professionals to develop the science in a wide range of application areas: 1) Providing tools to characterise products in food industry, consumer, agro-chemicals and drug delivery e.g. improving the understanding of the morphology of drug aggregates and their immunogenic properties, leading to safer therapeutic drugs and, ultimately, improvements in health care. 2) Enabling UK instrument manufacturers to maintain leadership in international markets, 3) Enabling new products, for example the project will aid new crop protection products where each new product is worth £50M/annum (a particular focus application of this TSB project).

Support for Programme Challenge, Roadmaps, Government Strategies

This project fully aligns with the ChemBio programme strategy and the Surface and Nanoanalysis strategic priority theme and roadmap. The roadmap specifically mentions the development of advanced SPM methods and analytical nano-mechanics, which are two of the key areas that will be developed here. In addition, the project is aligned with the UK's innovation agenda as expressed in the Technology Strategy Board's Medicines and Healthcare and High Value Manufacturing Key Application Areas. Further, the 2010 UK Nanotechnologies Strategy report from BIS identifies a number of priorities, including nanotechnology metrology and characterization, standardization and reference materials and the environment, health and safety aspects of nanotechnology, which are of rapidly growing importance, especially for nano-objects.

Synergies with other projects / programmes

This project builds on ChemBio project SA3 'Novel AFM modes for soft-surface imaging', which aims to develop imaging of soft samples with low curvature with AFM as well as the development of multi-frequency modes. This project will also position NPL to develop future EMRP and NMS proposals in the development of metrology for high speed AFM and high-resolution imaging of bio samples.

Risks

Risk 1: Technical feasibility, Mitigation: highly skilled scientists in place, world leading nano-characterisation tools available, good collaborators also lowers risk.
Risk 2: Small size and softness of nano-structures limit effective characterisation. Mitigation – alternative characterisation tools available such as photonic force microscope and ultrasonics. Size of structures can be increased if necessary.
Risk 3: The AFM tip may change the interfacial properties of the emulsion structure. Mitigation – novel tip chemistry, tip functionalisation and tip shape will be explored.

Knowledge Transfer and Exploitation

This work will be disseminated to UK stakeholders in various industry sectors via the following routes:
1. Methods and techniques developed in this project will be used to develop and characterise new nano-scale emulsion products for the crop protection industry (via collaboration with Syngenta and the University of Birmingham).
2. To other industrial sectors such as food, cosmetics and consumer products through publications in peer-reviewed journals, and presentations at national and international conferences.

Co-funding and Collaborators

This project will co-fund a TSB co-funded project on Smart Emulsion Technologies. As a result, co-funding of £210k has already been achieved, comprising £160k from the TSB and £50k from Syngenta (one of the world's leading agro-chemical companies). Project partners include the aforementioned Syngenta and the University of Birmingham (Prof I Norton).

Deliverables

1	**Start: 01/07/11**	**End: 31/05/14**	
Deliverable title: Develop valid imaging techniques for individual soft nano-objects and emulsion structures using low force, high resolution AFM			
2	**Start: 01/07/11**	**End: 31/05/14**	
Deliverable title: Develop nanoindentation methods for micron and nano-scale emulsion structures			
3	**Start: 01/07/11**	**End: 31/05/14**	
Deliverable title: Modelling of nanomechanics of soft nano-scale emulsion structures			

Project No.	NS002CF14	**Price to NMO**	£343k
Project Title	Traceable quantitative surface chemical analysis for industrial applications (SurfChem)	**Co-funding target**	£263k already won from EMRP
Lead Scientist		**Stage Start Date**	01/10/2011
Scientist Team		**Stage End Date**	30/09/2014
		Est Final Stage End Date	2016+
Sector	Advanced Manufacturing & Services – High value manufacturing & bioproducts	**Activity**	Development of existing capabilities

Summary

The work proposed in this project contributes to a wider body of research in the European Metrology Research Programme (EMRP) Industry "SurfChem" project. It will: (1) develop new certified organic reference materials suitable for the calibration and testing of techniques and methods for quantitative surface chemical analysis of organic surfaces. (2) Establish the suitability of ambient mass spectrometry (MS) measurements to monitor changes in surface composition for industrial samples such as packaging and pharmaceuticals enabling in-line and on-line monitoring of their manufacture. (3) Develop tip-enhanced Raman scattering (TERS) microscopy techniques for real time, in-situ measurement of catalyst structure and activity on a localised scale.

The Need

The availability of reference materials and methods to underpin the analysis of organic surfaces is minimal, despite the fact that such measurements are widely used to support innovation in industries such as healthcare, consumer products, packaging, catalysis and plastic electronics. There are currently no reference materials available for the determination of composition in mixed molecular systems. New developments in measurement, such as organic depth profiling, ambient MS and TERS require validated reference materials to optimise and benchmark performance. This fully accords with NMS strategy to support EMRP in its objectives to improve the competitiveness of EU (and UK) industry, enhance efficiency and effectiveness, create innovation and provide decisive knowledge.

The Solution

Generate organic reference materials with certified thickness and / or area density, including binary mixtures with certified compositions. This work builds upon the methods developed at NPL for a VAMAS interlaboratory study on organic depth profiling and there is substantial external demand and interest for more materials. Indeed, an extension to the original study started in April 2011. New materials combinations will be generated to suit the needs of industrial partners. The materials will be used to establish the capabilities of ambient MS techniques (desorption electrospray ionisation, DESI and plasma assisted desorption ionisation, PADI) for in-line, high throughput measurements. The ability of TERS to assess hydrogenation of unsaturated organic materials at a catalyst surface will also be investigated.

As part of the EMRP project, partnership with other European NMIs will enable access to techniques and instrumentation, such as synchrotron methods (Near Edge Adsorption Fine Structure, X-ray Standing Waves, and X-ray Fluorescence) and comparative methods (Indirect Nanoplasmonic Sensing) for catalyst surfaces.

Project Description (including summary of technical work)

1) Pure organic materials suitable for vacuum sublimation will be selected, which also provide an appropriate range of molecular weights, elemental compositions and functional groups. At least 5 suitable organic materials will be identified. The amount of material deposited during vacuum sublimation will be determined using ellipsometry and quartz crystal microbalance (QCM). Certified reference materials with an alternating layered composition and specified thicknesses will be generated. Methods for the determination of thickness and composition of organic materials will be compared and validated. The techniques to be used include spectroscopic ellipsometry, X-ray reflectivity, angle resolved XPS, synchrotron radiation XPS, cluster ion beam sputtering, ambient MS, ToF-SIMS, ATR-FTIR, Raman, NEXAFS, XRF and GXRF. The measurements will inform, support and initiate wider inter-laboratory comparisons and pre-normative studies under VAMAS, ISO and CCQM.
2) The capability of ambient MS to measure within the required sensitivity and with repeatability and speed of measurement that match industry guidelines will be assessed. This will employ the molecular reference materials and samples from industrial collaborators to establish the scope and effectiveness for in-line monitoring applications. This will include: Develop ambient mass spectrometry repeatability to better than 10% for robust on-line monitoring; develop a reliable procedure for ambient MS for on-line reaction monitoring for pharmaceuticals; establish limitations for speed of analysis; and resolve the important metrology issues of sensitivity of ambient MS to minor components, the importance of matrix effects and the time taken to achieve the reliable measurements necessary for a required level of confidence.
3) The TERS technique will be developed to allow local spectroscopic fingerprinting of chemical adsorbents reacting on catalyst surfaces. Application of this will be demonstrated with the selective liquid phase hydrogenation

of carbonyl compounds on platinum catalysts. Industrially relevant systems include the hydrogenation of cinnamaldehyde, crotonaldehyde and methylethylketone to important intermediates for the production of fine chemicals.

Impact and Benefits

Chemical metrology at surfaces underpins almost all subject fields in advanced engineering in European industry. It is a multidisciplinary field and requires the scientific treatment of measurement uncertainties and principles of metrological traceability. The development of a consistent metrological base for quantitative surface analysis supports innovation and quality of life. The support of a wide range of instrument manufacturers and users for the associated EMRP project provides evidence for the importance of this work in the relevant community. The shares of European instrument makers on the world market were 45% for AES, 60% for XPS (mainly UK) and 60% for SIMS instruments with total sales of over $200M per annum.

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns with BIS Nanotechnologies Strategy (2010) and underpins the quantitative analysis of organic surfaces and compound layers, 3D chemical analysis, ambient surface MS, optical and advanced SPM methods and cluster sputtering as outlined in the ChemBio Surface Analysis roadmap. The development of organic reference materials not only underpins existing techniques, but also innovative approaches being developed at NPL on behalf of the NMS. Engagement with EU measurement institutes through mechanisms such as EMRP is an important part of NPL and government strategy.

Synergies with other projects / programmes

This work builds upon developments made in a MET project on plastic electronics and supports current NMS projects, including IRD Programme project on plastic electronics and ChemBio projects SA1 and SA2. Electrochemical scanning probe methods to determine local structure and reactivity on catalyst surfaces are being developed by NPL's Materials Division as part of the associated EMRP SurfChem project.

Risks

Finding suitable organic materials may be difficult due to degradation, mobility and phase behaviour. However, rapid screening approaches, along with prior NPL experience, significantly mitigate this. TERS and ambient MS have progressed beyond proof of concept at NPL, and although part of the work is risky (TERS of catalysts) due to issues with obtaining reliable Raman enhancements in such systems, it is not critical to the main direction of the project and mitigated by work in other institutions involved in the EMRP project.

Knowledge Transfer and Exploitation

As the technical work in this project will deliver metrological traceability to a multi-billion Euro bundle of pan-European industrial sectors, it is crucial that the outputs of this work are disseminated widely to other NMIs and to key industrial players and other end-users. Dissemination of the outputs will be through the following routes: Publications (reports and scientific papers); oral presentations at leading international conferences; a project website with integrated database of project results accessible to registered users targeted to different user groups in the industry (instrument makers and end users industry and testing laboratories); and input into CCQM Surface Analyses WG, VAMAS TWA 2 "Surface Chemical Analysis" and ISO TC 201 & 202 working groups developing new documentary standards in surface chemical analysis.
The new traceable methods of surface chemical analysis and reference materials developed by the project will be disseminated in order to facilitate best practice amongst all project partners, the end user communities in the industry addressed and other European NMIs.

Co-funding and Collaborators

This project comprises NPL's input into the EMRP Industry SurfChem project (£263k). The SurfChem project is led by BAM (German DI) and has PTB (German NMI), INRIM (Italian NMI), METAS (Swiss NMI), and SP (Swedish NMI) as funded partners. Unfunded partners and collaborators include UK instrument manufacturers (Kratos, Thermo VG) and users of surface analytical instrumentation (Johnson Matthey, Molecular Profiles, Cambridge Display Technologies, Astra Zeneca and Pfizer). European partners include instrument manufacturers (SPECS, Omicron, Bruker, IONTOF, Mettler-Toledo) and a range of users (Innopsys, Tascon, Scienion, Heraeus, Sud-Chemie, Insplorion, Comet AG, Thales Alenia Space). An associated postdoctoral position is in place at Chalmers Catalysis centre and another is expected to be appointed at Nottingham University, in close alignment with the work at NPL on ambient MS in this project and SA2.

Deliverables

1	**Start: 01/10/11**	**End: 30/09/14**	
Deliverable title: Development, testing and dissemination of organic reference materials			
2	**Start: 01/10/11**	**End: 30/09/14**	
Deliverable title: Assessment of Ambient MS for in-line and high throughput surface measurement			
3	**Start: 01/10/11**	**End: 30/09/14**	
Deliverable title: Assessment of TERS to measure in-situ activity of catalysts			

Project No.	NMS/CBM/12006	**Price to NMO**	£495,528k
Project Title	CF1: Metrology for the characterisation of biomolecular interfaces for diagnostic devices (EMRP HLT04)	**Co-funding won**	£339,301k
Lead Scientist		**Stage Start Date**	01/06/2012
Scientist Team		**Stage End Date**	31/05/2015
		Est Final Stage End Date	2020
Sector	Health: Diagnosis	**Activity**	Development of Existing Capabilities

Summary

The work proposed in this project contributes to a wider body of research in the European Metrology Research Programme (EMRP) Health "Metrology for the characterisation of biomolecular interfaces for diagnostic devices (JRP-HLT04)" project. This NPL-led project will provide guides, standards and protocols for the quantitative analysis of biomolecular interfaces relevant to the needs of diagnostic device manufacturers.

The Need

In-vitro diagnostics are a linchpin in the drive for cost effective healthcare, point of care monitoring and personalised medicine. Without the rapid and reliable biomolecular analysis offered by advanced diagnostic assays, these goals cannot be realised. The global market for in-vitro diagnostics is consequently expected to grow and is estimated to exceed $50 billion by 2013. Many diagnostic systems rely upon interface functionality to detect the presence, activity or concentration of target biomolecules. The simple detection of a target is sufficient in some cases, but a level of quantification for more than one target is required for diseases such as diabetes, cancer and autoimmune syndromes. There is widespread recognition that poor interfacial quality is one of the most important limiting factors in diagnostic performance. For example, in standard ELISA assays, it is commonly estimated that only a few % of the immobilized antibodies are functional. This is almost certainly a substantial contributory factor to the poor precision and reproducibility of such assays. Additionally, these assays demonstrate a shelf life of the order of only a few days unless stabilizing agents, such as sugars, are used whereas an ideal assay should be viable for months, if not years. Therefore, there is substantial interest in developing methods to improve the performance, reproducibility and shelf-life of diagnostic interfaces. However, these developments are hindered by the lack of adequate and validated measurements of interfacial quality. Indeed, according to Prof. Sue Hill OBE, Chief Scientific Officer, Dept. of Health, "Metrology for characterisation of biomolecular interfaces for diagnostic services is an important area". Therefore, there is a need to provide measurements of biomolecular concentration, distribution and structure at relevant interfaces, which increasingly includes surfaces with nanoscale topography and nanoparticles.

The Solution

In collaboration with project partners:

- Reference materials for both the project and the wider research community will be developed and also methods by which the composition and thickness of the interfacial chemistry can be measured accurately.
- Methods to establish the quality, reproducibility and shelf life of biomolecular interfaces will be developed.
- The activity of diagnostic surfaces will be measured.
- Innovative approaches to determine the orientation and structure of biomolecules at an interface will be investigated; the results will be correlated with activity measurements.
- New and emerging approaches to biomolecular sensing with an emphasis on multiplexed and label-free analysis will be explored.

Project Description (including summary of technical work)

As part of the EMRP project, NPL's contribution will focus on:

- Developing reference surfaces, both planar and nanoparticle, with immobilised protein and peptide probes. This builds upon expertise developed in ChemBio project NB1 on quantitative analysis of biomolecules.
- Establishing uncertainty and traceability for commonly used methods to measure probe density and target binding including, but not limited to, XPS, ellipsometry, dual polarisation interferometry, QCM.
- Organising an inter-laboratory study to establish reproducibility and comparability of these and other methods.
- Fundamental metrology for the analysis of biomolecular interfaces with novel gas cluster ion beam sources in SIMS. This will include establishing the molecular information content from this novel approach and the influence of molecular size, surface attachment mechanism and orientation on secondary ion intensities.
- Fundamental study of ambient mass spectrometries to identify biomolecular targets binding on micro-arrayed probes. The specific application is to identify saccharide-binding proteins in a rapid and high-throughput manner.

Impact and Benefits

The most significant impact of effective diagnostic tools is in prolonging the useful and enjoyable life of citizens. Simple diagnostic tests which are portable, accurate and require minimal expertise to operate will have a major impact in the developing world. For example, for malaria this could avert more than 100,000 childhood deaths and 400 million

unnecessary treatments each year [Nature 444, 681, 2006] and tests for HIV, respiratory and diarrhoeal diseases, syphilis and many others are required. Accuracy is vital, for example, the standard diagnostic test for tuberculosis (TB) misses half of all cases. In the developed world, the growth of point of care and self-testing underpins the in vitro diagnostic device market. There is a continued need to improve the accuracy and reliability of devices to reduce the detrimental effects of false negative and positive results. This project enables the development and production of reproducible biomolecular interfaces, the critical component of most diagnostic devices. Through interactions with project collaborators, the hosting of workshops (e.g. 65th IUVSTA workshop, Peckforton Castle, UK, May 2012) and publications this project will influence improvement of reliability, performance and accuracy of diagnostic devices and make a significant impact in the detection and prevention of diseases.

Support for Programme Challenge, Roadmaps, Government Strategies

Improving the detection and diagnosis of disease is an important aspect of the UK strategy to mitigate the rising costs of modern healthcare by reducing the number of inappropriate and ineffective interventions and treatments. As a result of this drive, the UK places a high priority on the development of, for example, portable immunoassays [UK Technology Strategy Board, Biosciences Strategy 2009-2012]. The project is fully aligned with the NMS Strategy 2011-2015 and the ChemBio Programme Surface Analysis strategic priority theme and roadmap (e.g. surface analysis for biomolecular systems for diagnostic and other medical devices).

Synergies with other projects / programmes

The work in this project builds on developments from various ChemBio projects on the quantification of immobilised biomolecules, surface analysis and ambient mass spectrometry (e.g. projects SA1, NB1 and NB4). The project is also synergistic with EMRP-JRP NEW01 project around traceable characterisation of nanostructured devices and project proposal NB12.

Risks

- Suitable reference platforms are irreproducible due to poor control of linker chemistry or contaminants: This problem will be identified at a very early stage. Resource will be redirected to this activity to ensure a timely completion.
- The shelf life of the reference platforms is too short for interlaboratory studies: The shelf life required is of the order of months. If this is not achieved, special storage conditions, such as trehalose coating will be tried. This has been shown to be effective for ELISA platforms.
- Protein and peptides cannot be detected from the sample using ambient MS: Wide ranges of different solvents and reagents are available for DESI. These will be screened to select the most appropriate electrospray mixture for this type of analysis.

Knowledge Transfer and Exploitation

Dissemination of the project's outputs will be through the following routes: Publications (reports and scientific papers; oral presentations at leading international conferences e.g. the annual meetings of the American and European Vacuum Societies, AVS and EVS, the biannual European Conference on Applied Surface and Interface Analysis (ECASIA) and the biannual International Conference on Secondary Ion Mass Spectrometry. A special session in the upcoming ECASIA'13 (October 2013) will be organised; and a project website. Dissemination will also be through VAMAS TWA 2 "Surface Chemical Analysis" and the ISO TC201, which has initiated a working group on "surface characterisation of biomaterials", starting in 2012, and will produce new work items and standards relevant to the EC directive on in vitro diagnostic devices and this proposal. Further, there is an on-going plan to establish traceability for measuring the amount of biological material at surfaces at BIPM Consultative Committee on the Quantity of Matter Surface Analysis Working Group.

Co-funding and Collaborators

This project comprises NPL's input into the EMRP Health "Metrology for the characterization of biomolecular interfaces for diagnostic devices" project (£323k from EMRP). The project is led by NPL with funded partners BAM (Germany), PTB (Germany), INRIM (Italy) and SP (Sweden). Associated postdoc positions are expected at Chalmers University, TU Berlin and Berlin Charite research hospital. Collaborators include: KRISS, University of Washington, International Iberian Nanotechnology Laboratory, Orion Diagnostica, Farfield, Q-sense, Biolin, Medipan, University of Nottingham, CNR (Italy), JRC Institute for Health and Consumer Protection, Plasmore, University of Lugano, Scienion and Lausitz University.

Deliverables

1	**Start: 01/06/12**	**End: 31/05/15**	

Deliverable title: Cofunding for EMRP project "Metrology for the characterization of biomolecular interfaces for diagnostic devices (JRP-HLT04)"

Project No.	NS002CF12	**Price to NMO**	£311k
Project Title	Managing risks of nanomaterials (FP7 MARINA)	**Co-funding won**	£250k
Lead Scientist		**Stage Start Date**	June 2011
Scientist Team		**Stage End Date**	May 2014
		Est Final Stage End Date	2015+
Sector	Underpinning Metrology - Traceability & Uncertainty; Standards & Regulation	**Activity**	Development of existing capabilities

Summary

This ring-fenced project outlines NPL's input into a Seventh Framework Programme (FP7) NMP project entitled "Managing Risks of Nanomaterials (MARINA)", which aims to develop and validate the risk management methods for nanomaterials. The overall aim is to make the transition from toxicology studies of specific individual nanomaterials towards developing tools for a more integrated systematic health and environmental safety assessment and management approach that can handle the overall risks for types or classes of engineered nanomaterial based on their physicochemical properties.

The Need

Nanotechnology promises materials for industrial applications with new or enhanced physicochemical properties that are different in comparison to their bulk counterparts. As these new materials go through their life-cycle—from development, to manufacture, to consumer usage, to final disposal—different human groups (workers, bystanders, consumers), environmental compartments (air, soil, sediment, water) and species (e.g. worm, fish or humans) will be exposed to these materials. Emerging data have shown a range of toxic (hazardous) effects from engineered nanomaterials (ENM), suggesting that with increased use these ENM may result in a risk (product of hazard and exposure) to human health or the environment. While standard methods exist for hazard and risk analysis of conventional chemicals, these tools need to be modified and verified before application to ENM. For example, the environmental and toxicological effects of industrially-relevant ENM (e.g. titania, zinc oxide, silica and carbon nanotubes) have not been fully rationalised because of a) the inability to adequately characterise the nanomaterials, b) the lack of reference ENM and c) the lack of validated standard protocols. Reference ENM and standard protocols for their characterization are needed by industry and researchers in order to set standards against which measurements can be compared. In addition to the development of reference ENM and standard protocols, the EC's Scientific Committee on Emerging and Newly Identified Health Risks has identified the need to understand the physicochemical state of ENMs in biotic environments, thus requiring validated measurement techniques that can be used in the field.

The Solution

Development and provision of reference ENM and standard protocols through the generation of characterisation data (following guidelines of the Organisation for Economic Co-operation and Development [OECD]). Such data, e.g. data referring to particle size and surface properties, will contribute to reference dossiers with industrial, scientific and regulatory relevance. Development of metrology capability around the use of non-invasive characterisation techniques to investigate the accumulation of biomolecules on the surface of nanoparticles in media and the interactions of nanoparticle complexes with dissolved salts. Nanomaterial characteristics and behaviour will be measured during, and after exposure to, complex biological matrices using techniques that do not themselves influence the properties and behaviour of the ENMs. Nuclear Magnetic Resonance (NMR) will also be used to measure the surface area of ENM in liquid media. This technique will be evaluated against existing techniques e.g. BET surface area, which is limited by the fact that measurements can only be made with solid samples.

Project Description (including summary of technical work)

Working with other MARINA consortium members, NPL activity will contribute to:

1. *Reference nanomaterials*: a) Characterisation of ENM (e.g. titania, zinc oxide, silica and carbon nanotubes) for homogeneity testing towards reference material development, b) interlaboratory tests to establish harmonised protocols for ENM characterisation in liquid media. Sample aliquots will be provided by EC-Joint Research Centre (JRC) and analysis will be carried out, as recommended by ISO TC 229 WG3 PG5. NPL will investigate certain parameters, including particle size distribution, stability and surface properties. NPL will also partake in a study towards the validation of standard protocols for dispersion of ENM in liquid media
2. Non-invasive ENM characterisation of (in situ and post-test) complex media: a) Investigation of the use of non-invasive measurement technologies (such as Scanning Ion Conductance microscopy, Tip Enhanced Raman Spectroscopy and Desorption Electrospray Ionisation) for *in situ* and post-test characterisation of ENM; b) direct surface area measurements of ENM in liquid using NMR; results will be compared with other currently available techniques for surface are measurement e.g. BET technique.

Impact and Benefits

Overall, the project will lead to a comprehensive understanding of the properties, interaction and fate of ENM in relation to human health and environment. This project will contribute to meeting European objectives for the safe, integrated and responsible approach to the development of nanotechnology e.g. supporting pre- and co-normative activities such as the implementation of REACH. The project's outputs will help develop an overarching strategy for ENM risk management and enable EU regulatory bodies, agencies and authorities to make informed decisions and policies to safeguard consumers while taking full advantage of the advances that nanotechnology will bring to the economy and industry competitiveness. Impact will be measured by the successful translation and implementation of the MARINA platform to support future European policy, specifically horizontal standardisation, and harmonisation, as well as worker and consumer protection. This work will directly feed into the wider raft of research addressing the outstanding issues related to the characterisation of nanomaterials, with a focus on their risks.

Support for Programme Challenge, Roadmaps, Government Strategies

This project aligns with the TSB's Nanoscale Technologies Strategy (2009-2012) and BIS' Nanotechnologies Strategy report (2010) that identifies, as a priority, the need for further research to develop the required metrology infrastructure around ENM characterisation, standardisation and reference materials. This work sits within the ChemBio Surface and Nanoanalysis, Nanobiotechnology and Particles roadmaps and also supports the safe, integrated and responsible approach as laid down in "Nanosciences and Nanotechnologies: An action plan for Europe".

Synergies with other projects / programmes

MARINA aims to maximise coherence with ongoing international testing programmes (e.g. OECD Sponsorship Programme), as well as align with other related FP7 projects to minimise duplication of work and maximise complementary activity. For reference material and standard method development, ENM-related datasets will be generated under guidelines of OECD harmonised templates and according to regulatory endpoints and requirements of REACH. For the development of innovative platforms, NPL will take advantage of experience gained through its work as part of the Defra PROSPEcT project and technical capability (SICM, DESI and TERS) developed under the ChemBio Programme e.g. projects P5 and P6.

Risks

The technical capabilities required for successful delivery of this project are already established at NPL. However, there is a moderate risk associated with overall MARINA project coordination and timely delivery of each work package (WP) given the large number of consortium members. To mitigate this risk, the consortium's Steering Board will assess the progress of each WP and of the project in general, based on progress towards objectives, deliverables and milestones.

Knowledge Transfer and Exploitation

This knowledge will be disseminated to European laboratories and companies through a) the MARINA website, b) workshops c) publications in high impact journals d) suitable events, such as nanotoxicology conference series, Nanoimpactnet, Nanosafety cluster meetings. There will also be targeted dissemination to national and international regulatory bodies, namely OECD WPMN, ISO (e.g. TC 229 and TC 194), CEN (TC 352), European Commission, European agencies and national authorities, and key partners outside of Europe (USA, China, Japan, India etc.).

Co-funding and Collaborators

This is a ringfenced project that comprises NPL's input into the FP7 MARINA project led by the Institute of Occupational Medicine (UK). The MARINA consortium comprises 46 members from across Europe, inclduing EC-JRC, and recognises the relevance of the results to industry with the direct participation of the Nanotechnology Industries Association, the Food Environment Research Agency (UK) and industrial partners, including BASF and Nanocyl.

Deliverables

1	**Start: 01/04/2011**	**End: 31/03/2014**	
Deliverable title: Co-funding for FP7 MARINA project			

Project No.	NMS/CBM/12012	**Price to NMO**	£259k [£100K has been used to co-fund CBM12019] (NPL) + £125k (LGC)
Project Title	P13: Measuring the influence in changes in liquid environments on nanoparticle properties	**Co-funding target**	£241k
Lead Scientist		**Stage Start Date**	April 2012
Scientist Team		**Stage End Date**	April 2015
		Est Final Stage End Date	April 2018
Sector	Underpinning metrology / Standards and Regulation	**Activity**	Development of Existing Capabilities.

Summary

Nanomaterials hold great potential to form the basis of new products with novel or improved properties. However, the short and long term health and environmental impacts of these materials are still unknown. These must be established to ensure consumer confidence in these products. This joint NPL and LGC project will overcome current roadblocks by providing the capability to provide close to real time measurements of nanomaterial samples suspended in liquid and establishing reference materials with well-defined, narrow size distributions and improved homogeneity.

The Need

It is envisioned that new regulations on the production, use and final disposal of nanomaterials will be required and enforced by regulatory bodies. Current nanomaterial production dominates the nanotechnology market with revenues of £2.3 bn in 2007 and is expected to increase to £81bn by 2015, according to the UK Nanotechnologies Strategy. The UK is the 3rd biggest market in this area after the US and Germany. The UK has world leading manufacturers, such as Thomas Swan, Intrinsiq, Oxonica and Energetics, and has end users, in for example the food and health care industries and premium materials manufacturers. Currently the EU is investing hundreds of millions of Euros in determining the toxicological impact of these materials via the supporting of large pan-EU projects (Marina, NanoValid). Two roadblocks restricting these studies are the lack of suitable characterisation tools and reference materials. The properties of nanomaterials (size distribution, surface properties) change rapidly when subjected to different liquid environments and current measurement tools are too inaccurate to measure these changes. This results in contradictory findings, often between measurement runs of the same instrument. In addition, current reference materials are polydisperse, with a wide range of sizes and shapes, and heterogeneous. This means that it is unknown if the adverse effects are caused by the mean particle size or from the outliers, namely the extremes of the size and shape distributions. When supplied from a central store and changes in the reference material properties with time cannot be discounted, for example agglomeration of nanomaterials in suspension and the effect of changes in humidity for dry samples. Improvements are urgently required for environmental research organisations (DEFRA) and to support directives such as REACH.

The Solution

Only by providing improved measurement capability can scientifically sound physical and chemical data be linked to toxicological investigations and eventually lead to robust risk assessment processes. New generation of microreactors have the potential to 'dial-in' monodisperse nanomaterials with well-defined size distribution. However, these need improving and validating before the relevant stakeholders can accept and engage with them. The solution is to:

a) Validate current platforms for characterising nanomaterials in liquid media to determine their ability to follow changes in their properties in near real-time. Current capability includes:

- Ion concentration within nanomaterial suspensions indicating nanoparticle break-up and dissolution.
- Changes in the size distribution of nanomaterials in a liquid media, indicating particle agglomeration, adsorption/reabsorption of chemicals/proteins e.g. formation of the so-called protein corona, which can influence the bioactivity of the nanomaterial sample.
- Detection of reactive oxygen species on the particle/liquid interface.

The aim being to assess the ability to produce miniaturised versions of the above platforms which will be faster (high throughput and close to real time) and less expensive than their traditional counterparts.

b) Enable the production of monodisperse reference materials through the use of microreactor platforms and compare quality with those produced by batch process.

c) Demonstrate the application of the reference materials in *in-vitro* toxicology studies using a range of cell models and compare measurement variability to standard batch produced materials.

Project Description - The project plan tasks are as follows:

a) Investigate and optimise the ability to quickly characterise nanomaterials in liquid to study changes. These methods to include; 1) capillary-electrophoresis (CE) conductivity measurements of nanomaterial dissolution based on microchannels; 2) light scattering techniques (dynamic light scattering and nanoparticle tracking analysis; 3) reactive oxygen species (ROS) generation activity through the use of markers. In all of the platforms, miniaturised version will be investigated for improved measurements.

b) Investigate methods for reference materials synthesis using microreactor platforms. Compare physicochemical

properties to evaluate quality of the material produced here as oppose to by their large batch counterparts

c) Validate promising methods developed in a) with suitable reference and test materials in *in-vitro* toxicology studies.

Impact and Benefits

The ultimate beneficiaries of this project will be: factory workers handling the material, consumers and health/environmental protection agencies, with the knowledge that the risks associated with nanomaterials are understood. The characterisation methods developed in this project will be more accurate, reproducible and reliable than those currently used. This will be of benefit to various stakeholders in nanomaterial characterisation and in particular it will be taken up by the testing and research laboratories with nanotoxicological research capability such as LGC, University of Exeter, and University of Birmingham. These laboratories will be able to produce meaningful studies into the health and environmental impact of nanomaterial allowing the correct regulations to be set. The characterisation methods will also enable nanomaterial manufactures to ensure that their products comply with these regulations and will ultimately improve the UKs reputation and world class capability in this area.

Support for Programme Challenge, Roadmaps, Government Strategies

This project supports the NMS Strategy 2011-2015: *'The NMS laboratories will lead the development of characterisation tools, methodologies and reference materials for Nanomaterials to facilitate their application and to underpin environmental health and safety research'* (Strategy for the National Measurement system: 2011-2015*'* and the UK nanotechnologies strategy (BIS, 2010). In addition it aligns with the ChemBio Programme Nanobiotechnology and Particles themes and roadmaps by providing the raw characterisation capability to provide physical characterisation of nanoparticles for toxicity studies. Further, this work aligns with the requirements voiced by Defra's Nanotechnology Research Strategy Group – Task Force 1 for better characterisation tools and reference materials. Finally, the importance of reference materials and high-throughput nanomaterial characterisation has been identified as a priority in the recent Co-Nanomet produced strategy document 'European Nanometrology 2020'.

Synergies with other projects/programmes

This project will support the UK's activities on nano(eco)toxicology based research and the goals of current OECD's working party of manufactured nanoparticles (WPMN) programme. It links in with the cofunding projects for PROSPEcT (ChemBio project P5) and FP7 MARINA (ChemBio project CF12). It will also further develop ChemBio project SA1 outputs and leverages on existing collaborations with Birmingham, Exeter, NIA, Imperial College London and LGC as well as previous (NB8) and current (NB10) ChemBio projects.

Risks - Microchannels on a chip format for the synthesis/ characterisation of nanomaterials may result in blockages due to the particles attaching to the surface side-walls over time. This can be mitigated by: a) coating of the surface walls and b) use of quartz tubes and fused silica should conventional microchannels embedded in a substrate device not work.

Knowledge Transfer and Exploitation

Support and feedback will be sought directly from the toxicological community through NPL's participation of the MARINA project. The key findings will be communicated directly through high impact (peer review) journal publications at oral presentations at international workshops/conferences. The stakeholders will be informed through the committee structures such as: The Nanotechnology Research Strategy Group: Task Force 1 (as chaired by Defra) and will be instrumental for disseminating the findings to the relevant bodies (i.e. toxicological research organisations); The Nanotechnology Industries Association (NIA), leveraging on their link to the OECD global initiative for testing of nanomaterials; and ISO TC229 to draw up relevant ISO documents (standards). The findings lead to better nano(eco)toxicological studies and will eventually enable better regulation via bodies such as REACH.

Co-funding and Collaborators - The following organisations have expressed interest in partnering in this proposal: a) University of Birmingham, Natural History Museum and NIA for the supply of various test materials; b) University of Exeter for complementary in vivo work and c) University of Surrey in the light scattering experiments. Further input from toxicologists will be sought through events such as the upcoming SETAC workshop which NPL is leading. A joint TSB bid with NPL, LGC and Syrris will be submitted under the TSB *Technology Inspired Innovation* call for the further development of this technology for production of different types of reference material using microreactors. Further cofunding will be sought from the 2012 EMRP call 'Metrology for Industry'.

Deliverables

1	**Start: 01/04/12**	**End: 01/01/15**	
Demonstration of the ability to determine the change in nanomaterial properties in near to real time as evidenced by a peer reviewed publication			
2	**Start: 01/08/12**	**End: 01/12/13**	
Microreactor capability as demonstrated by the production of nanomaterial (gold)			
3	**Start: 01/08/13**	**End: 01/04/15**	
Application of the reference materials for *in-vitro* nanotoxicology studies			
4	**Start: 01/12/13**	**End: 01/04/15**	
Peer-reviewed publication and report on the improvements of the microreactor capability and nanomaterial production			

Project No.	NMS/CBM/12007	**Price to NMO**	£529k
Project Title	CF2: Metrology for Raman spectroscopy (EMRP NEW02)	**Co-funding target**	£323k (from EMRP)
Lead Scientist		**Stage Start Date**	1/06/2012
Scientist Team		**Stage End Date**	31/05/2015
		Est Final Stage End Date	2020
Sector	Underpinning metrology: Traceability & Uncertainty	**Activity**	Measurement infrastructure

Summary

The work proposed contributes to a wider body of research in the European Metrology Research Programme (EMRP) New Technologies "Metrology for Raman spectroscopy (JRP-NEW02)" project. This NPL-led project addresses several major challenges to establish Raman spectroscopy as a label-free, reliable and quantifiable technique: (i) Quantifiable measurements traceable to the mole and SI by conventional Raman scattering, (ii) Nanoscale Raman measurement in 2D using Tip-Enhanced Raman scattering (TERS) and (iii) 3D chemical imaging at high speed (one frame every 10 second) using multi-photon Raman scattering techniques.

The Need

Raman spectroscopy is currently used as a qualitative tool in the pharmaceutical, healthcare, biotechnology, nanotechnology, medical technology and forensic science sectors to identify and map distribution of substances in 2D or in 3D e.g. for studying the distribution of a drug in tissue or the uniformity of a biofunctionalised surface coating. However, these sectors are also calling for full chemical and structural identification of species at higher spatial resolution, which quantitative Raman spectroscopic techniques could provide. For example, a number of novel techniques have evolved to (a) increase the sensitivity *e.g.* surface enhanced Raman scattering (SERS), coherent anti-Stokes Raman scattering (CARS), stimulated Raman scattering (SRS), and (b) increase spatial resolution *e.g.* tip-enhanced Raman scattering (TERS). Multi-photon Raman scattering techniques such as SRS and CARS, even though relatively new, have already been applied in diverse fields including biochemical diagnosis, materials science and gaseous phase analysis and these techniques can overcome the problems observed in conventional Raman scattering. However, these techniques require a sound metrological platform to encourage wider uptake by industry so that the repeatability, reliability and quantification of the measurement is established. Further, instrument manufacturers have also called for the provision of new reference materials and standards, especially spatial resolution, depth resolution and confocality measurement standards.

The Solution

The proposed work will address the metrology issues related to conventional far-field, near-field (TERS) and multi-photon Raman scattering (SRS and CARS) which are urgently required to take Raman spectroscopy from a *qualitative tool to a quantitative technique* to meet the stakeholder requirements such as for documentary and reference standards for traceable quantification, spatial resolution and confocal volume. These are required for quality control, instrument-reliability, and innovative product and process development.

Project Description (including summary of technical work)

NPL's contribution to the EMRP project will focus on addressing the metrology issues related to:

- *SI-traceability for spatial resolution and amount of substance measurements by Raman scattering.* Develop methodologies and concepts for SI-traceable quantitative evaluation of Raman spectroscopic results covering: i) traceable in-depth profiling and ii) traceable amounts of substance measurements by Raman scattering for chemical and biochemical analysis.
- *Tip-enhanced Raman spectroscopy.* Develop the metrology of TERS through the production of reference samples and reproducible tips.
- *Multi-photon Raman spectroscopy.* Develop 3D chemical imaging at high speed (one frame every 10 seconds) based on SRS and CARS techniques. Quantify and map the distribution of Raman active molecules e.g. lipid and sulphur containing compounds in complex media such as tissue, hair, and plant and to investigate nanoscale interfacial interactions. The knowledge generated in the tasks above will be used to accurately map the distribution of the chemicals in 3D.

Impact and Benefits

This work will improve the accuracy of measurement of quantity and/or distribution of substances in complex mediums using Raman scattering techniques and ultimately establish Raman spectroscopy as a label-free, reliable and quantifiable technique for use in a variety of industrial sectors, including medical and pharmaceutical. Currently there are no standards in CEN and ISO on Raman scattering, and no surface chemical activities for standardization in CEN. The proposal will make significant contribution to provide the documentary standards as well as reference materials that are required for quality control, instrument-reliability, and innovative product and process development.

Support for Programme Challenge, Roadmaps, Government Strategies

This project addresses the technology needs for advanced SPM methods and quantitative analysis of organic and biological surfaces at the nanoscale as described in the ChemBio Programme Surface Analysis roadmap, the Co-Nanomet European Nanometrology report (2011) and the 'Nanostrand' Report (2008). In addition, it aligns with the ChemBio Nanobiotechnology roadmap around single molecule measurements and molecular-structure interactions.

Synergies with other projects / programmes

This project will build on developments made in ChemBio project, NB5 'Combined TIRF/TERS for nanoscale imaging and spectroscopy in liquid', a TSB project on 'Scalable, low-cost organic photovoltaic devices' (SCALLOPS), and the EMRP project 1I on 'Traceable quantitative surface chemical analysis for industrial applications'.

Risks

- Multilayer reference sample not successfully prepared: NPL and collaborator (PTB) have previous experience of making multilayer structure. The same procedure will be followed.
- Unable to produce TERS tips: NPL and ETH-Zurich has extensive experience on producing TERS tips, and they have been using it since inception of TERS.
- Unable to set up SRS system at NPL: NPL scientists will get preliminary training on a suitable system elsewhere e.g. visit Prof. Sunney Xie's laboratory at the University of Harvard to learn about the system. King's College London has expertise to set up CARS system, and assistance will be available from both the laboratories.

Knowledge Transfer and Exploitation

Dissemination of the project's outputs will through the following routes: Publications (reports and scientific papers; trade journals; project website; oral presentations at leading international conferences, including the possible introduction of a new session on Raman metrology at the International Conference on Raman Spectroscopy (ICORS) in 2012 to be held in Bangalore, India and in 2014 to be held in Jena, Germany. A summer school will be organised to bring the world experts to train, teach and talk on progress on Raman spectroscopy. Standardisation activity will be through the ISO TC 201 committee on Optical and Interfacial Analysis (OIA).

Co-funding and Collaborators

This project comprises NPL's input into the EMRP New Technologies "Metrology for Raman Spectroscopy" project (£323k). The project is led by NPL with funded partners including PTB (Germany), INRIM (Italy), CMI (Czech Republic), INMETRO, NMI (Germany), ETH-Zurich (Switzerland), Kings College London. Additional collaborators include the National Institute of Science and Technology, Renishaw, Nanonics and Guys and St. Thomas Hospital.

Deliverables

1	**Start: 01/06/2012**	**End: 31/05/2014**	
Deliverable Title: Cofunding for EMRP project "Metrology for Raman Spectroscopy (JRP-NEW02)"			

Project No.	NMS/CBM/12008	**Price to NMO**	£496k
Project Title	CF3: Traceable characterisation of nanostructured devices (TReND) EMRP NEW01	**Co-funding target**	£317k from EMRP
Lead Scientist		**Stage Start Date**	01/06/2012
Scientist Team		**Stage End Date**	31/05/2015
		Est Final Stage End Date	2020
Sector	Advanced Manufacturing & Services: High-value manufacturing and bioproducts	**Activity**	Methodology for new capabilities

Summary

The work proposed contributes to a wider body of research in the European Metrology Research Programme (EMRP) New Technologies "Traceable characterisation of nanostructured devices (TReND; JRP-NEW01)" project. It will develop traceable measurement and characterisation of physical and chemical properties of the next generation of integrated nanostructured semiconductor devices using novel 3D architectures. Specifically, NPL's contribution will focus on developing the essential metrology for 3D-Secondary Ion Mass Spectrometry (3D-SIMS) using argon cluster sputtering.

The Need

The micro and nanoelectronic world is experiencing a revolution in tackling the new challenges in terms of miniaturization, power consumption, power density and processing speed. Novel inorganic semiconductor materials (for example, Ge, InGaAs, GaN, SiC, etc.) and new 3D-architectures (e.g. multiple gate field effect transistors [FETs], nanowire tunnelling-FETs, etc.) with feature sizes < 30 nm are replacing traditional silicon devices. There is now a critical need for metrology to give traceable and quantitative chemical composition measurement of new materials in complex spatial arrangements with buried interfaces and with nm depth resolution. Concurrent with these developments is the emergence of electronics based on organic semiconductors, made of single molecules in highly ordered assemblies and polymeric semiconductors in thin films. This is an important new knowledge-based high innovation sector for the EU. The combined market for organic logic, batteries, sensors and conductors will be €9bn by 2019 and for integrated systems €47bn. Unfortunately, the techniques developed for the inorganic semiconductor industry do not directly apply and there is an urgent need for methods to give 3D nanoscale chemical and electrical imaging. In the current state of the art, 3D SIMS with C_{60} sputtering fails completely for organic electronic materials and there are no existing methods for 3D nanoscale electrical measurements. The challenge here is for metrology at the nanoscale and it is clear that no single technique can provide all the answers required by industry.

The Solution

To address the stated needs above, the project will:

- Develop methods for 3D nanochemical analysis of nanostructured organic electronic materials, (i.e. 3D chemical characterisation of nanolayers and interfaces with depth resolutions of better than 10 nm at depths of up to 400 nm and with spatial resolution to better than 100 nm.). By dramatically reducing the incident energy per atom from 333 eV/atom (typical for C_{60}) to 1.5 eV/atom, it has been shown that large Ar_{2000} clusters radically reduce damage and fragmentation during sputtering and allow successful depth profiles through molecular multilayers material with better than 5 nm depth resolution at a depth of 100 nm.
- Develop methods for 3D nanoelectrical characterisation of nanostructured organic electronic materials (i.e. the conductivity and charge mobility) of materials inside thin films with nanoscale resolution (better than 30 nm).

Project Description (including summary of technical work)

As part of the EMRP TReND project, NPL's contribution will focus on:

- Developing the essential metrology to enable 3D nanoscale chemical imaging of organic electronic materials using new massive argon cluster sputtering combined with SIMS for 3D chemical analysis of nanostructured organic electronic materials. This will be done by (i) provision of the fundamental metrology infrastructure for super-resolution 3D chemical imaging of organic nanolayers using massive argon cluster SIMS, (ii) quantification and depth distribution of impurities and additives in an organic nanolayer and (iii) metrology for 3D nanoscale chemical imaging of organic electronic and organic photovoltaic devices.
- Developing a novel method for 3D nanoelectrical characterisation of organic semiconductor nanostructures and nanostructured self-assembled reference materials for the metrological studies of the techniques. Develop novel measurement of electrical and opto-electrical properties of the surface and subsurface of organic thin films and combined analysis of a selected organic photovoltaic (OPV) device. This will be done by combining AFM nanoindentation and dc electrical measurements for electrical measurement and photoconductive atomic force microscopy (PC-AFM) measurements and modelling for optoelectronic measurement.

Impact and Benefits

The semiconductor and nanoelectronic industry constitutes a vast global market, its size being about $265bn. The market for equipment and materials can be estimated, on average, at $35bn for equipment and $32bn for materials.

On top of this, the sector is directly stimulating a much larger electronics applications industry totalling $1,500bn. The UK is an international leader in the innovation and development of organic electronics which is a rapidly growing sector. The combined market for organic logic, batteries, sensors and conductors will be €49bn by 2019. For all these markets there is an urgent requirement for 3D chemical and opto-electrical measurement at the nanoscale to improve device efficiency, lifetime and manufacturing processes.

Support for Programme Challenge, Roadmaps, Government Strategies

This project is aligned with the NMS Strategy 2011 – 2015, the ChemBio Surface Analysis priority theme and roadmap (Organic depth profiling using SIMS with cluster sputtering), a VAMAS TWA 37 survey of needs for the organic electronics industry, the Organic Electronics Association Roadmap for Organic and Printed Electronics (2009) , Strategic Research Agenda Organic & Large Area Electronics, 'Towards Green Electronics in Europe', UK Technology Strategy Board Electronics Photonics Electrical Systems technology pillar (2008), Plastic Electronics: A UK Strategy for Success (BIS; 2009), and The Current and Future Role of Technology and Innovation Centres in the UK (The Hauser Report; 2010).

Synergies with other projects / programmes

The work builds on developments made in previous ChemBio projects (e.g. SA1). Specifically, 3D SIMS using sputtering by argon cluster ions builds on a strong metrology foundation in SIMS at NPL and develops the capability which is a high priority measurement requirement in many industries including semiconductor, medical devices, printing, coatings, speciality chemicals and agrochemicals. The project is also synergistic with EMRP JRP-HLT04 project, (project proposal CB/2012/CF18), which is investigating the quantitative analysis of biomolecular interfaces relevant to the needs of diagnostic device manufacturers.

Risks

Argon clusters may not be able to successfully profile organic electronic materials for OPVs, which would stop the analysis of real world devices. NPL is one of only two laboratories with nitric oxide (NO) radical scavenging facilities to prevent cross-linking of polymers during sputtering. The NO gas can be used in the project. Alternative polymer materials can be used if required.

Knowledge Transfer and Exploitation

Dissemination of the project's outputs will be through the following routes: Publications (reports, articles in trade journals and scientific papers); oral presentations at leading international conferences; a project website, e-forum and online network; and provision of training to industry e.g. NPL will offer 5-days of dedicated instrument time and analysis for 3D chemical imaging of organic nanolayers to European enterprises to showcase the power of the techniques developed in the project with the requirement that case-studies are made public. Further dissemination will be through the development of international standards in SIMS for organic and nano-objects through ISO TC 201 working group and NPL's chairing of VAMAS TWA 2 on Surface chemical analysis.

Co-funding and Collaborators

This project comprises NPL's input into the EMRP New Technologies TReND project (£317K from EMRP). The project is led by NPL with funded partners including PTB (Germany), BAM (Germany), CEA (France), CMI (Czech Republic) and INRIM (Italy) and also ION-TOF working as an unfunded partner. Associated postdoctorate positions will be held at LETI and IMEC. Collaborators include Detech, Dipartimento di Scienze dell' Ambient e della Vita(East Piemonte University), Istituto Italiano Di Techologia, Sigma Aldrich, EMPA, FEI, MEMC, Eight19, Samsung, Rigaku, OEA, KTN-ESP, Asylum Research UK, Fraunhofer Institute for Photonic Microsystems, ST microelectronics, Universite Catholique de Louvain, PANalytical BV, Oxford Instruments.

Deliverables

1	**Start: 01/06/12**	**End: 31/05/15**	

Deliverable title: Cofunding for EMRP project "Traceable characterisation of nanostructured devices (JRP-NEW01)"

Project No.	NMS/CBM13012	**Price to NMO**	£215k
Project Title	Co-funding for FP7 NATURAL (CF1)	**Co-funding won**	£198k
Lead Scientist		**Stage Start Date**	01/04/2013
Scientist Team		**Stage End Date**	28/02/2015
		Est Final Stage End Date	2015 or 2016
Sector	Energy	**Activity**	Development of existing capabilities

Summary

This project will provide the co-funding for the FP7 NMP NATURAL project where NPL's part is a cross divisional activity to relate nanostructure and nano- physical and chemical properties (AS) to micro properties and microtribology (Materials).

The Need

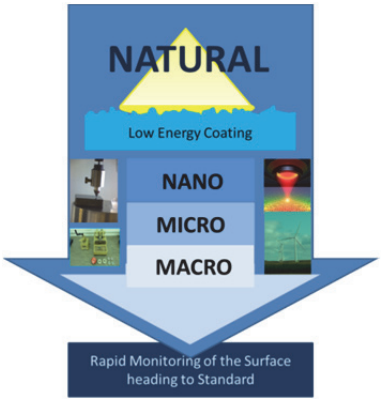
Atomic force microscopy (AFM) is generally based on line by line mechanical raster scanning and is regarded as very slow, typically taking over 15 minutes to complete a scan. In comparison to optical microscopy or scanning electron microscopy where a video rate imaging is regularly used. This limits many of the possible applications in the field of surface physics, biology, material science and metrology. . In addition certain key issues including quantification of properties and tip effects are not fully resolved. For accurate topographical images the tip must track the surface accurately, this becomes more challenging when increasing scan speed and imaging nanostructures, where there is increasing need.

The Solution

The project will link nanoscale properties of nanostructured coatings to, their micro, meso and macro properties with applications for the project in developing low energy coatings for anti-fouling applications (e.g wind turbine blades) but with wider applications in healthcare. It will provide co-funding to the recently won FP7 NMP NATURAL project. It will develop metrology capability in high speed AFM, XPS and tribology to study nanostructured surfaces and biomolecular adsorption on those surfaces.

Project Description (including summary of technical work)

The project will link nanoscale properties to micro properties by studying nanostructured surfaces and developing the following:



1)Rapid nanoscale topography method

- Develop high speed AFM for imaging of nanostructured surfaces
- Investigate role of feedback parameters to improve scanning and reduce scan-induced wear
- Optimise imaging for nanostructured materials

2. Nanotribology

- Develop fast AFM to give frictional properties
- Investigate possibility of fast AFM giving additional nanomechanical information related to, for example, surface stiffness, adhesion and surface energy
- Comparison with micro tribology of surfaces

3. Chemical characterisation

- Surface and nano-analysis of nanostructured surfaces and proteins adsorbed onto the surface using XPS/SIMS (NPL)
- Correlate surface chemistry and energy to nanostructured coatings

4. Initial stages of bio-molecular adsorption on nano-structured coatings

- Changes in chemical surface properties
- Changes in frictional properties of bio-molecular adsorption
- Investigate forces required to remove bio-molecules and nanoparticulates from the nanostructured surface

Impact and Benefits

The project will develop the NMI measurement capability in the area of high speed AFM scanning, development in the understanding of the first stages of biomolecular adsorption on nanostructured surfaces using surface analytical techniques.

In terms of the overall FP7 project, the development and characterisation of nanostructured surfaces will develop new surfaces for wind turbines that help prevent ice build-up, which can cause a loss of 5-10% of electricity production, and in sub-tropical environments, help reduce fouling of the blade by insects, which can reduce power production from

wind turbines by 50%. An extension of this impact is in the marine environment, where fouling of ships by marine organisms is believed to increase fuel consumption by 40% and conventional biocidal approaches to addressing this issue are a substantial concern due to their biological effects.

Support for Programme Challenge, Roadmaps, Government Strategies

This proposed project is fully aligned with ChemBio strategy (June 2011) in strategic priority theme 5: Surface and NanoAnalysis. Here there are "urgent requirements for detailed characterisation of surfaces and nanostructures than is currently possible". Key outputs of this project are "international standards in nanotechnology metrology and characterisation" (highlighted as a research priority in 2010 BIS UK nanotechnologies research priorities). In the surface analysis roadmap this project aligns through developing "advanced AFM methods" with enabling science in "analytical nano-mechanics" and "surfaces with topography". Key drives, challenges and deliverables that this project aligns with are in "standards and directives", "renewable energy", "energy efficient systems"

Synergies with other projects / programmes

The project builds on the work of SA3 on soft sample AFM imaging but develops the area of fast AFM imaging and the imaging of nanostructures. It has links to current EMRP projects (Biosurf, NanoChop), IRD INTERACt and also projects in the Materials Division.

Risks

Risk are low overall as the project team has great experience in wide ranging sectors and instrumentation. One risk is that the nano- characterisation may not give the required performance, which is mitigated by having experienced scientists, who can use a variety of approaches to obtain the required information and, if necessary, characterisation will be operated at different parameters to allow more accurate topographic and frictional properties to be obtained.

Knowledge Transfer and Exploitation

The outputs of this project will be disseminated via high impact peer reviewed publications and oral and poster presentations at national and international conferences. Input and development of international standards in ISO TC201 (Surface Chemical Analysis) and ISO TC229 (Nanotechnologies) are key outputs of this project. Although the overall aim of the FP7 project is focused on at the wind turbine industry, the techniques and samples analysed in this project have wide ranging industrial interest in any surfaces that suffer from bio-fouling, including those in the healthcare sector.

Co-funding and Collaborators

Co-funding has already been obtained from the EU FP7 NMP 2012 call.
Collaborators in the project include TWI (UK), TNO (Netherlands), L'Uredeerra (Spain), Applied Materials Technologies (UK), Global blade technology (Netherlands), Snelloptics (Spain), Van Wijhe Verf (Netherlands), Dantec Dyanamics (Denmark).
Additional collaborations in AFM will come from (University of Oxford), (University of Sheffield), (Luther College, USA) and Asylum Research UK.

Deliverables

1	**Start: 01/01/13**	**End: 31/12/15**	

CF for Natural project: i)Develop rapid AFM for imaging nanostructured surfaces, ii) Investigate the first stages of bio-molecular adsorption on nanostructured surfaces, iii) Microtribology of nanostructured surfaces

Project No.	NMS/CBM/12005	**Price to NMO**	£642k (£574k removed to co-fund Q-Aimds)
Project Title	NB12: Ambient imaging mass spectrometry with high resolution (NPL) (Strategic capability)	**Co-funding target**	£750 k
Lead Scientist		**Stage Start Date**	01/07/2012
Scientist Team		**Stage End Date**	31/03/2015
		Est Final Stage End Date	2018
Sector	Health - Diagnosis; Advanced Manufacturing & Services - High-value manufacturing & bio-products	**Activity**	Development of Existing Capabilities; Methodology for New Capabilities

Summary

Through close collaboration with academia and industry this project will develop ambient imaging mass spectrometry (AIMS) capability for the rapid analysis of innovative and complex products in nanobiotechnology and advanced manufacturing.

The Need

According to the Co-Nanomet 'European Nanometrology 2020' report, a key objective in metrology is achieving in-situ nanometre resolution imaging from life systems, particularly for detection of low levels of biomarkers and disease markers. In industry there is strong demand for methods to analyse complex mixtures (subtle chemical differences, complex matrices) combined with the ability for rapid ambient analysis (screening, quality control) and surface chemical imaging with spatial resolutions of better than 10 μm to resolve chemical distribution (biomarkers on skin, homogeneity of tablets, pharmaceuticals in tissue sections and agrochemicals on leaves). Consultation with industrial stakeholders confirms this demand, with real excitement around ambient mass spectrometry as a potential solution, with over 20 UK industries becoming involved in the last 5 years. Industrial consultation has stated that AIMS could enable: real time and rapid quality control that takes into account chemical differences; understanding efficacy of products with difficult chemistries; simultaneous direct analysis of small molecules, polymers and organometallics; minimal sample preparation. Yet a common problem was best stated by one stakeholder (Svetlana Riazanskaia, Unilever) 'no facilities and expertise of this sort are presently available in house, so without NPL we wouldn't be able to do this research.' For effective use in industry the first critical need is for repeatability, and through the ChemBio programme we have started to establish the underpinning metrology leading to repeatability's of 10% (a factor of 10 improvement). Presently there is no capability for quantification, a demand from industry, due to a lack in the fundamental underpinning metrology. Improvements in sensitivity and quantification on real world samples need to be developed to enable routine use. Previous ChemBio projects have found spatial resolution typically ranges from 100 μm to 1 mm. New concepts and methods are required to develop high-performance AIMS capability.

The Solution

This project will radically improve the imaging capability of plasma assisted desorption ionisation mass spectrometry (PADI MS) from 1 mm to 10 μm in collaboration with the plasma physics group at Liverpool University (Prof James Bradley). We will address the challenge of sub-micron resolution by establishing new capability using a combination of a focused laser for desorption combined with novel ambient ionisation. With a long-term goal of achieving a spatial resolution of 100 nm we will explore the integration of scanning probe microscopy to give near-field laser ablation. It will be important to ensure that AIMS is quantitative and sufficiently sensitive, so we will develop the fundamental metrology to understand the desorption and ionisation mechanisms to enhance these aspects.

Project Description (including summary of technical work)

Metrology to measure the analytical sensitivity of important ambient MS techniques (DESI, PADI, paperspray). Fundamental study of the desorption and ionisation mechanisms of DESI and PADI and (1) develop methods to enhance sensitivity to 1 ppb (2) measure the quantification accuracy of DESI, PADI and paperspray including determination of matrix effects and (3) interpretation of mass spectra using searching of public chemical databases i.e. PubChem, LipidMaps, KEGG. Characterisation of an imaging PADI capability that radically improves spatial resolution from 1 mm to 10 μm using a novel microfabricated plasma source, developed in collaboration with an EPSRC-NPL funded post doc (Dr. Andrew Bowfield). Establish high-resolution (500 nm) AIMS capability at NPL exploring near-field laser desorption and other novel desorption ionisation mechanisms, suitable for biomolecules from tissues, skin and additives on manufacturing products. With industry collaboration ensure standardisation enables use of AIMS for solving complex industrial problems.

Impact and Benefits

At the end of this project, AIMS will be capable of (a) < 10 μm PADI spatial resolution (b) sensitivity and quantification for 1 ppb trace detection (c) sub-micrometre analysis (d) application to industrial problems in nanobiotechnology and high-value manufacturing (for personal care products such as hair products, laundry, cosmetics, and surface

treatments e.g. glass, packaging, food processing). More specifically, this work will impact three areas that have been highlighted as UK Government priorities through the provision of analytical methods that can rapidly analyse complex formulations and systems: life sciences and stratified medicine (through capability for ambient tissue imaging and diagnostics); food and agriculture (rapid in situ analysis of agrochemicals on plants); and advanced manufacturing (increased analytical capability for product development). From the health and biotechnology sector improvements in quantification and sensitivity will be beneficial for rapid point of care (POC) analysis of dried blood spots; enhanced speed for process analytical control; MS miniaturisation; enhanced drug metabolism/pharmacokinetics on tissues; and enable non-destructive, quantitative chemical imaging of irregular samples. Further, the establishment of high resolution AIMS will be a step towards intercellular MS imaging for biological applications.

Support for Programme Challenge, Roadmaps, Government Strategies

The NMS Strategy Document 2011-2015 highlights growth and innovation as a National challenge, emphasising the need to support priority sectors health and advanced manufacturing through 'strategic capability building' of underpinning science for the NMS to be internationally competitive. This project aims to deliver this through measurement science in UK world-leading areas in nanotechnologies, regenerative medicine and new production technologies. It aligns with the ChemBio Nanobiotechnology theme and roadmap through advances in mapping cells and POC devices to leading metrology for diagnostics and regenerative medicines, ultimately supporting regulation in nanomedicine and building a strong UK bioscience sector. This project also aligns with the ChemBio Surface Analysis theme and roadmap and improving analysis of biological tissue through AIMS to improve medical imaging and diagnostics, coinciding with key TSB challenges (Nanoscale Technologies Strategy 2009-2012) in diagnostics, imaging, and drug discovery and disease prevention. The European Technology Platform for Nanomedicine (Roadmaps in Nanomedicine Towards 2020) also highlights the need for improvements in imaging systems and the establishment of translatability of research into product development. Finally, this work will aligns with the biological nanometrology objectives outlined in Co-Nanomet's European Nanometrology 2020 report (2011).

Synergies with other projects / programmes

This project builds on developments in ChemBio projects NB4 "Reliable analysis of skin and tissue using DESI and ambient methods" and SA2 "Ambient and imaging mass spectrometry" which have established international recognition for NPL and the NMS. The proposal is also aligned to the recently won EMRP project "Metrology for the characterisation of biomolecular interfaces for diagnostic devices (HLT-04). Future work would look to move to nano-resolution (< 100 nm) ambient MS; application in the development of POC diagnostics and medical *in vivo* imaging.

Risks - Spatial resolution dependent on sensitivity – Mitigation: research to improve ionisation and collection efficiency in 1.
Large step changes needed to improve quantification - Mitigation: Basic fundamental understanding of techniques.

Knowledge Transfer and Exploitation - Dissemination will be through: 1) Peer-reviewed publications in high-impact journals, organisation of an IUVSTA workshop on ambient MS and oral presentations at international meetings. We will lead the Ambient Surface Mass Spectrometry session at British Mass Spectrometry Society and contribute to the leadership of imaging MS in the American Society for Mass Spectrometry. 2) Development of international ISO standards and CCQM SAWG. ISO TC 201 on surface chemical analysis has recently established a new study group on IMS. 3) A stakeholder workshop enabling industry to conduct trial experiments and provide a good practice guide for AIMS. Direct consultation and guidance to industry, government departments (NHS, FERA, DSTL, HO) and NMIs (KRISS, BAM) to enable establishment of their own analytical capability.

Co-funding and Collaborators -The project has strong stakeholder support from industrial partners (AZ, GSK, Novartis, Unilever, P&G, Dow, Syngenta, Croda, Pilkington, Johnson Matthey, BP, Perkin Elmer, Smith and Nephew, GE healthcare, Molecular Profiles) and instrument manufacturers (Thermo, Waters, Elforlight, KR analytical). The project will benefit from equipment loans and access to equipment otherwise unavailable in an NMI, and industrially relevant samples and materials (in-kind value ~£60k). Collaboration with internationally leading academic groups including Purdue, ETH-Zurich, University of Nottingham, University of Liverpool, Loughborough University, and Justus-Liebig University. Co-funding will be sought through TSB, EMRP and FP7 with the companies and academic groups identified above. As part of ChemBio project NB4, NPL already has an EPSRC co-funded (worth £225k) post-doctoral researcher to develop imaging PADI.

Deliverables

1	**Start: 01/07/12**	**End: 31/03/15**	
Fundamental metrology and quantification of ambient surface MS as evidenced by a good practice guide and 4 peer-reviewed publications			
2	**Start: 01/07/12**	**End: 01/03/14**	
Establish 10 μm resolution PADI imaging capability (iPADI) and 3 peer-reviewed publications			
3	**Start: 01/11/12**	**End: 31/03/15**	
Establish laser ablation imaging and innovative desorption/ ionisation to achieve nanoscale (500 nm) chemical images.			
4	**Start: 01/07/13**	**End: 31/03/15**	
Advance key application areas in ambient MS as evidenced by a stakeholder workshop			

Project No.	NMS/CBM12017	**Price to NMO**	£574k has come from CB/2012/NB12
Project Title	Co-funding for EMRP Project ind56 (Q-AIMDS) (Strategic capability programme)	**Co-funding won**	£358,350 from EMRP grant
Lead Scientist		**Stage Start Date**	01/04/13
Scientist Team		**Stage End Date**	31/03/16
		Est Final Stage End Date	
Sector	Health-Diagnosis; Advanced Manufacturing and Service – High-value manufacturing & bio-products	**Activity**	Development of Existing Capabilities; Methodology for New Capabilities

Summary

This European Metrology Research Project aims to bridge the gap between the established high vacuum surface analysis tools and the emerging ambient surface analytical tools in order to meet needs of the medical device industry for quality manufacturing, new product development and failure analysis.

The Need

State of the art and emerging medical devices feature surfaces that have been carefully engineered to enhance biocompatibility, encourage healthy tissue integration, and resist bacterial infection. Manufacture and certification of devices that employ these advanced biomaterials will require robust, traceable, reliable, and reproducible chemical metrology tools that are sensitive to surface layers, surface contaminants, defects and the 3-D distribution of chemical constituents in the near-surface region. Existing analytical tools are either poorly suited to a high throughput manufacturing environment or lack the required surface sensitivity, reproducibility, and spatial resolution. Improvements in chemical metrology are critical for development of new materials and for quality management of state of the art devices. Development of better surface analytical tools is now essential in order for the medical device industry to meet emerging regulatory requirements, ensure device safety and improve patient outcomes.

The Solution

Through the use of a synergistic suite of techniques, the consortium will bridge the gap between existing metrological tools and the needs of the medical device industry. The consortium will develop standard methods, protocols and materials, improve. We will improve the state of the art spatial resolution, depth resolution and sensitivity for both high vacuum and ambient surface analysis methods and we will adapt and validate these tools for ready application to production line medical devices.

Project Description (including summary of technical work)

The main objectives for Q-AIMDS objectives for NPL are to

- To assist in the development of well characterized, quantitative, traceable standards for relevant surface treatments and contaminants.
- To develop the underpinning metrology need to use 3D-SIMS analysis to study defects in thin films and at buried interfaces.
- To improve the spatial resolution for 3-D ToF-SIMS imaging of organic materials
- To enhance sensitivity and reproducibility for analysis of surface layers and contaminants using ambient mass spectrometry.
- To Improve both the lateral and in-depth spatial resolution for 3-D chemical state imaging with ambient mass spectrometry
- To develop statistics and informatics tools to improve the accurate identification of organic surface species including both contaminants and engineered surface components.

Impact and Benefits

The project will address the need for repeatable and reproducible analysis of device surfaces by generating protocols, producing standard platforms and validated methods suitable for total quality management and failure analysis of implanted medical devices. The medical device industry is of importance both economically and in terms of human wellbeing. The global market for medical devices is estimated to be greater than 200 billion € and is growing at 9 % annually. The outcomes of this JRP will support continued growth of EU medical device industry and help this EU industry remain competitive in an environment of increasingly stringent regulation.

This highly regulated industry has a direct impact on the health and well-being of an estimated 100 million people in the EU who have a permanent implanted medical device. Regulatory agencies are now requiring more thorough chemical surface characterisation of implantable medical devices and advances in metrology are essential for the

industry to meet these new regulatory requirements. The outcomes of this JRP will help facilitate the reliable manufacture of advanced biomaterials used in implanted medical devices, which will enable the industry to meet these emerging regulatory requirements and ultimately improve patient outcomes.

Support for Programme Challenge, Roadmaps, Government Strategies

The NMS Strategy Document 2011-2015 highlights growth and innovation as an overarching National challenge, emphasising the need to support priority sectors health and advanced manufacturing. This states the need for 'strategic capability building' of underpinning science for the NMS to be internationally competitive. This project aims to deliver this through measurement science in UK world-leading areas in nanotechnologies, regenerative medicine and new production technologies. It aligns with the ChemBio Nanobiotechnology theme and roadmap through advances in mapping cells and POC devices to leading metrology for diagnostics and regenerative medicines, ultimately supporting regulation in the medical device industry and building a strong UK bioscience sector. This project also aligns with the ChemBio Surface Analysis theme and roadmap and improving analysis of biological tissue through AIMS to improve medical imaging and diagnostics, coinciding with key TSB challenges (Nanoscale Technologies Strategy 2009-2012) in diagnostics, imaging, drug discovery and disease prevention. The European Technology Platform for Nanomedicine (Roadmaps in Nanomedicine Towards 2020) also highlights the need for improvements in imaging systems and the establishment of translatability of research into product development. Finally, this work will aligns with the biological nanometrology objectives outlined in Co-Nanomet's European Nanometrology 2020 report (2011).

Synergies with other projects / programmes

The projects builds on developments from SA1 and aligns closely with other surface and nano-analysis projects including NiCE-MSI, AIMS-HI, Scallops, and the EMRP projects Bio-Surf and TREND.

Risks

Model systems required for the study difficult to produce – Mitigation: several alternative systems will be considered.
Spatial resolution limited by sensitivity – Mitigation: research to improve ionization efficiency
Fragmentation, matrix effects and differential sputtering make complicate quanititative interpretation of results – Mitigation: Research into fundamentals of sputtering, fragmentation and ionization processes.

Knowledge Transfer and Exploitation

Dissemination will be through:

- Close collaboration with an advisory committee involving industrial, academic and government stakeholders.
- A project website including both a public section and a restricted collaborative working area for partners.
- Four peer-reviewed publications in high-impact journals and 2 press releases conferences.
- Four presentations at international conferences
- Organization of a special session on ambient surface characterization methods at Biointerfaces 2013.
- Contribution to international standards development throught ISO TC 201, BIPM CCQM SAWG and EN ISO 13485:2012
- A stakeholder training session on ambient mass spectrometry enabling industry to develop familiarity with best practices and conduct trial experiments. (This is a co-funding deliverable of CB/2012/NB12).

Co-funding and Collaborators

The project is a technical collaboration between the funded partners (BAM, INRIM, PTB NPL) and the unfunded partners (DFM, Medtronic and SMN) and Research Excellence Grants to LUH, UNOTT and WWU.

Deliverables

1	**Start: 01/04/13**	**End: 31/03/16**	

Deliverable title: Cofunding for EMRP Project - Chemical metrology tools to support the manufacture of advanced biomaterials in the medical device industry.

Project No.	CBM12019 (linked to P13 and M5)	**Price to NMO**	£ 100k (has come from CBm12012) £110k (has come from CBM13016))
Project Title	NanoReg	**Co-funding won**	£160k
Lead Scientist		**Stage Start Date**	01/05/13
Scientist Team		**Stage End Date**	31/04/16
		Est Final Stage End Date	
Sector	Underpinning metrology / Standards and Regulation	**Activity**	Development of Existing Capabilities; Methodology for New Capabilities

Summary

The aim of this F7 research project is for the advancement of regulatory risk assessment and testing, integral to develop infrastructure for regulation of nanoproducts. The project will develop high-throughput analysis tools to measure the dynamics of nanomaterial in biological/environmental relevant medium. This project is being partly delivered by the projects P13 and M5.

The Need

The links between research outputs and regulation is poor, with nanomaterial properties often measured at a single point in time, not taking into account the dynamical properties of nanomaterials as it enters the biological liquid medium. Even if the dynamics are taken into account, the methods proposed are often laborious and time consuming; this is very much the case for measurement of solubility and reactive oxygen species. The need to improve analysis speed and thus to make high-throughput measurement is clear.

The Solution

One strategy to speed up analysis time is through the concept of miniaturisation, which can be subsequently automated e.g. during liquid handling. Through miniaturisation methodologies, the amount of sample and reagent used will be reduced and subsequently increase analysis time. This is true in the case of microwell plate technology to the more sophisticated microTAS (microTotal Analysis Systems). The latter is a technology that has been introduced in the 1990s, involves a network of microchannels fabricated on a glass device is able to carry out several processes in a single instrument: handling, separation, reaction and detection.

Project Description (including summary of technical work)

In this project, we will:

a) Develop methods to measure the dynamics of dissolution by using CE(capillary electrophoresis)-conductivity microchip, a microTAS type device.

b) Develop methods for the measurement of ROS using microwell plate technology

c) For a) and b), we will conduct studies to progress towards method validation for sensitivity, linearity, etc. Reference materials as well as a large suite of well characterised commercial nanomaterials with a wide range of physico-chemical characteristics and properties, will be used for such a purpose.

Impact and Benefits

• The economic impact of nanotechnology has been estimated ~ $US 254 billion in 2009 and this has been forecasted to grow to ~ $US 2.5 trillion by 2015. One potential barrier in achieving this level of growth is the effect that regulation has on market barriers. The market will benefit from better clarity associated with the potential toxicity and reducing uncertainties to perform risk assessment on nanomaterial, so as to create: safer environments for workers, safer products and improve public perception on nanoproducts. This project, which develops better tools for measurement, will support this drive.

• Project resulted in NPL (~£60k) being outsourced by Leeds, developing PCA and QSARs methods

• Project is in synergy with: P13, MARINA and 3rd party work (ECHA). Project output to feed into ISO TC229, UK Task Froce 1 (the NRSG co-ordination group), Nanocluster (F7 research strategy).

Support for Programme Challenge, Roadmaps, Government Strategies

- Supports NMS Strategy 2011-2015: '*The NMS laboratories will lead the development of characterisation tools, methodologies and reference materials for Nanomaterials to facilitate their application and to underpin environmental health and safety research*' (Strategy for the National Measurement system: 2011-2015' and the UK nanotechnologies strategy (BIS, 2010).
- Aligns with the ChemBio Programme Nanobiotechnology and Particles themes and roadmaps by providing improved characterisation capability (high-throughput) for the measurement of dynamic properties of nanomaterial.
- Aligns with the requirements voiced by Defra's Nanotechnology Research Strategy Group – Task Force 1 for

better characterisation tools and reference materials.

- Co-Nanomet produced strategy document 'European Nanometrology 2020' that identifies the need for high-throughput methods. Also supported by "Nanocluster F7 research strategy 2020" (the report is still in draft stage)

Synergies with other projects / programmes

- Builds on output from previous projects: PROSPEcT and the goal of OECD's working party of manufactured nanoparticles (WPMN)programme, IRD microfluidics
- Builds on output from 3rd party work (ECHA, NanoClay, Leeds)
- Links with currently running nano-projects: F7 MARINA, NMO P13, EMRP NanoChop
- 2 x NERC Phd studentships with Birmingham and in the past Imperial College (1 NPL CASE award).

Risks

a) Baseline drift in CE-conductivity microchip has been reported. Mitigation: Investigate the source and develop protocols associated with pre-conditioning of microchannels to remove drift.
b) Unknown variability due to fabrication of the microchips. Mitigation: Investigate chip to chip variability.
c) Potential blockages within the microchip. Mitigation: filter solutions
d) Microwell evaporation. Mitigation: Investigate the rate of evaporation and how tight fitting lids can be incorporated to reduce this effect.

Knowledge Transfer and Exploitation

Dissemination will be through:

• Peer review publications, oral presentations in international conferences

• Participation in industry focused workshops, as organized by DEFRA and KTN Nano

• Networking with links to: EU networks (e.g. NaoSafety Cluster and Nanofutures, joint EU-US nanosafety research initiative) OECD WPMN programmes, CEN and ISO for standardisataion, UK's Task force 1, NIA.

• Book entitled Nanomaterial Characterisation: An Introduction, already in the pipeline through R. Tantra as editor and Wiley and Sons.

Co-funding and Collaborators

- Co-funding already in place (This project is being partly delivered by the projects P13 and M5.)
- £60k from University of Leeds for QSARS work.
- Project has a total of funded 59 partners; we are in close collaboration to ~10 partners with NIA leading the WP that we are involved in
- UK partners: DEFRA, KTN Nano, Leeds, HPA and IOM

Deliverables

1	**Start: 01/05/13**	**End: 31/08/15**	

Deliverable title: Develop methods for measurement of microchip CE-conductivity. Demonstrate the ability to determine the change in nanomaterial properties, as evidenced by peer review publications.

Project No.	CBM13016	**Price to NMO**	£107k (£110k removed to co-fund CBM12019)
Project Title	Nanotechnology Standardisation	**Co-funding target**	N/A
Lead Scientist		**Stage Start Date**	01/04/2013
Scientist Team		**Stage End Date**	31/03/2015
		Est Final Stage End Date	2017+
Sector	Underpinning metrology; standards and regulation	**Activity**	International obligations

Summary
This project will fund NPL's cross divisional leadership in UK, European, and International nanotechnology standardisation activities. The consists of i) leading and participation in activities to revise and write nanotechnology standards, ii) UK representation at nanotechnology standardisation meetings and iii) dissemination of the benefits of nanotechnology standardisation to UK stakeholders through targeted technical articles and presentations. The effort is cross-divisional and builds on the research and outputs of all NPL's NMS Programmes in the nanotechnologies field.

The Need
Standardisation in nanotechnologies is a prerequisite for the successful introduction of nanotechnologies across a vast range of industrial sectors. Here, standards in vocabulary, measurement and characterisation, environmental, health safety and environment and lifecycle assessment are essential. According to the NMS Strategy Document 2011-2015, "Nanotechnology will play a significant role in future product innovation and in tackling the national challenges." Further, the document states that "Standardisation is a vital component of business innovation, enabling the pull-through of products, services and processes into the market". The UK has led the development of nanotechnology standardisation since its inception across Europe and worldwide. This has been a major success, enabling the UK to have a leading influence on the successful development of these standards to the benefit of UK stakeholders.
It is vital that NPL continues to contribute to this process to progress the UK lead in this important area.

The Solution
The project will contribute to UK, EU and international standards development by: i) leading the development of standards; ii) commenting on draft standards; iii) representation at nanotechnology standards meetings; iv) building on NMS nanotechnology programmes work and using these outputs in contributing to new standards; v) disseminating the benefits of nanotechnology standardisation.

Project Description (including summary of technical work)
NPL will provide expertise and leadership in the following areas:

- Lead the project developing ISO DTS 8004-6 defining vocabulary for nano-object characterisation. This project is due for completion in 2013.
- Lead revision of ISO TC TS 27687 Vocabulary for Nano-objects, the first standard published within ISO TC 229 Nanotechnologies.
- Lead the development of an ISO new work item in terminology for nanofilms, nanocoatings and nanolayers.
- Membership of the UK nanotechnologies standards committee NTI/1 (held 3 times per year).
- Helping to develop the UK strategy for nanotechnology standardisation through participation in the strategy group for the UK BSI Nanotechnologies NTI/1/ committee.
- Provide UK head of delegation at meetings of the European CEN 352 Nanotechnologies Standardisation Committee.
- Provide liaison between ISO TC201 (surface chemical analysis) to ISO TC229 (Nantechnologies).
- Lead the UK delegation to the international ISO nanotechnology standardisation committee, ISO TC 229.
- In ISO TC229
    - Provide leadership in development of strategy for ISO TC 229 WG2 on measurement and characterisation.
    - Provide UK expert advice on vocabulary and terminology to ISO TC 229 WG1 on vocabulary and terminology.
    - Provide UK expert advice on measurement and characterisation to ISO TC 229 WG2 on measurement and characterisation.
    - Provide metrology support as a member of the metrology study group of ISO TC229.
- Participate in new projects concerned with the size measurement of nanoparticles.

Articles will be written for the technical press and presentations will be given at meetings promoting the benefits of nanotechnology standardisation to the UK nanotechnology industry.

Impact and Benefits

Strong representation on national and international standards bodies and committees and related activities will enable the expertise developed through the NMS Programmes to reach a wider audience of beneficiaries. Contributions to drafting international and national specification standards will enhance the UK NMS reputation and ensure international alignment. UK participation in nanotechnology standardisation will ensure that the UK has had a major impact on the worldwide nanotechnology community. The standards that are being developed are starting to have a major effect on the ability of the nanotechnology industry to manufacture cost-effectively and safely, with due recognition of the requirements for control of environmental impact.

Support for Programme Challenge, Roadmaps, Government Strategies

Nanotechnology has been identified by many Government reports and surveys as a key priority for the future of UK industry (Taylor Report, Royal Society, TSB, Nanotechnology KTN). This project aligns with the NMS Strategy Document 2011-2015, TSB's Nanoscale Technologies Strategy (2009-2012), BIS' Nanotechnologies Strategy report (2010) and the Co-Nanomet European Nanometrology 2020 report (2011) that all identify, as a priority, the need for further research to develop the required metrology infrastructure around nanotechnology standardisation and reference materials. This work aligns with the ChemBio Surface and Nanoanalysis, Nanobiotechnology and Particles roadmaps and also supports the safe, integrated and responsible approach as laid down in "Nanosciences and Nanotechnologies: An action plan for Europe". In Europe, EU Mandate M/461on "Standardization activities regarding nanotechnologies and nanomaterials" identifies four areas for standards development, including methodologies for nanomaterial characterisation.

Synergies with other projects / programmes

This project builds on the previous ChemBio project M5 and cuts across all NMS programmes where nanotechnologies are important. Inputs are received from across the NMS programme portfolio where nanotechnologies are of interest. This project complements the activities of the Pan-Programme KT, which is designed to disseminate the outputs from the programme to a wide community of end users.

Risks

Overall a low risk project. Loss of key members of staff is the major risk as staff with the correct experience and on the committees are difficult to replace immediately. Mitigation: multiple staff on the project.

Knowledge Transfer and Exploitation

The entire project is about the transfer of knowledge and expertise into nanotechnology standards. Thus, the main output from the project is the development of national and international standards that will be widely adopted by a wide range of industry sectors. There will also be specific technical articles published on the benefits of nanotechnology standardisation.

Co-funding and Collaborators

Co-funding will come via a number of EU FP7 NMP projects which require standardisation input including Nano-define (75% chance of £75k for standards work), Nano-Reg (won, standardisation input in negotiation) and No-Tox (25% chance of £40k for standards).
In terms of collaborators, the very nature of the work involves collaboration with many organisations and firms.
In the UK collaborators include: GSK, Nanosight, Institute of occupational medicine, Nanotechnology KTN.
In Europe collaborators include: BAM, LNE, JRC-IRMM, Nanotechnologies Industries Association, BASF.
International collaborators include: PTB, AIST, NIST, NPL India and representatives from the more than 40 national standards bodies that are members of the international committees.

Deliverables

1	**Start: 01/04/13**	**End: 31/03/15**	

Representation at UK, European and International Nanotechnology Standardisation Meetings and Projects

- Participation in UK, European (CEN) and international (ISO) nanotechnology standardisation meetings
- Leadership of and Participation in specific projects defining new and revised nanotechnology standards
- Dissemination of the benefits of nanotechnology standardisation to UK stakeholders

Project No.	NMS/CBM13011	**Price to NMO**	£300k
Project Title	Nanoanalysis Maintenance (SA5)	**Co-funding target**	N/A
Lead Scientist		**Stage Start Date**	01-Apr-13
Scientist Team		**Stage End Date**	31-Mar-16
		Est Final Stage End Date	
Sector	Underpinning Metrology	**Activity**	Maintenance of Capabilities

Summary

NPL is a leading NMI for surface chemical analysis and is leading the development of metrology and international standardization in areas which are a UK focus. To be at the forefront of metrology and to ensure the robustness and longevity of standards requires the complex equipment to be correctly calibrated and carefully maintained. This project will maintain core NMS Surface and Nanoanalysis capability, enabling measurement of the chemical properties of surfaces at micro and nanoscales and of nanoparticles. This is key to understanding and problem solving of surface issues in many sectors and industries. A suite of instruments ranging in value is necessary to be calibrated and maintained and training provided for users. This will allow the on-going industrial and academic collaborations that result in high profile publications and national and international liaisons as well as a growing measurement service for UK customers.

The Need

Surface analysis techniques at scales of microns and nanometres are key to understanding and characterising surfaces used in high technology and innovative industries worldwide. Current expertise is based upon the underpinning scientific research the Surface and Nanoanalysis Group performs in the fields of innovation, trade, industrial competitiveness and quality of life, making this emerging research area accessible for real-world applications. Solutions can be made to a wide range of problems in areas such as aerospace, chemicals, pharmaceuticals, health, personal care, packaging, electronics, IT equipment, polymers, sensors, transport, biofilms and nanoparticles using the latest instrumentation.

The Solution

Provision of the maintenance of a complementary suite of instruments to provide current surface molecular and elemental analytical capability along with emerging optical and nanoparticle measurement techniques to aid surface characterisation. This will allow the necessary metrology for mass spectrometries and electron spectroscopies for surface and interface analysis, analytical nanoprobes, biosurfaces, nanomaterials in the enviromnment, standardisation and traceability.

Project Description (including summary of technical work)

Maintenance involves calibration according to ISO 23830, ISO/DIS 17862, ISO 13084, ISO 15472, ISO 21270 and ISO 24237, monitoring of contamination, updating control charts and equipment maintenance as necessary, updating procedures and software, training, trouble shooting and servicing of high value instruments and systems (SIMS, XPS, Orbitrap, AFMs, evaporator, TERS system, ellipsometer, and more common laboratory equipment such as optical microscopes, a centrifuge, a spin coater, analytical balance and glove boxes.

Impact and Benefits

This project will allow all other projects from across NPL involving surface analysis and nanoparticle measurement to take place. It will also allow a continued and increased provision of surface and nanoanalysis measurement services to industry, nanoparticle characterisation measurement services, reference materials, software, standards and guides and reference data.

Support for Programme Challenge, Roadmaps, Government Strategies

Economic growth is the principal theme of Government strategy and at the heart of this is innovation and high value manufacturing such as the pharmaceutical sector and the emerging plastic electronics sector. The chemistry at surfaces and interfaces is central to the correct operation and functionality of these products. NPL has established an elite centre of excellence in surface chemical analysis which works in partnership with important UK businesses (for example, GSK, Unilever, P&G, Smith & Nephew, plastic electronic companies, Croda and Syngenta) to support

innovation. The value and potential of standardization to the innovation ecosystem is being recognized ["Concept to commercialisation: A strategy for business innovation, 2011-2015". NPL is an international leader in the development of the measurement standards infrastructure for surface chemical analysis, ensuring that international documentary standards are based on robust science and address UK priorities ["The NMS strategy document, 2011-2015"]. This requires excellent scientists who are international leaders combined with state-of-the-art instruments which are correctly calibrated and well-maintained.

Synergies with other projects / programmes

Projects within the Surface and Nanoanalysis Group and their follow-ons: ChemBio SA1, SA2, SA3, SA4, M5 P13;TSB SET, Detergents; FP7 MARINA; IRD INTERACt, Microfluidics; Third party Measurement Services, NanoMaPPP; EMRP Biosurf, SurfChem, TReND, Raman; SR-NiCE-MSI, XPS of Nanoparticles.
Other projects that are owned by other groups and divisions include Graphene, EMRP NanoChop, IRD immobilization, TSB SCALLOPS, SECM/SICM.

Risks

Risks are low. However, if instruments are not correctly calibrated and maintained the risks to the robustness of the measurement infrastructure are high.
Suppliers may not deliver servicing or spare parts on time, mitigated by having service contracts for key instruments.

Knowledge Transfer and Exploitation

Analysis for all other associated projects above, which includes a measurement service for customers outside NPL. Collaborators in standards work, TSB, FP7 and EMRP projects are indirect customers. These include industrial, academic and NMI partners.

Co-funding and Collaborators

Co funding is encouraged by working jointly with instrument suppliers but suppliers are more likely to be collaborators or provide in-kind funding by lending items. For basic maintenance, this is still an unlikely prospect. Strong collaborations with UK and international businesses including Unilever, GSK, AZ, Croda, Syngenta, Smith & Nephew, BP, plastic electronics companies, Dow Corning, Medtronic, 3M, Molecular Profiles, Kratos, Ionoptika, Thermo, Samsung, Shimadsu, Du Pont, GE Healthcare and leading academic groups at Universities of Oxford, Imperial Nottingham, Birmingham, KCL, Bath, UCL, Liverpool and internationally at Purdue, Washington, Kyoto, Seiki, Tsingua, and University Catholique Louvain.

Deliverables

1	**Start: 01/04/13**	**End: 31/03/16**	
Deliverable title: Maintenance of SIMS			
	Start: 01/04/13	**End: 31/03/16**	
Deliverable title: Maintenance of XPS			
	Start: 01/04/13	**End: 31/03/16**	
Deliverable title: Maintenance of Orbitrap			
	Start: 01/04/13	**End: 31/03/16**	
Deliverable title: Maintenance of TERS			
	Start: 01/04/13	**End: 31/03/16**	
Deliverable title: Maintenance of AFMs			
	Start: 01/04/13	**End: 31/03/16**	
Deliverable title: Maintenance of Evaporators, QCM etc.			

Project No.	CB/2011/BA30	**Price to NMO**	£685k
Project Title	Live cell imaging beyond the diffraction limit	**Co-funding target**	
Lead Scientist		**Stage Start Date**	April 2011
Scientist Team		**Stage End Date**	March 2013
		Est Final Stage End Date	March 2016
Sector	Health - Drugs and Therapies	**Activity**	Methodology for new capabilities

Summary - Development of a super-resolution microscopy technique that will enable the elucidation of molecular-level events and interactions that control and give rise to diseases such as Alzheimer's. This project will help biomedical scientists in industry and research labs by validating and providing access to the latest instrumental techniques and supporting expertise. Importantly, the instrument will be able to image live versus fixed cells; its development will leverage existing NPL capability in super-resolution and single molecule imaging and the project will utilise the expertise in biophotonics from the NMS Physical Programme.

The Need - Conventional fluorescence microscopy approaches can provide detailed information about the location and organisation of specific molecules within cells, but they are limited in resolution by diffraction to >250 nm. Electron microscopies can provide very high resolution, but only in highly processed samples without the same ability to label specific proteins. In recent years there has been a surfeit of new techniques proposed for overcoming diffraction, which limits the resolution of widely used techniques such as laser scanning confocal microscopy. While these new microscopy approaches have enormous potential to advance molecular biology in the UK, the equipment is only just becoming commercially available, the methods used to generate the images are poorly understood and they often impose restrictions on samples, limiting their applications. We have developed a dSTORM (direct Stochastic Optical Reconstruction Microscopy) imaging capability, which can provide 10 nm to 20 nm resolution in fixed cells. However to fully understand biological processes it is necessary to image living cells. With structured illumination microscopy (SIM), we will be able to image living mammalian cells at resolutions of 50 nm to 100 nm in near real-time. Several instrument manufacturers—e.g. Nikon, Leica Microsystems and Carl Zeiss—are beginning to commercialise super-resolution imaging techniques. However, the technology remains nascent and there are real questions around understanding the accuracy of the images and determining the true resolutions obtainable by the different techniques.

The Solution - We will construct an instrument for structured illumination microscopy, which will enable sub-diffraction resolution (50-100 nm) in living cells. This method uses sinusoidal linear illumination patterns to shift information from undetectable spatial frequencies into the detectable range. Acquisition of a small number of images, (typically 7) each with a different phase or orientation of the illumination pattern, allows a super-resolution image to be mathematically constructed in near real-time, permitting living cells to be imaged, and the evolution of structures and processes to be followed in time. However this requires the rapid switching of illumination patterns which can only be achieved with spatial light modulators (SLMs) and ferroelectric liquid crystal retarders. By exploiting non-linearity's in fluorescence, higher spatial frequencies can be obtained, yielding resolutions up to ~50 nm. Drawing comparisons with fixed cell approaches this project will examine the advantages and limitations of a new live-cell imaging approach called structured illumination microscopy (SIM) and will disseminate the knowledge and solutions developed, including standards, to potential users and commercial developers of instrumentation. Through this effort we will strengthen NMS capability in the area of super-resolution microscopy of cells and provide the underpinning metrology required to validate the resolution and performance of the techniques. We will exploit this capability to expand our work on neurodegenerative diseases and collaborate with others to apply the methodology to other biomedical problems.

Project Description - The project will include the sourcing of components; assembly and testing of the hardware; software development and testing of the capabilities of the system by imaging standard samples and living human cells. This project has been divided into the following work packages:

1.1 Design and component selection: A preliminary design for the system will be developed and components sourced.
2.1 Assembly of system: Basic mechanical assembly, optical alignment and electronics connection of components.
2.2 Acquisition software development: Development or adaptation of control software, e.g. for SLM's
3.1 Testing of system: Validation of system and component performance and fine-tuning.
3.2 Analysis Software Development: Production of code to take SIM frames and reconstruct super-resolution images.
4.1 Preliminary Cell Imaging: Demonstration of the performance of the system on living and fixed cells using model cells to validate the super-resolution capability and compare with the dSTORM technique. Cell imaging of fixed cells visualising proteins involved in neurodegenerative diseases e.g. alpha-synuclein or beta amyloid.

Impact and Benefits

The availability of reliable, accurate super-resolution microscopy will have a significant impact on UK quality of life through improvements in the understanding of cellular processes, especially in neurodegenerative diseases. In

addition, targets for drugs and other therapeutic interventions will be identified more rapidly and their effects on cells will be understood more completely. In contrast to the dSTORM capability currently under development at NPL, the ability to image living cells will enable more rapid and dynamic processes to be investigated. Together with the Kaminski lab at the University of Cambridge we are already investigating the mechanisms of pathogenesis in Parkinson's disease, where at least two different disease processes (α-synuclein aggregation and Parkin-mediated mitophagy) and where super-resolution imaging could improve understanding. Through collaboration, we will be able to directly facilitate research in this area. A multi-technique capability will enable an understanding of the image formation process in each technique; its reliability, pitfalls, and accurate assessment of the true resolution achieved. This will enable the NMS to support instrument manufacturers and end-users and the microscopy community in the UK and Europe. This could take the form of direct collaborations, publications or standards development.

Support for Programme Challenge, Roadmaps, Government Strategies - Aligned with the TSB priority "Aging population" due to the relevance to neurodegenerative diseases. Responds to the European regulatory initiative REACH, which aims to minimise chemical tests on animals and imposes a need for better tools to carry out in vitro (cellular) tests. Strongly aligned with EMRP 2011 Health Call topic: "Improved measurement and imaging at the molecular and cellular level to support innovation in pharmaceuticals, regenerative medicine and targeted drug delivery strategy". Aligned with ChemBio theme roadmaps, specifically: Cells and tissues: cell imaging, microscopy; real-time imaging; single molecule/cell characterisation. Nanobiotechnology: Single Molecule measurement; labelling of biomolecules; imaging.

Synergies with other projects / programmes - This project brings together skills and experience from a wide range of projects, including previous ChemBio projects in single molecule imaging; ChemBio project BA21 and an NPL-EPSRC Postdoctoral Fellowship on super-resolution imaging; work from the Physical programme on adaptive optics and wave front modelling in microscopy and corresponding expertise in the use of SLM.

Risks - Late delivery or failure of key components. Ample time has been allowed for components to be delivered. Component failure could be a challenge but we will work with the manufacturers to find solutions or utilise alternative components.

Knowledge Transfer and Exploitation - Publication of scientific in the Biophysics, Optics and Neurobiology areas. Dissemination through appropriate KTN events (ESP, Biosciences and Nanotechnology KTNs) and to other NMIs through EMRP activities and presentations at the CCQM Bioanalysis Working Group. Presentations at international conferences such as MAF (Methods and Applications in Fluorescence); US Biophysical Society; RMS MICROSCIENCE or European Microscopy Congress 2012. Dissemination of the new NMS super-resolution capability through the preceding fora, NPL website and other networking media, leading to further collaborations. Future work could feed into ISO and other standardisation bodies.

Co-funding and Collaborators Submission to the EMRP Health call, with strong support from potential collaborators including PTB and INRIM. We are already collaborating with UK academics, (University of Cambridge, joint EPSRC postdoc), (University of Strathclyde) and (KCL) with the possibility of joint studentships. Other UK academics have expressed interest in collaborating with us on the application of super-resolution microscopy to their biological systems, including the Medical Research Council. Additionally, we will look to represent the UK at the European level through attendance at meetings, e.g. of the European Light Microscopy Initiative (ELMI), which brings together scientists working in the fields of light microscopy and manufacturers of equipment such as Leica and Nikon.

Deliverables

1	**Start: 01/04/11**	**End: 31/06/11**	
Design of system and sourcing of components: Outline optical design and parts list. Key components to be sourced include microscope frame and objective, laser, spatial light modulators and drivers, ferroelectric liquid crystal retarders, and camera.			
2	**Start: 01/07/11**	**End: 31/09/11**	
System build: As components arrive they will be integrated into the system and the control and data acquisition software will be developed, building on our existing code base.			
3	**Start: 01/10/11**	**End: 30/09/12**	
Development and testing: Preliminary testing and imaging will be carried out. Test images will be used in the development of the data analysis software, which will be needed to reconstruct the super-resolution images. Preliminary evaluation of resolution.			
4	**Start: 01/02/12**	**End: 31/03/13**	
Application to cellular imaging: The first imaging of living cells will be done. The results will be used to fine-tune system performance. Also fixed cells will be imaged and the results compared with the dSTORM platform.			
5	**Start: 01/04/11**	**End: 31/03/13**	
Measurement of tissue optical properties: To complete work begin under the Physical programme. Collection of a database of *ex situ* tissue optical characteristics using OCT and goniometry. Statistical analysis to correlate with histopathology and create a predictive model for optical diagnosis. Investigate application to OCT endoscopy for use *in vivo*.			

Project No.	CB/2011/CF16	**Price to NMO**	£170k
Project Title	Conformation-targeting nanoprobes for in-serum diagnostics of Alzheimer's dementias	**Co-funding target**	£130k already won from TSB
Lead Scientist		**Stage Start Date**	01/10/2011
Scientist Team		**Stage End Date**	30/09/2014
		Est Final Stage End Date	2016+
Sector	Health: Diagnosis	**Activity**	Methodology for new capabilities

Summary
This project comprises NPL's contribution to a TSB-funded project that aims to establish a measurement capability for the differential diagnosis of toxic soluble precursors of senile plaques in serum. Such a capability is a major goal in the diagnosis of Alzheimer's disease with a significant impact anticipated for the UK and global public health.

The Need - An ageing population is leading to an increased prevalence of age-related diseases such as neurodegenerative disorders e.g. Alzheimer's, which are anticipated to become the second most significant healthcare issue by 2040, thus leading to an impaired quality of life and profound social and economic burdens. The early diagnosis of such neurodegenerative diseases is *the* bottleneck for the development of anti-neurodegenerative therapies on a patient-group-stratified basis. Indeed, currently, there is a lack of cost-effective measurements to enable early diagnoses and therapy control necessary for implementing preventive or curative measures. Research into both the early recognition and efficacious treatment of these disorders requires objectively measurable parameters to enable neurological and psychiatric clinicians to develop strategies for prevention and cure. The most reliable diagnosis of Alzheimer's dementias (AD) is the post-mortem analysis of ex-vivo brain specimens of insoluble senile plaques or amyloid fibrils. Biomarker-based measurements able to differentiate these debilitating forms at the earliest possible stage are needed to mitigate AD symptoms, prolong autonomous living and reduce the public health burden.

The Solution - Brain lesions result from a developmental chain of peptide monomers over soluble oligomers to fibrillar structures, and comprise short peptide fragments collectively known as amyloid-β peptide (Aβ) that are produced by proteolysis of a large amyloid precursor protein. Soluble, diffusible ligands of Aβ accumulate early in the brain and perturb normal synaptic function, thereby causing memory deficits. It is these ligands that are the most crucial biomarkers responsible for the pathology of AD. Therefore, differential assays with the ability to detect and measure these pathogenic forms should be performed in serum to make clinical use affordable. This project will provide a measurement platform based on the folding-responsive detection of early-stage amyloid precursors to underpin solutions for the diagnosis of AD in blood samples. The project will see the development of rapid and cost-effective serum bioassays for direct detection and correlative measurement of toxic Aβ. This will be done using specifically engineered nanoscale probes functionalised with strong Aβ binders that target soluble Aβ ligands. The binders act as molecular baits to enable the selective trapping of Aβ in toxic conformations. This format allows for the validation of differential specificity of the nanoprobes towards diffusible ligands in clinical samples through the selection of molecular baits by a multitechnique approach combining mass-spectrometry, biophysical and biochemical methods.

Project Description (including summary of technical work)
The project makes use of low molecular weight amyloid breakers developed by Senexis Ltd. and conformational sensors developed in house. These molecular modalities exhibit differentially selective and exceptionally high affinity profiles to soluble oligomers and are to be used as molecular baits to recognize and capture the amyloid precursors in serum (first spiked and then clinical samples). Metal nanoparticle-amplified baits, nanoprobes, will be used. The main strategy is the direct capture of soluble Aβ ligands from serum by the nanoprobes and their subsequent on-probe detection and comparative measurement using MALDI. The nanoprobes only harvest Aβ precursors and at concentrations, which are well below those of most abundant serum components, to give the unambiguous assignment of obtained data with analyte signals, which are further enhanced by physicochemical properties of metal nanoparticles. In parallel, the measurements will provide crucial information on conformational preferences of the captured oligomers, which is necessary for nanoprobe optimisation and the development of diagnostic tests for conformational diseases. The reproducibility and subsequent standardisation of the measurements is ensured by eliminating extensive sample processing from the analysis thus offering advantages over other methods such as 1) increased analysis speed, 2) ability to discriminate between different Aβ at different stages of amyloidogenesis, and 3) the avoidance of complications in analysis due to interference from high abundant components. Importantly, nanoprobes can be tailored rationally as defined by binding assays thereby excluding the limitations of the current AD tests.

Impact and Benefits
Today, neurodegenerative amyloid-related diseases affect over 50 million people in the developed world alone and the prevalence of all ageing-related diseases is likely to double by 2020. Furthermore, 1% of the world's population lives with dementia with overall associated costs exceeding 1% of global GDP on 2010 at £390 billion. As a result, the market for AD diagnostics and treatment is expected to grow exponentially with a compound annual growth rate

of 5-10%. This work will aid companies' developing diagnostics and therapeutics for neurodegenrative diseases where reliable and cost-effective biochemical assays are lacking. For example, the development and improvement of the nanoprobes will involve high throughput screening methods and identification of interferences. The general methods to do this will be useful to the wide community of analysts in research labs. Further, this work will also enable major advances in other measurement capabilities (MR imaging and spectroscopy) by drawing interrelations between early stages (amyloid ligands) with late stages (brain lesions) and their correlation with disease phenotype and severity, which will eventually provide a comprehensive and more accurate description of AD at the molecule-tissue level.

Support for Programme Challenge, Roadmaps, Government Strategies

The project supports the National Dementia Strategy (Living with Dementia, Department of Health, 2009), with particular relevance to objectives "Good-quality early diagnosis and intervention for all" and "Good-quality information for those with diagnosed dementia and their carers". Also aligns with Technology Strategy Board in developing nanotechnology capabilities to address major healthcare challenges of living with ageing and growing population within the Technology-inspired collaborative research and development themes. The project aligns with the ChemBio Bioanalysis and Nanobiotechnology themes and roadmaps. For example, protein structure and identity to aid early diagnosis, immobilisation on surfaces and mass spectrometry.

Synergies with other projects / programmes

The proposal links directly to current ChemBio projects BA19 and BA22, which aim to understand and measure protein misfolding and specifically its implications in neurodegenerative diseases (Alzheimer's dementias). These projects look to understand and develop new measurements of protein misfolding at sub-cellular levels (BA22) and nanoparticle-assisted detection of protein biomarkers in biological fluids (BA19). Thus, this project builds upon the current research and provides a clear application focus for nanotechnology-assisted diagnosis of diseases.

Risks

(i) The desired sensitivity cannot be achieved: conformational biomarkers act at the autonomous folding level, which in AD case is amplified by oligomerisation. Therefore, in-serum AD tests are not limited to the sensitivity of immunoassays, and are seen as those of ultimate sensitivity. (ii) Bait supply from project partner is delayed: partner baits are β-sheet peptide breakers that can be made in house (technology is known) as well as purchased from alternative sources.

Knowledge Transfer and Exploitation

The outputs of this work will be disseminated in peer-reviewed and trade journals and at trade and scientific forums. KTNs such as the Sensors and Instrumentation and Healthcare Technologies KTNs will be employed to broaden our access to the industrial community. Findings will also be fed back to contacts at Alzheimer's Research Trust and Cure Parkinson's Society. Further, the results of the work will be made available to the project partners outlined in ChemBio projects BA19 and BA22.

Co-funding and Collaborators

The project forms part of a TSB collaborative R&D grant (worth £130k) with Senexis Ltd. (a Cambridge-based SME specialising in anti-AD agents). Other collaborators involved in this project are clinicians form SW London and Cambridge NHS hospitals.

Deliverables

1	**Start: 01/10/11**	**End: 30/06/12**	

Deliverable title: **Benchmark Aβ-nanoprobe measurement platform**

Measurement platforms using Aβ-based nanoprobes to establish detection limits (sensitivity and selectivity) and binding kinetics of diffusible oligomers in spiked plasma, aiming at nanomolar sensitivities with uncertainties <10%.

2	**Start: 01/07/12**	**End: 30/06/13**	

Deliverable title: Conformational bait selection and monoplex assays

Engineered bait candidates will be identified and tested. Best bait-based nanoprobes will be selected against the established benchmark platform for the detection of one diffusible ligand followed up by optimisation studies.

3	**Start: 01/07/13**	**End: 30/04/14**	

Deliverable title: Multi-modal nanoprobe assays

Multiple nanoprobes with different baits and nanoprobes with multiple baits will be assessed for compatibility with the monoplex platform to allow the detection of ligands and their relative ratios at given time points during amyloidogenesis. This phase will look into an optimal means to measure aggregation kinetics and increases in Aβ oligomers.

4	**Start: 01/07/13**	**End: 30/09/14**	

Deliverable title: Nanoprobe assays in clinical samples

The scoring of the fittest nanoprobe for the measurement platform (monoplex and possibly multi-modal formats) using clinical samples. The phase is expected to commence in parallel with phase 3, to ensure the timely validation of the platform.

Project No.	NMS/CBM/12009	**Price to NMO**	£283k
Project Title	CF4 Chemical and Optical Characterization of Nanomaterials in Biological Media (EMRP NEW03)	**Co-funding target**	£184k from EMRP
Lead Scientist		**Stage Start Date**	June 2012
Scientist Team		**Stage End Date**	May 2015
		Est Final Stage End Date	May 2015
Sector	New technology / nanotoxicology	**Activity**	Nanomaterials characterization

Summary: The project will provide guides, standards and protocols for the detection and chemical and optical characterization of nanomaterials in biological media such as serum and blood. This forms part of a €2.4M European project led by LGC.

The Need: Nanotechnologies, as an enabling technology, are increasingly being used to overcome scientific, commercial and industrial challenges through the engineering of application-specific nanoscale materials. This has led to nanotechnologies being incorporated into over 1300 commercial products with a global market currently worth €9.6 billion and expected to reach €16.6 billion by 2015. As the impact of nanotechnologies on human life becomes more prevalent it is becoming increasingly important to be able to characterise nanomaterials for their potential effects on human health. To achieve this, the characterisation techniques must go beyond the current methods for measuring physical properties such as size, charge and shape to allow characterisation in appropriate biological milieu. This is critical as the physical and chemical properties of nanomaterials frequently change in biological systems, altering their functional properties. To date metrology has largely been focused on the development of methods to characterise nanomaterials for their physical properties in their native monodispersed powder forms or in idealised simple matrices. For example in the recent iMERA-Plus project T3.J1.1 'Traceable characterization of nanoparticles'. As a consequence the ability to measure changes in nanomaterial physico-chemical and optical properties when they are poly-dispersed in the more complex biological matrices that they naturally encounter is severely lacking. This limits understanding of the functional properties of nanomaterials as well as their potential for harmful interactions with biological systems. Overcoming this requires the development of quantitative measurements traceable to appropriate reference systems which can be applied to a range of biological matrices of differing complexity.

The Solution: The proposed project will develop and validate methodologies for the physical, chemical and optical characterisation of nanomaterials in biological matrices. Emphasis will be placed on physico-chemical measurement techniques which can be used for multiplexed characterisation, while optical measurement will address the needs of the nanobiotechnology industry. The project will join the expertise of European institutions LGS, NPL, PTB, BAM and JRP-IRMM and provide comparability and, where possible, a traceability chain for the measurement of NP physico-chemical and optical properties in complex biological matrices. For metal oxide NP these measurements include size distribution, shape, surface area, concentration, size-based elemental composition, surface and bulk chemistry. For fluorescent NPs traceable measurements will also be established for determination of absolute quantum yield. These parameters will be determined using highly accurate methods available to NMIs and the link to commonly employed methods will be established. Characterised materials will be generated along with handling and dispersion protocols in conjunction with stakeholder requirement to enable comparable measurements to be performed in the laboratories of the different participating NMI's.

Project Description (including summary of technical work): The EMRP project related to this project addresses six specific scientific objectives, which will be met in 5 technical work packages as follows: (1) Select reference nanomaterials for the chemical and biological characterisation. (2) Select available and appropriate cell based models for biological characterisation. *These two objectives will be addressed in WP1 which will deal with the selection of the nanomaterials and cell models to be used in the project as well as the baseline characterisation work to ensure measurement comparability between the NMI's.*

(3) Validate physical measurement techniques for characterising nanomaterials based on properties such as size, charge, agglomeration state and concentration in biological systems. *This objective will be addressed in WP2 which will validate the use of physical and chemical measurement techniques in a serum based biological system.*

(4) Develop a method for simultaneous characterisation of size, shape and chemical composition of nanomaterials in biological systems and in dispersions. *This objective will be addressed in WP4. Based on the outputs of WP2, this work package will combine physical and chemical analysis methods to allow simultaneous characterisation.*

(5) Develop methods for characterisation of fluorescent nanoparticles. *This objective will be addressed in WP3 which will develop traceable methods for measuring the fluorescent properties of nanoparticles such as quantum dots.*

(6) Develop measurement techniques for biotechnology using fluorescent nanoparticles. *This objective will be addressed in WP5 which will investigate the measurement issues faced by developers of fluorescent nanoparticle based diagnostic platforms.*

NPL will participate to WP1 and 2 and will lead WP5.

Impact and Benefits: Direct impact will result from the establishment of new measurement capability within the NMIs themselves. The methodology proposed in this project will enable NMIs to perform traceable and accurate

measurement of the physico-chemical and optical properties of nanomaterials in biological matrices. The academic and industrial stakeholders will work with the NMIs to support and validate the reference measurement procedures developed during the lifetime of the project and demonstrate utility for assessing/validating end-user assays. Outside of the immediate consortium, wider target beneficiaries for the project will be: nanobiotechnology and nanomedicine organisations, who will benefit from standard materials and validated protocols with which to perform their analyses; regulatory and legislative bodies who will be able to make decisions and recommendations based upon coherent and comparable data; manufacturers of nanomaterials who will benefit from a standards and regulatory framework that is fit for purpose and does not impose unmerited restrictions.

Support for Programme Challenge, Roadmaps, Government Strategies: The NMS recognises the impact Nanotechnology has in product innovation and encourage the development of metrology to underpin related EH&S research [NMS Strategy Programme 2011-2015]. This project supports the "Early and reliable diagnostics" target of the ChemBio "proteins" roadmap, underpinned by the technologies "immunochemical detection" and the deliverables "clinical standards" "early diagnosis" and "functional healthcare biomarkers". The development of improved uncertainties for fluorescent and point-of-care immunoassays supports the traceability requirements of the EU's IVD directive. The development of new diagnostic tools has been supported by a number of recent TSB calls. The need for improving metrology for characterising nanoparticles in biological media has been recently highlighted by a number of reports such as the 2009 IOM's CELL-PEN report and 2009 DEFRA's EMERGNANO report. Furthermore, the project will lease with a number of UK commercial partners, thus supporting their development.

Synergies with other projects / programmes: This project will enable capabilities for measuring nanomaterials properties in complex matrixes. Properties will include size, size distribution and core-shell characterization (e.g. surface functionalization, protein corona, etc.). The project will have direct impact on IRD project INTERACt and EMRP JRP h06. This project will also build on work done previously on fluorescent nanoparticle based diagnostics under the Regenitherix and Mologic TSB projects (co-funded by ChemBio and IRD projects) and on the uncertainties of ELISA assays, most recently under the ChemBio project BA24 which is supporting the CCQM pilot study on ELISA, P58.1. It will have synergy with other nanoparticle based diagnostic work in the future, specifically the recently won NIHR project on fluorescence based lateral flow assays.

Risks: (1) Aggregation or dissolution of particles resulting in poor comparability between techniques, repeatability and reproducibility (Medium). The effect of dispersion protocols on the aggregation state of particles will be investigated and a selected protocol will be used across the project for comparison purposes. A preliminary study of particle dissolution rates will be undertaken to assess the potential impact of this risk. Where dissolution is demonstrated samples will be prepared and analysed within a restricted time frame. (2) Inability to distinguish particle aggregation from the association of particles with components in the biological medium (High). By correlating results from different techniques it may be possible to distinguish these effects through, for example, a change in the mean particle density. Extraction of the particles by FFF followed by ICPMS may provide insight into the fraction of components associated with particles. (3) Chosen antibodies are incompatible or unstable in the selected assay format (Medium). Antibody pairs which are known to be compatible in other assays will be selected. Early testing will reveal any major problems.

Knowledge Transfer and Exploitation: Training, dissemination and exploitation activities will include:
(1) a workshop focussing upon the metrology of the characterisation of nanomaterials in biological systems co-ordinated by LGC, to be run in the final year; (2) draft of at least two standards to be proposed to the relevant standards bodies; (3) dissemination of results through peer-reviewed publications and presentations to international conferences; (4) publication of press releases and case studies as well as specifically targeted "non-specialist" articles to inform the wider scientific community and lay readers; (5) secondment opportunities to reinforce collaborations; (6) formation of a stakeholder group which will disseminate the project output to the target stakeholder community.

Co-funding and Collaborators: Co-funding is from EMRP: Funded partners are LGC, NPL, PTB, BAM and IRMM. Associated postdoc positions are expected at PTB. Collaborators include: NanoSight Ltd, Izon Science Ltd, Postnova Ltd, NanoCo Ltd, Diagnostik Net-BB, the University of Birmingham, Nanotechnologies Knowledge Transfer network and Helmholtz-Zentrum Berlin. Stakeholder supporters also include: MoLogic Ltd, Neotherix Ltd, Argento Diagnostics, the Nanotechnology Industry Association (NIA), UK Health and safety laboratory (HSL) and Institute for Occupational Medicine (IOM).

Deliverables

1	**Start: 01/06/12**	**End: 31/05/15**	

Deliverable title: Cofunding for EMRP project "Cofunding for chemical and optical characterisation of nanomaterials in biological systems (EMRP NEW03)"

Project No.	CBM13001	**Price to NMO**	£270k
Project Title	BA 36: Facilities for biotechnology measurements	**Co-funding target**	£60k
Lead Scientist		**Stage Start Date**	01/04/2013
Scientist Team		**Stage End Date**	31/03/2016
		Est Final Stage End Date	
Sector	7. Underpinning metrology	**Activity**	Provision of Standards & Maintenance of Capabilities
Project Champion			

Summary: The NMS supports a leading biophysics capability, which gives the UK a strong position in biometrology in Europe. This ring-fenced project will maintain core NMS bioanalysis facilities and equipment enabling biomolecular measurements in native and near-native environments, which include biomolecular analysis and engineering, detection and imaging. The facilities are necessary to meet existing legislative requirements and to maintain measurement services for the UK industry.

The Need: The impact of health disorders (metabolic, genetic, infectious, neurodegenerative, cancers…), food and environment challenges, increase with changing demographics. These constant societal needs are responded to by industry through research and development for more efficient therapies and diagnostics and personalised medicine. Genuine and reliable measurements as well as their repeatability and standardisation up to the point of biological standards and standard materials are lacking, but are under increasing demand. Core biomolecular measurements must be maintained, (and improved via discretionary projects) to keep pace with societal and economic needs to continually improve the health and well-being of the UK citizen. Underpinning metrology funded by the UK government is equally necessary for international efforts to bring and sustain biometrology and traceability of biologically meaningful measurements.

The Solution: Meeting minimum requirements for the outlined needs necessitates three main areas of maintenance:

- maintain biophysical analysis facilities at current levels as the core equipment and knowledge base to ensure adequate representation of customer requirements in bioanalysis areas
- maintain cell-based analysis facilities in providing cell-based bioanalysis models and contributing to biophysical alternatives of animal testing (three R's)
- maintain assays and methods for low-level biomolecular detection in complex biological matrices (e.g. serum, cells)

Project Description: In all areas the project will provide maintenance, calibration, testing and training necessary for the continuous exploitation of the capabilities at current levels to ensure that customer requirements are addressed in full:

- maintain (and where necessary replace) core equipment including spectroscopy, liquid chromatography, calorimetry for biomolecular analysis. Maintain and continue quality assurance regime.
- maintain core cell-culture facilities including cell, molecular and micro-biology culture, live-cell microscopy
- maintain core facilities including biomolecular mass spectrometry, SPR, immunochemistry

Impact and Benefits: The project has universal impact on all bioanalysis priority areas as per the NMS strategy, on the delivery of all projects in the bioanalysis area in the NPL and on the support of bioanalysis projects within CCQM and EURAMET, on the implementation of biologically meaningful standards and on progress beyond the state of the art in developing SI traceable reference measurements and reference materials. Biometrology as a whole (current and long-term) is the major beneficiary of the project. All considered these NMS capabilities need to be at least maintained for the UK to preserve its leading position in biometrology.

Support for Programme Challenge, Roadmaps, Government Strategies: The project links directly to the NMS strategy in Strategic Priority 1, particularly in 1.2 Drug Discovery (lead development, biomolecular structure determination, safety evaluation), 1.3 Diagnostics (low-level detection in complex matrices), 1.4 Regenerative Medicine (cell-based therapeutics, tissue-engineered medical products, gene therapy vectors), 1.6 Long-term biometrology (reference methods and measurands). The project conforms to and build upon "Guidance for Industry" documentation (BSI, EC, FDA, EMEA, WHO), documentary ISO standards (measurement of quantities in samples of biological origin).

Synergies with other projects / programmes: The project provides the maintenance aspects of all ChemBio projects in the NPL's Biotechnology area. Synergies with non-NMS projects include current "BiOrigin", "NanoChop", and future EMRP projects. All completed and current TSB, NIHR, DEFRA projects and measurement services through direct third-party contracts (Oxford Nanopore, Sigma Tau, Orthos, P&G, Arecor, Shire Pharmaceuticals, GSK etc.).

Risks: The risks for the maintenance of facilities are low.

Knowledge Transfer and Exploitation: Active, future and associated projects, both NMS and non-NMS, are obvious dissemination routes for the project. Direct KT is through analyses enabled by the project. Customers are as

above, and others from pharmaceutical, healthcare and diagnostics industry, UK and European funding bodies through subcontracting. International comparisons, representations in standardisation committees, participation and presentations at international conferences, symposia and trade fairs are not covered by this project.			
Co-funding and Collaborators: For the maintenance project co-funding is expected to come from analysis work without taking into account the value to derive from the synergy with the other projects, as above, which is envisaged to be greater. Collaborators include regular industry customers, academic groups from Bristol, Cambridge, Edinburgh, Oxford, UCL, St George's University of London, UK/EU government organisations such as DSTL, JRC (Ispra, IRMM), AHVLA, clinicians from GSTS Pathology, UCL's Clinical Institutes, MRC laboratories and Hospitals, TSB Cell Therapy Catapult, with all contributing unique and specific expertise when required.			
Deliverables			
1	**Start: 01/04/2013**	**End: 31/03/2016**	
Deliverable title: Provision of biophysics facilities (spectroscopy, calorimetry, chromatography, synthesis) incl. calibration, maintenance and servicing			
2	**Start: 01/04/2013**	**End: 31/03/2016**	
Deliverable title: Provision of cell-based facilities (cell culture, autoclave, live-cell microscopy), incl. calibration, maintenance and servicing			
3	**Start: 01/04/2013**	**End: 31/03/2016**	
Deliverable title: Provision of low-level detection facilities (bio mass spectrometry, SPR, immunochemistry)			

Project No.	NMS/CBM13002	**Price to NMO**	£678k
Project Title	Extracellular cues in cell development	**Co-funding target**	£325k
Lead Scientist		**Stage Start Date**	Apr 2013
Scientist Team		**Stage End Date**	March 2016
		Est Final Stage End Date	
Sector	3.2 Drugs & therapies 6.1 High-value manufacturing & bio-products 7.3 Standards & regulation (future)	**Activity**	Development of Existing Capabilities; Methodology for New Capabilities

Summary: The project will provide a reference methodology enabling detailed description of biophysical extracellular guidance (biomolecular cues, physical forces) on cell development. Objectives include (i) parameterised interdependencies between extracellular biomolecular and physical factors and cell responses, (ii) deterrence factors for biofilm formation in bacteria-challenged environments, and (iii) 3D profiling of cell-microenvironment systems.

The Need:

The restoration of damaged or ageing tissues is a challenge of the highest priority for the UK healthcare, e.g. the cost to the NHS of managing a chronic wound alone is conservatively estimated at £3 bn per year, which is around 3% of the total out-turn expenditure on health for the same period (*NHS evidence; Nursing Times, 104, 3, 2008*). The global market potential for cell therapy is broadly estimated at $180 bn by 2018 (*Life Science Intelligence, MedMarket Diligence and Scrip reviews of product developments at ~150 companies, 2010*). Only a fraction of this value (<3% in 2010) is being realised. Research and industry demands centre around ways of stimulating tissue restoration or preventing metastasis and, on devices (scaffolds, implants) that reproducibly deliver and thus can be commercialised. Barriers to commercialisation include high costs associated with processing and managing personalised tissue treatments (grafts, transplants), batch-to-batch variations of commercial biomaterials, and the length of time to go through clinical trials to demonstrate effectiveness. Here existing regulations serve to limit the wide scale use of advanced therapies (*EC/1394/2007; 2001/83/EC*). If regulatory routes can be shortened from the current 10-15 years by using relatively small and inexpensive clinical trials, then new technologies may be commercialised within 3-5 years. Parameterised performance assessment of advanced medicinal products in response to physical extracellular environments could significantly shorten the time to commericalisation by providing reference points against which new technologies can be assessed. However, this exposes severe gaps in the area as the awareness of parameterised protocols and materials remains low. In response to this, NIST in the US has launched a tissue engineering advanced technology program with government funding in excess of $50M, and this has attracted a $70M co-share from industry, to support 26 metrology projects in the first phase! Measurement needs for further progress are universal and NPL's role would be to concentrate on measurable reference interactions of cells in their micro-environments or niches provided by scaffolds, cell culture and environmental forces. By providing accessible metrology enabling parameterised interdependencies between biophysical forces that are generated by cells, and forces that the cells are exposed to, NPL will help facilitate this necessary step change. Specifically the objectives of this project, the quantitation of cell-niche interactions in functional and spatially controlled terms (a main industry drive) has no underpinning capability at present. NPL is strongly positioned to address all these issues by capitalizing on developed capabilities including spectrometry, spectroscopy and microscopy measurements of cell behavior and extracellular interactions, new biomolecular engineering capability and on active partnerships with academia and industry in other areas that are being introduced in NPL, e.g. time-lapse HS AFM in liquid.

The Solution:

The project will provide a step change for the understanding of physicochemical aspects of extracellular guidance on cell development. Combined measurement capabilities for the characterisation and monitoring of cell behaviour in response to extracellular environments, both stimulating and detrimental, will be developed. These will be turned into efficient quantitative methodologies to be used as reference tools for optimising i) advanced medicinal products and devices for controlled cell differentiation in 3D culture, or onto 'intelligent' surfaces and ii) will introduce metrics to assess cellular responses in bacteria-challenged environments. Direct metrology support for quantitative extracellualr guidance at the NMI level is crucial and most timely as tissue-engineered medicinal products are: attracting growing investment; the measurement challenges and issues are clear (particularly so in the industry); and the process of introducing standards for tissue engineered products has been launched internationally (*FDA, standard medical devices, ASTM Committee F-04 standards*).

Project Description: The project will be conducted in three interrelated phases.

- The first will provide extracellular microenvironments supported by naturally derived and synthetic substrates in 3D culture with varied physicochemical properties. These will be cross-characterized based on specific cellular responses probed by endpoint assays (cell specific biomarkers), label-free and real-time bioelectrical impedance monitoring (cell growth/arrest, morphological changes), fluorescence microscopy (focal adhesion, motility), atomic force microscopy (force measurements, temporal monitoring in liquid) and structured illumination microscopy (live cell imaging, cellular dynamics).
- The second phase will develop mammalian and bacterial co-culture systems to assess interspecific bacterial and cellular interactions in the model microenvironments, and establish deterrence factors against biofilm formation. "Intelligent" tuneable antimicrobial responses will be used.
- The third, final, phase will exploit 3D depth profiling of morphological cell plasticity by high-resolution spectroscopy and microscopy techniques to allow quantitative measurements deep inside cell-microenvironment systems to be calibrated versus reference response metrics established in the previous two phases.

Impact and Benefits:

The project will impact through a newly established biometrology capability, which will be tailorable to end-user needs as per current and emerging market trends. The project will provide an enhanced ability to satisfy regulatory requirements in cell therapy and advanced medicinal products and will contribute to the EU's commitment to reduce animal testing by implementing the "three Rs" programme. Beyond its lifetime the project will advance the development of reference tissue-engineered products and will establish

UK leadership in the standardisation of activities in cell therapy industry, which will in turn enhance competitiveness for UK industry with active follow-up engagement in the international arena. A minimal amount of in vivo testing using reference parameters, and eventually materials, will be defined for their clinical potential and these will be deposited in an accessible information database. The information may also find use for screening cell therapy combinations (cell/scaffold/environment) through comparisons of performance with reference methods and materials. The impact of project outcomes is not limited to cell therapy and will be applicable to other industry sectors including healthcare and cosmetics, diagnostics and food. Thus, aside from being aligned with major trends in markets, the project will impact on the ability of the UK industry to exploit an extensive body of research knowledge (Nobel Prize in medicine, 2012) into commercial products, this is important as to date the UK is failing to compete at the translation and commercialisation stages (*BIS, Government office for Science, "UK growth opportunities for the 2020s"*, *2010*).

Support for Programme Challenge, Roadmaps, Government Strategies:

The project supports the NMS strategy in the priority theme 1, 1.4 regenerative medicine, conforming to the key areas of "physicochemical nature of extracellular guidance on cell development", "robust methods for controlling, monitoring and validating cell growth…", "validation and standardisation of 3D cell systems as models". The project conforms to EMRP challenges particularly in "…reference measurement procedures and reference materials of a higher order" (the EMRP Outline 2008); is aligned with EC directives related to advanced medicinal products by enabling "…interaction and compatibility between cells or tissues and the structural components …" (2007/1394/EC), and is supportive of efficacy endpoints for comparative analysis and quality criteria of tissue engineered products outlined in EMEA for "...cell-specific endpoints… morphological, structural and functional parameters, which are relevant for the targeted function…" (CAT/CPWP/573420/2009). The project conforms to all aspects of excellence in the NPL's science and "Metrology 2020" strategies, to roadmaps and biomedical landscapes of EUROHORCs, ESF and ESFRI in relation to cell therapy and biomaterials challenges, and to TSB long-term strategy through the establishment Cell Therapy Catapult.

Synergies with other projects / programmes:

This project stems from the recognition of the industry needs for a reliable metrology support in biophysical characterization of cell-based therapies. The individual phases of this project build upon previous government-funded projects (NMS, TSB and NIHR) and direct industry contracts (Xeno Medical, Orthos, RepreGen, Neotherix, HiMedica, P&G) that addressed different measurement issues as to biomarker detection, biomolecular interactions at biointerfaces, biomedical scaffolds and live cell imaging. The project is aligned with cell biology aspects of the current EMRP projects – "NanoChop" and "BiOrigin". The project will translate developed technologies and capabilities into a new methodological capability tailorable to stakeholder needs.

Risks: Lack of different microenvironments (low). Mitigation – various microenvironments are commercially available, synthetic materials are provided in house and by stakeholders. Batch-to-batch variations of a microenvironment (medium, low after mitigation). This risk is a fundamental reason for the outlined needs. Mitigation – response metrics are at cell viability levels, where variations in responses are of a "go/nogo" choice, and risk can be identified at early stages.

Knowledge Transfer and Exploitation:

Project outputs will include paper publications in scientific and trade journals and presentations in conferences and industry forums. A stakeholder group in the form of an industrial club will be designed by the end of the project to enable the continuing availability of the established capability to the UK industry. One case study will be identified at the end of the project. The newly established TSB Cell Therapy Catapult will be exploited for engagement with stakeholders during the project. Commercial benefits will be ascertained with economically viable outputs patented and IPX residing with partners as per appropriate collaboration agreements. Wider engagements with LGC (cell biology), BIA (BioIndustry Association) and the Alliance for Regenerative Medicine will broaden dissemination in industry. Engagements with specialist BSI, BIPM and VAMAS working groups will help keep abreast and influence standardisation policies applicable to the project.

Co-funding and Collaborators:

Main routes for co-funding in partnership with industry and biomedicine stakeholders will be by leveraging project funding through R&D and measurement services. A continuous effort will be on collaborative applications to charities, NIHR, EU research (FP7, ERC) programmes and on industry-led technology applications (TSB). Such ventures are interdisciplinary and will be undertaken without duplicating expertise and capabilities, which will provide efficient stakeholder partnerships including clinicians from UCL (Biochemical Engineering), ICR (MRI), Royal Free Hospital London, Bristol University MedSchool, industry (Athersys Inc, Xeno Medical, Orthox, P&G, Tissue Regenix, Neotherix, Orla PT, Sanofi-Aventis). We will strengthen cooperation with the TSB's Cell Therapy Catapult (Guy's NHS Hospital London), RegenMed Programme (UCL), UCL Centre for Stem Cells and Regenerative Medicine and envisage close links with the Francis Crick Institute.

Deliverables

1	**Start: 01/04/2013**	**End: 01/04/2015**	
Deliverable title: cross-mapping of extracellular microenvironments, cell response metrics, three paper publications			
2	**Start: 01/03/2014**	**End: 01/06/2015**	
Deliverable title: mammalian and bacterial co-culture systems, two paper publications			
3	**Start: 01/04/2015**	**End: 31/03/2016**	
Deliverable title: 3D depth profiling, two paper publications, a stakeholder workshop, one case study and good news story			

Project No.	CBM13003	**Price to NMO**	**£700k**
Project Title	BA39: Quantitative intracellular delivery	**Co-funding target**	£250k
Lead Scientist		**Stage Start Date**	Apr 2013
Scientist Team		**Stage End Date**	March 2016
		Est Final Stage End Date	
Sector	3.2 Drugs & therapies 7.3 Standards & regulation (future)	**Activity**	Development of Existing Capabilities; Methodology for New Capabilities

Summary: The project will define factors influencing uncertainty and reproducibility of intracellular delivery by relating physicochemical structural profiles of delivery vectors with their transfer efficiencies into live cells and will establish reference methods and measurands to enable a quantitative measure of intracellular delivery.

The Need: Molecular therapy provides imminent therapeutic control of major diseases including cardiovascular, genetic disorders and cancers. The global market is esimated to be worth over $100 billion by 2015, with revenues >$5-10 billion this year alone (*IMS Global Insights reports and Scrip reports*). Therapeutics are available, but their systemic use in clinic is hampered both by uncertainties in delivery and, the structural inconsistency of delivery vectors compromising drug manufacturability. Recent initiatives in industry (*Genzyme Corp.* – Erickson's case, Novartis-led global clinical trials of gene treatments for *glioblastoma multiforme*) and venture capital (*Merrill Lynch Health Care Fund into Neuorologix, ARCH Venture Partners into GenVec*) build upon the need for more efficient and quantitative intracellular delivery (*Bloomberg reports, 2010, Global Industry Analysts Inc., Global report on Gene therapy markets, 2011*). This also emphasizes a critical need for a harmonised legislation and suitable standards for gene therapy products (*2001/83/EC, 2002/98/EC, 2003/63/EC, 2004/24/EC, 2004/27/EC, 2008/29/EC*). To enable the systemic assessment of the safety and efficacy of delivery technologies a measurement capability for quantitative and correlative measurements of intracellular delivery is needed. Such a capability must include the development of reference methodologies to validate parameterised gene delivery measurands. NPL are uniquely positioned to provide significant input into this area through building on their expertise in biomolecular measurements of cell and membrane interactions and protein quantitation in complex biomatrices (cell extracts, biofluids).

The Solution: Molecular therapy has reached a critical point where quantitative control over macromolecular transfer is necessary for any further progress (*Scrip Reports on drug delivery technologies, 2010*). Current macromolecular drugs that modulate genetic reactions overcome the problems of stability, excretion and uptake by phagocytes, release from endosomes and entry into the nucleus. The major remaining barrier is untraceable transfer and uptake by the target cells as a function of structural inconsistency of delivery vectors (*FDA Guidance for Industry: Gene Therapy Clinical Trials; EMEA Guidance on the Quality, preclinical and clinical aspects of gene transfer medicinal products, EMEA/273974/05*). To better understand factors improving intracellular delivery, advanced measurement capabilities for the quantitative assessment of delivery vectors, their uptake to target cells and potential specificity of targeting will be developed in this project. The project will provide methodology to measure the interaction and transfer of delivery vectors across membranes, quantitation of drug delivered, or therapeutic target. The project will also explore techniques that could be used to quantitate delivery at a sub-cellular level (organelle specific). Given the complexety and extent of the required measurements a direct support at the NMI level is indispensible.

Project Description: The measured parameters will be systemised into delivery measurand sets. Quantitative methodologies to underpin future reference methods will be developed. Delivery measurands will relate to physicochemical parameters of delivery vectors, which are necessary for the formulation of future reference materials. Complementary to this is uncertainty evaluation in the measurements. The levels at which these can be determined currently cannot be identified as there are no benchmark delivery standards and no uncertainty given against which new levels can be assessed. The main focus of the first two years will be on (i) quantitative measurements of vectors and their delivery with preliminary uncertainty evaluation. The work will start from the state-of-the-art advanced measurements involving chiroptical (spectral biophysical), mass spectrometry (spectral chemical) and microscopy (live imaging) methodologies using cells and intracellular matrix (cell lysates) – end of year 2, (ii) molecular engineering aspects will constitute an integral part of the project to facilitate specific measurements (e.g. labelling, fluorescent markers, vector targeting and monodispersity) and innovation towards benchmark delivery vectors – analysis techniques and model vectors available at the end of yr 2; (iii) following stakeholder consultations, an emphasis will be made on correlation between label-free mass spectrometry and microscopy measurements by the end of yr 3. By the end of the project we will aim to trial the established capability in collaboration with industrial stakeholder(s) on a specific disease model.

Impact and Benefits: The direct impact of the project is through establishing a reference capability for quantitative and repeatable measurements of intracellular delivery. Concerns over the absence of ISO standards for drug delivery and vector materials will remain unless such a capability is established first. NPL's verified intracellular delivery will enable the UK industry to address essential regulatory requirements and confer a competitive advantage. The project will benefit industry by paving the way for future molecular therapy standards. Steps beyond the life of the project will be taken towards standardisation in international arena through pre-normative research within VAMAS and the development of documentary standards through appropriate technical committees in ISO and steering groups in BSI. The overall impact of this project on industry is integral to that on healthcare and clinic. By the end of the project we anticipate to address gene delivery issues of a specific genetic disorder. Genetic disorders comprise >15000 different diseases. Most vulnerable age groups are children, with over 30% of all infant deaths due to single-gene disorders that can be cured by a single macromolecular drug if delivered into the cell (*Public Health Reports 1960 and thereafter*). >10% of all paediatric hospital admissions (average for the developed world) are for children with genetic disorders, whereas the mortality rate for boys with Duchenne muscular dystrophy (DMD), which can be treated only genetically, remains 100%!

Support for Programme Challenge, Roadmaps, Government Strategies: The project supports and aligns with the key UK and EU government strategies and programme roadmaps under: (i) NMS strategic priority theme 1 – Bioanalysis, with key elements and areas of 1.2. Drug Discovery.: "biomolecular structure determination in native environments…", "robustness determination of emerging direct-analysis technologies", "chemical characterization across the length scale…". 1.4. Regenerative medicine: "gene therapy vectors - materials to support systemic use…", "quantitative and traceable measurements of intracellular delivery…", "cell

imaging and tracking". 1.6 Long-term biometrology: "primary reference methods and measurands", "higher order reference standards". (ii) BIS strategy as in "Life Sciences 2010 - Delivering the Blueprint (BIS economic paper #2)": "process innovation – e.g. use of new research or delivery methods in drug development…'' as being ''one of the key drivers of productivity, economic growth and standards of living''. (iii) TSB-RCUK mainstream focus areas "Creative industries" – advanced materials, bioscience and healthcare – and their implementation under the "concept to commercialisation". (iv) EMRP (Outline 2008, Health Grand Challenges): "…from qualitative towards quantitative multimodal measurement procedures" and "…traceable measurements methods for analyte/matrix-combinations with increasing complexity…". (v) EMEA Committees for Medicinal Products for Human Use *(Advanced Therapies and Gene Therapy Working Parties*) focused on standard macromolecular transport as also per challenges in FP5 (*Chronic and degenerative diseases*), FP6 (*Life Sciences, genomics and biotechnology for health*) and FP7 (*NMP theme - metrology for nano-enabled therapies*).

Synergies with other projects/programmes: The project builds upon previous NMS projects (BA19, BA21 and BA23) providing measurement and technology capabilities for quantitative detection of low abundance biomarkers in biomatrices including cell lysates by mass-spectrometry; interfacial biomolecular orientation and recognition in near-native environments by chiroptical spectroscopy; illumination microscopy for live cell imaging beyond the diffraction limit. The project is synergistic to the objectives of new EMRP projects (2012-2015), HLT10 and NEW03, and to the associated capabilities aimed to link biomolecular structure with origin of disease and to provide optical characterization of biological nanomaterials.

Risks: Medium risks may include (i) low detection levels of material in cells or inefficient on-probe spectrometry and spectroscopy analysis and (ii) unobvious correlation between mass spectrometry and optical microscopy quantitation approaches. (i) Concentrations of delivered material can vary in femto-to-nano molar ranges which are within the confidence range of mass spectrometry, in addition depletion and isolation protocols prior to analysis will eliminate the issue. (ii) Understanding factors behind possible discrepancies between different quantitation methods is of interest to stakeholders and is embedded into both the very problem of intracellular delivery and the project.

Knowledge Transfer and Exploitation: Generated IPX will be protected whenever appropriate. Quantitation approaches in the field of drug delivery remain novel, particularly with contribution from our clinical collaborations (DMD, cancer). Engagement with relevant KTNs, Bioscience and Biotech/Healthcare Special Interest Groups at NPL (now in the measurement networks, will broaden our access to industry. KT within EU NMIs will be through secondments (PTB, LNE). These engagements will provide co-funding opportunities to maximize the exploitation of the measurement science. Wherever appropriate the results will be disseminated in trade journals and forums, including best practice guides and reported to appropriate working group in standardisation bodies (BSI, BIPM). Conference presentations and paper publications will be used to influence regulation (BIPM, BSI, ISO), as a step towards standardisation for drug delivery.

Co-funding and Collaborators: Primary *co-funding* will be pursued with project partners though TSB, EMRP and FP7. The TSB Cell Therapy Catapult will provide a focused vector for external funding directly conducive to applications. Established partnerships with clinicians and industry will be used for attracting funding from NIHR and Biomedical charities (Welcome Trust, Cancer Research). *Collaborators* include UK and EU industry stakeholders from pharmaceutical and instrument manufacture sectors (GSK, MedImmune, Swedish Biomimetics 3000, Themis Biosciences, Sigma Tau, Shire Pharmaceuticals, Waters, Bruker, Applied Photophysics), NMIs (PTB, BAM, LGC, LNE), clinicians from UCL (Institutes of Child Health and Ear, MRC LMCB), Cambridge, CRUK, and academia groups providing specific expertise, Oxford (nanoSIMS), Cambridge (gene therapy), LCN (liquid AFM).

Deliverables

1	**Start: 01/04/2013**	**End: 01/05/2015**	
Deliverable title: Experimental measurement methodologies and delivery protocols for quantitation of intracellular delivery *in situ* and *in cellulo*. At least one paper publication and best practice guide to disseminate the techniques developed.			
2	**Start: 01/07/2013**	**End: 01/05/2015**	
Deliverable title: Physicochemical profiling of delivery vectors, measured stability and efficiency; engineering capabilities for identify enhanced metrics compared to commercial vectors. Two paper publications and potential IPX.			
3	**Start: 01/05/2014**	**End: 01/06/2015**	
Deliverable title: Spectral imaging for temporal monitoring of delivery mechanisms across membranes by synergizing chiroptical spectroscopy and fluorescent microscopy. One paper publication on the techniques developed and mechanisms of delivery.			
4	**Start: 01/05/2015**	**End: 30/03/2016**	
Deliverable title: Reference methodology and quantitative measurement of intracellular delivery with <10% uncertainty. One paper publication, trade journal article, presentation at pharma/regulatory meeting, case study and co-funding opportunity.			

Project No.	CBM13004	**Price to NMO**	£620k
Project Title	BA40: Primary biophysical standards of microbial membrane resistance	**Co-funding target**	£230k
Lead Scientist	Baptiste Lamarre	**Stage Start Date**	Apr 2013
Scientist Team		**Stage End Date**	March 2016
		Est Final Stage End Date	
Sector	3.1 Diagnosis 3.2 Drugs & therapies	**Activity**	Methodology for New Capabilities

Summary: The project aims to develop the first primary physical standards of antibiotic membrane resistance, which will develop measurements that relate microbial membrane composition with microbial resistance to commercial and emerging "last-resort" polypeptide antibiotics. Comparative quantitative measurements will be performed to provide a new methodology for assessing resistant membranes and their susceptibility to new antibiotics which will be experimentally challenged using both membrane-active and conventional antibiotics. Primary physical standards of resistant membranes will be used by industry as a reference tools for screening platforms to develop new antibiotics.

The Need: The challenge of antimicrobial resistance, which is notoriously associated with the emergence of "superbugs" (MRSA) and severe revenue losses in antibiotics sales (*The Economist, reports, 2004*; *PhRMA, Industry profiles, 2004, 2007, 2008)*, is far more fundamental and widespread than individual companies can take on. In the UK, 44% patients acquire MRSA infection on their final admission (*National confidential study of deaths following MRSA infection, UK's National Statistics and Department of Health*). Conservative annual estimates give >100,000 cases of hospital-acquired infections in England alone causing >5,000 deaths, with the cost to the NHS exceeding £1bn per year (*National Statistics*, *HPA and Parliament reports*). Antimicrobial resistance is traditionally referred to as the failure of conventional antibiotics whose targets are single reactions in the physiology of growing bacteria. These antibiotics are inactive against mature cells and resistance to them is a natural selection process which occurs at the genetic level and can be sped up with the frequent use of antibiotics. More alarming are the next generation of "superbugs", e.g. VRSA, that evolve from attempts to treat MRSA with most powerful or "last-resort" antibiotics that target bacterial membranes. However, resistant membranes incur formidable costs for bacteria to develop and this spurred companies to develop membrane-active antibiotics derived from host defence polypeptides (*plectasin, Novozymes and Sanofi-Aventis; pexiganan, Access Pharmaceuticals*). This current transition strategy from research to market is limited to bioactivity tests against MRSA, which take no account of membrane resistance development. All "new-era" antibiotics are polypeptides including the "last resort" antibiotics (*vancomycins, gramicidins, polymyxins*). Against each of these, membrane resistance is possible (*VRSA against vancomycin*). Sufficient evidence exists for generic biophysical factors that drive resistance development. These can all be grouped into lipid composition and biomarkers, membrane thickness and permeability, peptide-lipid interactions (strengths and extent of folding) and the like. What is entirely missing is the availability of measurable reference points and primary standards of antibiotic membrane resistance. Only concerted systems biophysics measurements at the NMI level can provide these.

The Solution: The solution for pharmaceutical industry to antimicrobial resistance is two-fold:

1) better understanding of membrane resistance
2) generation of more efficient membrane-active antibiotics

While (2) is already attracting considerable investment and re-focus of antibiotic programmes in Big Pharma, (1) is only becoming to be acknowledged due to the relatively recent emergence of resistant biomembranes. It is clear however that without having an adequate measurement foundation for (1), (2) is set for yet another failure on a similar or even larger scale given the rise in the use of the "last-resort" antibiotics (*Society for healthcare epidemiology of America reports*, *2011*) and in superbug outbreaks (*NIH outbreak of deadly KPC*, *2012*) Primary physical models and standards of membrane resistance that will support future reference materials of antimicrobial resistance are necessary and can be delivered through systems biophysics measurements including lipidomics and comparative biophysical microbiology and microscopy analysis with non-pathogenic bacterial cells.

Project Description: The project will focus on the development of the first primary physical standards of microbial membrane resistance. This project will use the input of physical sciences to look at the death rates of bacterial cells in real time in order to develop measurable reference points, and produce a primary standard for antibiotic resistance. It will be achieved by setting up a new methodological capability for the measurement of membrane-based antimicrobial resistance. This will comprise of quantitative lipid analysis of membrane composition by molecular biophysics, and mass spectrometry including antibiotic-lipid binding ratios and antibiotic biokinetics using non-pathogenic resistant bacteria. The project will specifically develop:

- comparative biophysical (CD, LD, FTIR, ITC) and mass spectrometry (MALDI, ESI, SIMS) analyses of membrane lipid composition for non-pathogenic susceptible and non-pathogenic resistant strains
- live-cell fluorescence microscopy methods coupled with stain-dead antimicrobial assays enabling antimicrobial biokinetic measurements in real time
- mechanisms and kinetics measurements of antibiotic-membrane interactions measured at the single bacterial cell level using chemical and topographic imaging

- model biomembranes emulating bacterial cell lipid composition

Impact and Benefits:

- The direct impact and benefits of this project will be through the provision of a quantitative metrological support for membrane-related microbial resistance against membrane-active antibiotics
- Development of the first primary physical standards of membrane resistance (there is no primary standard at present) that would be used by industry as reference tools for screening platforms for new antibiotics
- Improved measurement rationale for membrane-active polypeptide antibiotics capitalising on the NPL's established and unique membrane biophysics capabilities
- Beyond the lifetime of the project, development of reference protocols, reference membrane materials and documentary standards for antimicrobial membrane resistance which will help enhance competitiveness for UK drug discovery industry

Support for Programme Challenge, Roadmaps, Government Strategies: The project supports the NMS strategy within the Bioanalysis theme, where it is aligned with 1.2 Drug Discovery in "lead development – high throughput and high content screening for lead identification and optimisation", and "biomolecular structure determination in native environments", and with 1.3 Diagnostics in "reference standards and control materials for molecular and protein diagnostics". It supports key EU policies on strengthening EU competitiveness in drug development as to: "…*physicochemical* and other relevant *properties* of the *active substance*, including *biological activity* for biological medicinal products…" (2003/63/EC), "…the *3-D structure of proteins and other macromolecules*, which is important for elucidating *protein function and essential for drug design*..." (2002/834/EC). Individual approaches in biotechnology tend to be associated with individual biomolecular targets. This imposes validated reference points for comparative analysis as set in EMEA documents: "…if the appropriate higher order structural information cannot be obtained, a relevant biological activity assay could indicate a correct conformational structure…" (CPMP/ICH/5721/03). The project conforms to WHO reports on antimicrobial resistance as in: "hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA),….resistant to first-line medicines, more expensive therapies are used", and in "achievements of modern medicine are put at risk by AMR. Without effective antimicrobials for care and prevention of infections, the success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised" (*WHO and joint FAO/OIE reports, 2008-2011*).

Synergies with other projects / programmes: The project aligns with the EMRP "BiOrigin: metrology for biomolecular origin of disease" project, uses new capabilities established in BA22 and BA23, and adapts results from our recent TSB study of molecular diagnostics of *M. tuberculosis*.

Risks: antibiotics cannot be obtained (low); mitigation – all antibiotics in the project are commercially available and will also be provided by stakeholders and/or through our established polypeptide synthesis capability. Access to non-pathogenic strains is limited (low); mitigation – project will use ATCC strains using our microbiology capability; polypeptide resistant non-pathogenic strains are supplied by stakeholders.

Knowledge Transfer and Exploitation: Project results will be disseminated through peer-reviewed paper publications in scientific journals, publications in public and trade journals (Drug Discovery World), presentations at the international and national conferences and symposia (Protein Society Symposia, Biotechnology Congresses, PepCon, ACS meetings) and presentations at industry-focused independent forums (Science Capital). The results will be disseminated through the "Resistance Surveillance Project" sponsored by BSAC and industry (Pfizer, Cempra, Basilea Pharmaceutica). The results will be made available to standardisation and regulatory bodies through participation in appropriate CCQM and BSI committees. IPX will be pursued when deemed appropriate and will be translated into innovative measurement services or services via licensing agreements. A workshop at an industrial site will be organized in the end of the project.

Co-funding and Collaborators: Co-funding will be sought from relevant calls from TSB (e.g. fighting infection through detection, sepsis, feasibility and R&D calls), EMRP (Health, Industry), NIHR (EME programmes), BSAC (annual responsive grants), ERC and other third party opportunities, including direct contacts with industry. Key collaborators include UK companies (Orla PT, Isogenica, Eluceda, GSK), NMIs (PTB, LGC, JRC), and academic groups from UCL (fast AFM, lipid bilayers), Oxford (nanoSIMS), Bristol (bacteria strains bank, experimental resistant strains), Edinburgh (bacterial motility), Paris (biokinetics statistics).

Deliverables

1	**Start: 01/04/2013**	**End: 30/11/2014**	
Deliverable title: comparative analyses of membrane lipid composition, one peer-reviewed paper publication			
2	**Start: 01/02/2014**	**End: 31/03/2016**	
Deliverable title: model biomembranes for bacterial lipid composition, one peer-reviewed paper publication			
3	**Start: 01/09/2013**	**End: 30/11/2015**	
Deliverable title: biokinetics measurements by live-cell microscopy with antimicrobial assays, one peer-reviewed paper publication			
4	**Start: 01/01/2015**	**End: 31/01/2016**	
Deliverable title: antibiotic-membrane interactions by chemical and topographic imaging, two peer reviewed paper publications			

Project No.	NMS/CBM13013	**Price to NMO**	£120k
Project Title	Contract Management (M1)	**Co-funding target**	N/A
Lead Scientist	Alice Harling	**Stage Start Date**	01/04/2013
Scientist Team		**Stage End Date**	31/03/2014
		Est Final Stage End Date	
Sector	Management	**Activity**	Programme Management

Summary

This project will deliver effective contract management for the programme. Work in this project will ensure timely invoicing and reporting to the NMO each month and delivery of an annual progress report to the NMO and programme working group.

The Need

Contract management is essential to ensure seamless delivery of the science projects in the programme while attending to all reporting and invoicing requirements of the NMO. A central point of control is also required for effective operational oversight and governance of the programme.

The Solution

This project will deliver effective contract management through a contract manager dedicated to this programme. They will have oversight of all:

- Project delivery;
- Invoicing;
- Contract status and variations;
- Monthly and annual reporting.

Project Description (including summary of technical work)

1. Attend meetings as necessary to support contract delivery and the needs of the NMO
2. Prepare reports monthly (invoices, progress report and financial forecasts)
3. Liaison with working group, industrial advisory groups & clubs
4. Manage delivery of the contract and submit change requests and contract amendments as necessary
5. Analysis of programme performance and revenue forecasts for the financial year
6. Ensure that the contract is managed to NPL's ISO 9001 accredited quality system
7. Deliver annual report and present programme progress to working group and the NMO as required.

Impact and Benefits

This project will ensure that all operational, financial and reporting requirements for the programme are met. The work in the programme covers the oversight of delivery from all the technical projects and hence is where ultimate responsibility lies for the success of the programme.

Support for Programme Challenge, Roadmaps, Government Strategies

Not applicable.

Synergies with other projects / programmes

Not applicable.

Risks

The main risks are the inability to deliver the monthly reports and invoices to the NMO and the failure to deliver the annual report to the programme working group. Both of these risks are mitigated by the availability of a large pool of senior managers who are available to step in to assist or take over delivery if adverse circumstances are causing problems with the completion of the key tasks of this project.

Knowledge Transfer and Exploitation

Not applicable.

Co-funding and Collaborators

Not applicable.

Deliverables

1	**Start: 01/04/2013**	**End: 31/03/2014**	

Contract management including production of monthly invoices and reports to the NMO			
2	**Start: 01/04/2013**	**End: 31/03/2014**	
Produce annual report and present progress to the NMO and working group			

Project No.	NMS/CBM13014	**Price to NMO**	£100k
Project Title	Programme Management and Formulation (M2)	**Co-funding target**	N/A
Lead Scientist	Helen Compton	**Stage Start Date**	01/04/2013
Scientist Team		**Stage End Date**	31/03/2014
		Est Final Stage End Date	
Sector	Management	**Activity**	Management

Summary

This project will formulate a proposal of work for inclusion in the 2014/15 programme and engage with key stakeholders to ensure maximum impact is achieved from the science delivered by the programme. To achieve these objectives the project will:

- Maintain and develop the programme strategy and roadmaps;
- Consult with key stakeholders in government, industry, academia, regulators and other end users in order to determine future measurement requirements or other related issues that need to be addressed by the programme;
- Develop a series of project proposals for prioritisation by the programme working group;
- Implement and maintain a balanced scorecard for the programme as a measure of the impact of the programme on the UK economy and society.

The Need

New measurement requirements are constantly emerging from all areas of UK life. For example, new technologies require new underpinning metrology and standards, as do new regulations or environmental targets. To underpin areas such as growth in the economy, public health issues or mitigation of environmental impacts these measurement requirements must be successfully addressed as early as possible. In order to achieve these objectives effectively an overview of the research priorities and how to address them is required. Maintaining and developing a programme strategy and roadmaps achieve this objective and allow, in conjunction with knowledge of specific technical requirements obtained through stakeholder consultation, the formulation of a work programme that address UK measurement needs. Both the careful design of any programme of work coupled with the continual review of opportunities for increased impact are essential in order to make sure that the maximum value possible is extracted from the investment made in the technical projects.

The Solution

The views of a wide range of stakeholders from industry, regulators, government and other end users will be garnered through a wide ranging consultation process in order to capture current and emerging measurement requirements. This process will include looking at independent evidence of measurement needs as expressed in government reports, foresight activities, industry roadmaps etc. as well as conducting meetings, surveys and interviews as required that focus on specific topics of interest. Collation and assessment of information from all sources will enable the programme strategy and roadmap to be developed which will guide the future direction of the programme. The detailed technical requirements will then be formulated into a series of projects for prioritisation by the independent programme working group. Projects that receive the highest ranking will form a programme of work, which will be initiated at the start of the next programme cycle.

In addition to the programme formulation, work will be undertaken to understand and maximise the impact of the research. This will be assisted by the implementation and maintenance of a balanced scorecard for the programme consisting of a number of key metrics. The balanced scorecard has been implemented at NMS NMI level previously and now NPL is looking to achieve something similar at individual programme level.

Project Description (including summary of technical work)

- Horizon scanning, capture and analysis of Industry and Societal needs to feed into current and future programme direction;
- Development and updating of programme roadmaps and strategy;
- Engagement with programme stakeholders to:
  - Realise outputs and maximise benefits to the UK;
  - Ensure alignment of programme with UK Government, Industry and Societal drivers;
- Oversee preparation of project proposals for review and prioritisation by the programme working group;
- Submission of final programme proposal for contracting;
- Liaison with the NMO programme supervisor to deliver maximum impact and efficient delivery;
- Identification of exploitable material for increased impact through channels provided by the Pan-Programme KT programme and other KT avenues;

- Assessment of the impact of the programme through use of a balanced scorecard;

Impact and Benefits

Effective programme management will maximise the outcomes to key stakeholder communities from the outset of the technical work and ensure knowledge transfer activities in the programme are efficient and effective. The programme as a whole addresses many measurement challenges across the broad sweep of the UK economy and society. Therefore, the design of knowledge flows and exploitation plans in technical projects which occurs during the formulation process is essential for delivery of the wide benefits of the programme to the broadest possible audience.

Support for Programme Challenge, Roadmaps, Government Strategies

This project underpins the work of the whole programme through development of an overview of key societal drivers and measurement requirements as captured in the programme strategy and roadmaps. These key programme documents are utilised during development of technical projects to guarantee that all the technical work in the programme is aligned to addressing the metrology needs of the UK.

Synergies with other projects / programmes

This project will interact with the other NMS programmes so that synergies and common goals can be identified to ensure that the maximum value is returned from the investment in the NMS portfolio.

Risks

This project has no technical risks but is dependent on the availability of senior staff to assess and interpret the societal drivers in order to develop the programme strategy and roadmaps and hence determine the future technical work required in the programme.

Knowledge Transfer and Exploitation

The main functions of this project are to ensure the development of a new programme of work and to measure and increase the impact of the programme. Improvement of the programme impact will be achieved through proactive intervention in the technical projects within the programme rather than through direct knowledge transfer activity in this project.

Co-funding and Collaborators

Not applicable.

Deliverables

1	**Start: 01/04/2013**	**End: 31/03/2014**	
Programme Management and Formulation			

Project No.	NMS/CBM13015	**Price to NMO**	£163k
Project Title	Programme-level KT: International Representation (M3)	**Co-funding target**	N/A
Lead Scientist		**Stage Start Date**	01/04/2013
Scientist Team	NPL scientists	**Stage End Date**	31/03/2014
		Est Final Stage End Date	2014+
Sector	Knowledge Transfer	**Activity**	Knowledge Transfer

Summary

The aim of this project is to maximise the impact of the Chemical and Biological Metrology (ChemBio) Programme through high-level knowledge transfer (KT) activities and to represent UK interests through participation in high-level metrology and standardisation committees for the benefit of UK industry and regulators. The objectives of the project are:

- To support the organisation of, and participation in, key science conferences that have a broad scope, covering wider interests than a single technical area in the Programme to aid in formulating UK views to the benefit of UK industry e.g. Gas 2013.
- To represent UK interests on international measurement committees core to NPL's NMI role: e.g. CIPM Consultative Committees and EURAMET Technical Committees.
- To achieve high impact knowledge transfer through support for secondments.

The Need

Knowledge transfer is the vehicle through which the knowledge and benefits developed in the ChemBio Programme are disseminated to industry, government, regulators and other end users. As such it is an essential component of the Programme. KT activities are embedded within each technical project for maximum effectiveness in transferring knowledge generated in projects to the relevant user communities. Much of the work of the ChemBio Programme is disseminated through presentations and papers at both national and international meetings and this work is largely included within technical projects. However, there are several crosscutting KT activities that are essential in order to gain the maximum benefit from the ChemBio Programme. A key role for the Programme is to represent UK interests on many international measurement and standardisation committees such that UK industry and government benefits from: the prevention and reduction of trade barriers (support for the MRA); better-informed regulation; and the harmonisation of industry standards.

The Solution

Maintain international representation on high-level and influential CCQM and EUROMET metrological committees as well as supporting work in top-level technical committees under the auspices of VAMAS.

Project Description (including summary of technical work)

Represent relevant UK NMS interest on key, high-level international committees such as: CCQM plenary and it's working groups; and VAMAS (TWA 2 Chair).

Impact and Benefits

Strong representation on International standards bodies and committees and related activities will enable the expertise developed through the Programme to reach a wider audience of beneficiaries. Contributions to drafting international and national specification standards and active participation in relevant CIPM Consultative Committees and EURAMET will enhance the UK NMS reputation and ensure international alignment. UK NMS reputation will be further supported by active involvement in activities supporting dissemination and understanding of standards such as providing keynote lectures and providing editorial input to technical publications. One of the most beneficial mechanisms for achieving high impact KT both into and out of NMS Programmes is the secondment of key staff to other institutions and companies. This project will support a small number of secondments where support is not available from other sources.

Support for Programme Challenge, Roadmaps, Government Strategies

Aligns with NMS Strategy 2011 – 2015 for working with partners through standards organisations.

Synergies with other projects / programmes

The activities detailed will link strongly with all projects within the ChemBio Programme and provide additional routes for the dissemination of project outputs. This project complements the activities of the Pan-Programme KT, which is designed to disseminate the outputs from the programme to a wide community of end users.

Risks

This is a low risk project as it builds on existing well-founded interactions and uses the output of prior technical work undertaken in core projects in the ChemBio Programme that was itself selected through extensive consultation with UK industry on their needs. The main risk is non–acceptance of UK work by the wider community. This can be mitigated by ensuring up-to-date contacts with the wider stakeholders and using a rigorous review process for acceptance of new

work. Maintenance of credible representation on these bodies is important and needs to have planned succession when required on a long-term basis.

Knowledge Transfer and Exploitation

The project is, in itself, KT and exploitation through international representation activities. Feedback of international activity and strategy to relevant UK stakeholders will provide awareness and identification of opportunities.

Co-funding and Collaborators

Collaborating organisations include NMI's (e.g. NIST, VSL, PTB, LNE, KRISS, NMIJ), standards development organisations (e.g. BIPM/CIPM, ISO, CEN, BSI), regulators (e.g. UKAS), learned institutes (e.g. RS/RAE, IoP,) - and appropriate companies, trade organisations, etc.

Deliverables

1	**Start: 01/04/2013**	**End: 31/03/2014**	

Deliverable title: Ensure International representation on measurement and standardisation bodies.

Contents LGC Projects

MD3e	Programme Management	2013	139
MD4d	Programme Formulation and Strategy	2012	141
MD4e	Programme Formulation and Strategy	2013	142
NB10	In vitro Nanotoxicology	2011	143
NB11	NanochOp	2012	145
OA7	Improved CRMs for Food Analysis	2010	147
OA12c	Reference material certification and support	From 2011 contract but started 2012	149
OA12d	Reference material certification and support	From 2012 contract but starts 2014	151
OA12e	Reference material certification and support	From 2013 contract but starts 2015	153
OA13	Direct analysis for organic purity assessment	2012	155
OA14	Ion Mobility Standards	2012	157
OA15	RMPs & CRMs for Therapeutic Drug Monitoring	2013	159

Project BA1	Industrial Consultation and Analytical Feasibility Study for Emerging Metrology Requirements to Support Biofuels

Project Objectives

- To inform BIS strategy on the global and UK specific metrology needs to support legislation for existing and emerging biofuels.
- To establish capabilities for supporting the emerging diversity of biofuels.
- To collaborate with EU/international-supported activities for the production of reference materials to inform biofuel specification.

Background and Rationale

Biofuels and the energy sector are one component of the newly emerging knowledge-based 'bioeconomy'. Considerable attention is being devoted globally to renewable energy supplies and biofuels offer an important addition to supplement/replace conventional fossil fuels.

Biofuels can be categorised as 'first' to 'fourth' generation. Current 'first generation' biofuels are derived from products of conventional food crops (the starch, sugar and oil feedstocks from crops such as wheat, maize, sugar cane, palm oil and oilseed rape). These are converted to biodiesel and bio-ethanol for use as automotive fuels. Given these feedstocks are important food sources, investment has been seen in a broader range of feedstocks (inc. lignocellulose in dedicated energy crops such as perennial grasses, and from forestry, the co-products from food production and domestic vegetable waste biomass – 'second generation' biofuels). 'Third generation' fuels include new feedstocks from novel non-food oil crops, the use of marine organisms and the direct production of hydrocarbons from plants or microbial systems. Synthetic biology offers future potential to produce novel chemicals through re-design of biological pathways or organisms – such 'fourth' generation biofuels are attractive for use within the existing transport infrastructure without conflicting with current engines, supply-line modifications or fuel standards. Such breadth of feedstocks and variety/complexity of processing efficiencies has a large effect on the biofuel quality, a cause of increased concern to industry and end-users alike. The metrology required to support this evolving activity is not well defined or understood internationally.

The EU has set an ambitious target that, by the year 2020, 20% of the EU energy consumption will be from renewable sources. Member States have been set a target requiring 10% of transport fuels to be from renewable sources. Policy frameworks such as the EU Biofuels Directive and Renewable Transport Fuel Obligation (RTFO) for the UK, target 5% of transport fuel supply to be from biofuels by 2010 and 10% by 2020. Fuel standards play a major role in defining the opportunities for biofuels. The revised EU Fuel Quality Directive (98/70/EC, 2007) effectively limits the amount of bioethanol blended with petrol, and biodiesel with mineral diesel, to a max. 5%/vol, to avoid adaptation of the existing car fleet. EN228 (unleaded petrol; EU Auto Oil Directive) sets EU fuel standards for petrol/ethanol; EN14214 (fatty acid methyl esters (FAME); UK EN590; all EU diesel) for diesel/biodiesel. However biofuels have a limited ability to replace fossil fuels whilst conforming to European fuel standards.
A current EU FP7 initiative (Biorema), involving collaborators aims to address these issues by producing two RMs for biofuels for a global market. However, specific consideration for the local source of the biofuel and local environmental conditions will be required, indicating presence/absence, tracing of regional origin and quality of biofuels (including under storage conditions) to be of measurement importance.

With such a complex set of problems and the likely pace of change in the field, this project sets out to:

- consult widely with the community, both locally and internationally, as to the major metrology barriers to trade and innovation.
- establish a core capability for addressing specific issues which may include the provision of traceable standards, labelled materials, and reference methods for the traceable value assignment of priority measurands.
- interact with current EU framework projects by providing analytical measurement to support their goals.

This will enable the development of an informed strategy combined with the capability for the provision of traceable measurement to support the future requirements for reference materials in this field.

Impact

Economic: The UK's consumption of biodiesel has risen 10x in the past two years with its global production quadrupling during 2000-05; in the same time period, the global production of bio-ethanol has more than doubled. The major supplier of UK biofuels is now selling >100mn litres of biofuel/week, 10% of the UK road fuel market. The industry is calling for reference methods and standards but, as yet, priorities are undecided.

Quality of Life: At all levels globally, the main drivers for the development of bioenergy and biofuels are climate change, energy security and rural development. The political motivation to support biofuels arises from each individual driver or combinations thereof. Policies designed to target one driver can be detrimental to another as different biofuels have widely differing environmental, societal and economic impacts.

Innovation: Traceable methods for the characterisation of source of feedstock and proposed utility of the fuel will be essential for the innovative use of sustainable fuels. The project aligns with the highlighted TSB priorities relating to energy and the environment.

Science Value: The major challenge facing industry is the 'at site' testing of the materials. Provision of consensus on the need and direction for the development of traceable methods and standards for biofuels, and the reproducibility and repeatability of industry practice.
NMS Capability: Identification of the consensus need for traceable methods and standards for biofuels is essential to extending NMS science input internationally in an appropriate manner that leads to removal of trade barriers, and ensures consumer and environmental protection through the rapid assessment of product origin and quality.

Deliverables

No.	Deliverable	Start	End	Cost
1	CEW a consultation report on industry requirements for metrology in the biofuels industry is reported to BIS (cost met by Programme Strategy project).	Apr 09	Dec 09	
2	CEW a core capability, initially for the analysis of two priority markers, has been developed. CEW core capability has been disseminated at relevant conferences and via at least 1 peer-review publication.	Apr 10	Jan 12	
3	CEW the developed approaches have been used to value assign candidate reference materials from the EU FP7 project.	Apr 11	Jun 13	
4	CEW BIS Measurement Board presentation given. CEW project management activities completed. CEW articles prepared for CBM website, describing progress and outputs of the project.	Apr 09	Jun 13	
Total cost				£185K

Project Ref:	BA10 + BA10b				
Title:	Standardisation of MicroRNA (miRNA) Measurement				
Start Date:	October 2011	End Date:	May 2013	Price:	£210k + £170k

Vision
A developed framework for standardisation of miRNA measurement that helps UK biotechnology and healthcare industries exploit recent developments in miRNA analysis.
This will be achieved through evaluation of method performance for miRNA profiling technologies across multiple platforms, and robust methods and reference standards for interrogating processes within and between platforms.
Relevance to UK Economic Impact; UK Quality of Life; and UK NMS Science and Innovation.

Impact & Benefits
This field promises to have a significant impact on the UK priority business sector of healthcare - pharmaceuticals and diagnostics. miRNA offers new routes for therapeutic intervention which could help reverse the declining drug development pipeline. A framework for standardisation to support miRNA analysis, early in its application, will help improve product quality, shorten clinical acceptance and impact positively on regulatory acceptance and compliance for related *in vitro* diagnostic products. These will strengthen routes to market with clear associated economic benefit.
Diseases such as cancer can largely be seen as gene regulation disorders. With 1 in 3 of us expected to develop cancer during our lives, improved methods for diagnosis and treatment are paramount to enhancing the health of UK citizens. miRNA analysis is offering new avenues for developing such therapeutics and diagnostics. Global market estimates are $330m for 2010.
The lack of standards, metrics and protocols for assessing system performance of new technologies is known to be a significant barrier to measurement and innovation. Robust tools and standards are critical for ensuring the accuracy of measurement. There are currently no such tools for use as internal QC controls for method development and cross-platform comparisons to resolve measurement inconsistencies in miRNA analysis.
Positioning the UK NMS, through LGC, at the forefront of new nucleic acid measurement solutions will maintain and enhance its international reputation in genomics and ensure capability is available to apply such miRNA tools and approaches appropriately.

Support for Programme Challenge
Strategic priority relating to Bioanalysis; Healthcare – Diagnostics and Theme Roadmap – Genes, RNA analysis.

Support for Government Strategies
Supports NMO Draft Strategy and NMS interventions by addressing Healthcare priorities. The project also aligns with the Technology Strategy Board priority for Healthcare.

The Need
miRNA analysis is an emerging field which has immense potential for understanding the regulation of gene expression, developing therapeutic interventions and discovering novel biomarkers associated with various disease conditions.
As such, it is offering novel therapeutic interventions and disease diagnostics. However, the field is very much in its infancy and reliable, robust methods and standards have yet to be developed and fully validated.

Current State of the Art
Recently discovered miRNAs are small, non-coding regulatory RNAs, 20-23 nucleotide long, known to modulate gene expression at the pre- and post-transcriptional level in many species. Hundreds of miRNAs have been identified and their number is ever increasing. In humans, conservative predictions indicate that up to 30% of genes may be regulated by miRNAs and are known to control a variety of cellular functions including development, metabolic pathways, cell proliferation and differentiation, disease development and cell death.
The small size of miRNAs, the varying level of sequence conservation between miRNA species, their relatively low abundance in cells, the presence of miRNA precursors in the background and the ability of some miRNAs to regulate expression of multiple genes is challenging miRNA analysis.

The Solution
Microarray, real-time PCR and high throughput sequencing approaches are currently being developed for miRNA analysis.
Typically miRNA profiling involves a series of complex steps which are highly sensitive to technical manipulations. Factors impacting on assay performance include RNA quality, selection of reverse transcription strategies and kits, PCR and assay detection systems, and detection limits of the platforms.
Although several miRNA microarray kits have been launched recently on to the market, there has been little effort to standardise procedures for within or cross-platform comparison.

Metrology Capability to be Delivered
Supports the CBKB Bioanalysis themes.

Project Description
The project will select and evaluate miRNA extraction and analysis approaches, identifying the critical points of variability and uncertainty so as to allow robust analysis of miRNA to be developed.

A panel of synthetic miRNA spike-in standards consisting of 2-5 target miRNAs will be developed and tested by spiking-in to complex RNA, so as to evaluate platform/assay performance as well as cross-platform comparison.
Recommendations and guidance notes will be developed to establish a framework for standardisation of miRNA measurements.

Exploitation/Spin Offs
Exploitation will be directed to the key stakeholder communities through trade journal articles, peer-reviewed scientific papers and conference presentations, and the standard panel product.

Co-funding
N/A.

Knowledge Transfer Plan
Knowledge transfer of the developed strategies will be directed to industrial parties in the healthcare sector and to the key measurement and research communities (such as MGED, ERCC, MAQC, CLGSS, EuroGentest). This will be achieved through the Medicines and Healthcare KTN, peer-reviewed publications and presentations at scientific meetings. Moreover, method transfer through the CBM web-site will be undertaken.

Deliverables		Start	End	Price
1.	CEW a minimum of 3 miRNA extraction and analysis approaches have been identified and evaluated.	**Apr 10**	**Mar 11**	
2.	CEW the robustness and major sources of variability of the best approach from D1 have been determined.	**Apr 11**	**Sep 11**	
3.	CEW a panel of miRNA standards has been developed. CEW the developed panel has been evaluated in a complex RNA background. Evidence: Standard reference panel, guidance notes and peer reviewed scientific paper(s)	**Oct 11**	**May 13**	
4.	CEW project management activities completed. CEW articles prepared for CBM website, describing progress and outputs of the project. CEW framework for standardisation of miRNA measurements has been disseminated to relevant analytical communities	**Apr 10**	**May 13**	

Proposal No.	BA25	Price to NMO	£494k
Proposal Title	Metrology for cell imaging	Stage Start Date	April 2011
		Est Final Stage End Date	March 2014

Summary
This project will produce a prototype fluorescent cell based reference material that is compatible with advanced 3D imaging systems to support CCQM in the understanding of the uncertainty associated with cell measurement in 2D and allow the development of traceable methods for cell measurements in complex 3D systems. This prototype reference material will respond to the demand for reference materials to support innovation in the fields of regenerative medicine and drug discovery.

The Need & Current State of the Art

Over two decades of research have demonstrated that, with respect to traditional two-dimensional (2D) cell culture systems, three-dimensional (3D) cell models can improve the physiological relevance of cell based assays and advance the quantitative modelling of biological systems from cells to living organisms. These improvements have fuelled advances in regenerative medicine where the development of cell based products in 3D matrices are revolutionising healthcare provision. For cell based assays the advantages of 3D *in vitro* systems opens up the potential to model complex diseases or physiological states allowing development of safer pharmaceutical products.

As with many emergent technologies, the ability to develop new products is usually in advance of the techniques to measure the quality of their key components. This gap between product/model development and the availability of suitable metrology is now becoming a hindrance to innovation and commercialisation and is driving a global call for reference standards and measurement guidelines. In the USA, a Multi Agency Tissue Engineering Science (MATES) report on advancing tissue science and the 2010 Regenerative Medicine Promotion Act identified calibration standards for measuring cells in tissue engineered products as a critical requirement for supporting innovation in the field. In Europe, the International Society for Stem Cell Research (ISSCR), the UK Department of Health and the Innovative Medicines Initiative have warned there is a need to produce standardised guidance on how to measure cell quality (including viability) in cell therapy products.

State of art – Effort within CCQM to define the measurement uncertainty associated with fluorescence based cell measurements in 2D has been led by an LGC pilot study. However, there have been a number of recent advances in the development of standard 3D scaffolds which can support cell growth. A set of three 3D reference scaffolds have been developed in the USA as calibration standards, while in the UK, a 3D Plasma coated polystyrene scaffold which has the same chemistry as standard cell culture plastic, has allowed direct comparison of measurement between 2D and 3D systems. Quantitative 3D imaging is also becoming important for cell measurements particularly those based on fluorescence. However, reference standards for cell based measurements in 3D systems have yet to be developed and quantitative information embedded in the 3D datasets cannot yet be fully exploited.

The Solution & Metrology Capability to be Delivered
Supporting innovation in the development of cell based models for regenerative medicine and drug development applications requires a cell reference material to allow cell characterisation and advanced cell imaging in these complex systems. A significant proportion of cell based measurements utilise fluorescent technologies to label cellular events in real time and characterise their behaviour and function. Therefore, a fluorescent cell reference material will have maximum impact. This material will support effort through CCQM to understand the uncertainty associated with fluorescent cell measurements in 2D systems and use this data as a baseline for measuring changes in uncertainty when analytical approaches and imaging techniques are applied to cells in 3D systems

Impact and Benefits
This project will develop a prototype fluorescent cell based reference material for calibration of fluorescent analytical platforms in 2D cell models and for examination of measurement uncertainty in 3D cell based systems. Economic and innovation impact will be through support for the UK regenerative medicine industry competing in a global market worth in excess of £2 Billion per year and the European cell-based assay market worth in excess of £150m per year. Quality of life impact will be through the provision of reference standards supporting the development/characterisation of new cell based therapies and safer pharmaceuticals. This project will also impact on NMI capability by supporting the UK lead position in cell metrology through CCQM.

Support for Programme Challenge, Roadmaps, Government Strategies
Aligns with the CBKB theme “Bioanalysis” and technical sub-theme “Cells and Tissues” through underpinning metrology. This project also aligns with the “Cells and Tissues” roadmap for deliverables “cell model systems”, “microscopy”, and “real time and cell imaging”. It also supports the CCQM BAWG cell metrology roadmap and the TSB regenerative medicine roadmap 2011.

Knowledge Transfer and Exploitation Plan
Guideline documentation relating to cell characterisation in cell therapies will be produced. Scientific findings of the project will be disseminated through peer review publications and presentations at relevant scientific conferences.

Deliverables

1	**Start: 01/04/11**	**End: 31/01/12**	
Establish fluorescent cell model Considered effective when (CEW): A fluorescent cell model is established within the NMI and measurements are optimised using imaging techniques.			
2	**Start: 01/02/12**	**End: 30/11/12**	
Measurement of fluorescent variability CEW: Cell to cell variability within the population has been established using image based analysis and reduced to minimum levels using clonal selection.			
3	**Start: 01/12/12**	**End: 31/08/13**	
Assessment of measurement uncertainty and application in 3D systems CEW: Variability in measurement uncertainty has been assessed on different analytical platforms and changes measured in 3D reference scaffolds			
4	**Start: 01/09/13**	**End: 31/03/14**	
Application of the cell model as a calibrant and dissemination activities CEW: The use of the fluorescent cells have been assessed as a calibration tool between imaging systems and/or platforms. CEW: Dissemination activities have been completed			
5	**Start: 01/04/11**	**End: 31/03/14**	
Knowledge transfer Disseminated through peer reviewed publications and presentations. Methodology and updates will also be published on the UK NMS website.			
6	**Start: 01/04/11**	**End: 31/03/14**	
Project Management CEW: Project delivered on time and to budget			

Proposal No.	BA26	Price to NMO	£485k
Proposal Title	Clinically Relevant Protein Metrology	Stage Start Date	June 2011
		Stage End Date	March 2014

Summary

Current requirements of the EU *in-vitro* diagnostic directive (IVDD) highlight the importance of establishing "higher order" reference methods for *in-vitro* diagnostic (IVD) devices.

Over the past ten years, LGC has established itself as one of the world leaders in being able to carry out traceable protein quantification, demonstrated via the matrix certified reference values for biopharmaceutical therapeutic drugs. The proposed programme of work applies this expertise to establish "higher order" methods and procedures for clinically relevant peptides and proteins in serum. The methods developed will be used to participate in clinical proficiency testing (PT) schemes in order to ascertain the direct benefits of traceability for the chosen peptides/proteins. The final component of the project is focused towards investigating the impact of post translational modifications (PTMs) on current protein measurements methods and establish the requirements for providing reference measurements for this sub-set of measurands in the future.

The Need & Current State of the Art

Routine blood tests are an essential component of prognostic and diagnostic medicine, however these often use arbitrary international units (IU) to facilitate comparability, which lack traceability to SI. The current EU market for *in-vitro* diagnostic test kits is greater than €10 Billion. The EU *in-vitro* diagnostic devices directive (IVDD) has established the requirement for routine devices to provide results that are traceable to higher order standards, where available. The perceived impact of this requirement is three fold.

- The comparison of results over space and time requires expression of results in a common set of units. The anchoring of these units underpins the foundations for such comparisons.
- Once established the harmonisation of results will have major health benefits to patients by improving the chances of correct diagnosis. The cost of misdiagnosis is often overlooked, often leading to more costly interventions and/or a diminished quality of life of the patient.
- In addition this opens up the market for IVD testing devices, in that new approaches will become less constrained as the innovators are no longer aiming at what is often the "moving goalpost" of a PT or other consensus value.

Whilst previous CBM programmes have enabled the establishment of traceability of small molecule metabolites and drugs via the provision of certified reference materials and reference values for proficiency testing schemes, little has been done in the growing and important area of peptide and protein biomarkers.

The Solution & Metrology Capability to be Delivered

LGC scientists have established methods and approaches for the fully traceable value assignment of peptides and proteins. The methods used were based on re-engineering the tried and tested approach of isotope dilution mass spectrometry, which is the basis for most reference methods and is key to establishing a direct link to the SI for matrix samples. These approaches have recently been tested on serum and real patient samples and for the first time, enabling the provision of fully traceable measurements on important peptide and protein markers. The dissemination of traceability and its impact on this large group of increasing important biomarkers is yet to be realised. This will be achieved by working with PT providers, clinical laboratories and IVD manufacturers to establish mechanisms and approaches for linking the IDMS approaches and results from real clinical samples.

Impact and Benefits

The benefits of traceability for the area of clinical diagnosis are already well documented. However, the current low number of reference materials and reference measurement services highlights the need for greater effort in the provision of reference measurements in the protein and peptide areas. This project will go some way to address the current imbalance.

Support for Programme Challenge, Roadmaps, Government Strategies

Healthcare - Evaluation of new technologies for diagnostics. This project supports the NMO Draft Strategy relating to Healthcare.

Knowledge Transfer and Exploitation Plan

Key peer review publications and conference presentations will be produced.

Deliverables

1	**Start: 01/06/11**	**End: 31/05/12**	

Assessment of reference measurement procedures for two circulating peptides in serum

- Provision of traceable peptide standards for the selected peptides
- Characterisation of serum matrix materials and value characterisation of currently provided PT samples.

2	**Start: 01/06/12**	**End: 31/12/12**	

Assessment of digestion methods for a selected target protein in serum

- Assessment of enzymes other than trypsin for quantitative digestion of target proteins
- Evaluation of equimolar release of target peptides
- Provision of peptide standards for enzymatic products
- Provision of a primary traceable protein standard for use as a primary calibrator

3	**Start: 01/01/13**	**End: 31/12/13**	
Assessment of reference measurement procedures for a clinically relevant protein in serum • Evaluation of providing traceable reference values in matrix materials for the target protein • Characterisation of serum matrix materials for the traceable value assignment of samples used in PT schemes			
4	**Start:**	**End:**	**Deleted**
Investigation of methods and approaches for the characterisation and relative quantification of clinically relevant glycoproteins • Characterisation of glycoprotein/glycan • Isolation methodologies for glycopeptides • Evaluation of strategies for glycoprotein quantification			
5	**Start: 01/01/12**	**End: 31/03/14**	
Knowledge Transfer • Peer review higher order molecular measurements for priority clinical measurands			
6	**Start: 01/07/11**	**End: 31/03/14**	
Project Management • Project managed on time and to budget			

Proposal No.	BA27	Price to NMO	£505k
Proposal Title	Mechanisms for SI traceable bio molecular metrology	Stage Start Date	October 2011
		Est Final Stage End Date	March 2014

Summary
Whilst cutting edge molecular techniques offer considerable potential for diagnostic biomarker measurement, the lack of higher order reference methods and materials is a major hindrance for ensuring consistency when translating preclinical research into new diagnostic tests. The European *in-vitro* diagnostics directive (IVDD) recognises this, with tests now required to demonstrate traceability to higher order reference materials if they are available. Unfortunately, such materials do not usually exist for nucleic acids, due to a lack of higher order measurement approaches to assign such values. Established molecular diagnostic strategies often use arbitrary international units (IU) to facilitate comparability, which lack traceability to SI. This project will investigate the feasibility of providing traceability to the SI concept of Unity through enumeration (counting) of nucleic acid target molecules. We will evaluate the potential of a number of different higher order absolute molecular counting approaches for assigning target copy number values to nucleic acid based-materials. We will also investigate the potential of the approaches being developed to convert IU to SI and establish whether the mechanisms for assuring commutability of such measurements will facilitate traceability of more complex biomarker measurements.

The Need & Current State of the Art
It is increasingly clear that more accurate quantitative assessments of nucleic acid biomarkers is a requirement to fully exploit their diagnostic potential. Current quantitative molecular assays typically generate analogue intensity signals based on population averages. Quantification then occurs through comparison to a reference standard, or report an amount relative to an internal control. In many cases reference standards are defined by arbitrary international units (IU) which makes traceability to SI problematic. Previous attempts to assign SI values to nucleic acid reference materials has proved difficult, due in part to the analogue, relative, nature of the signal generation from a population of discrete molecules. Recent developments in absolute molecular measurement approaches offer the potential for performing higher order measurement to which more precise values can be assigned thereby offering the potential for revolutionising biomolecular metrology. By investigating digital enumeration methods to count individual molecules this project aims to meet the need for development of higher order methods to enable traceability of molecular measurements to SI.

The Solution & Metrology Capability to be Delivered
Nucleic acid enumeration will take advantage of a number of newer digital technologies that afford absolute molecular measurement. Technologies like next generation sequencing (NGS) and digital PCR offer the potential for higher order measurement, but while they present the possibility of absolute or 'near' absolute quantification, their utility for such measurement needs to be investigated. Using an established single target model, as well as a more complicated mixed-cells gene expression model, the project will investigate how a series of higher order measurement methods can provide traceable measurement. Real and synthetic versions of key sequences will be assessed for comparability. The study will define the uncertainty associated with the many steps involved in performing molecular measurement. By actively investigating higher order measurement capability, which the NMI is uniquely placed to address, the knowledge generated will facilitate the development and monitoring of commercial IVD tests.

Impact and Benefits
This work facilitates the improvement of clinical diagnosis/prognosis tools by developing molecular enumeration approaches traceable to the SI concept of unity. This project investigates methods for performing higher order measurement as a mechanism for defining SI and will explore application of uncertainty to the whole process of molecular measurement for power calculations. This will assist UK companies in the development of diagnostic tests by providing a mechanism for demonstrating traceability yielding economic and quality of life benefits. Standardisation will allow improved clinical comparability of multi parametric tests for managing complex diseases linked with changing demographics (e.g. ageing population) could also be developed that would have a high economic and quality of life impact as prevalence of diseases like arthritis, cancer, heart disease are correlated with age.

Support for Programme Challenge, Roadmaps, Government Strategies
Healthcare - Evaluation of new technologies for diagnostics. This project supports the NMO Draft Strategy relating to Healthcare.

Knowledge Transfer and Exploitation Plan
Key peer review publications and conference presentations will be produced as well as method dissemination via CBM website.

Deliverables

1	**Start: 01/11/2011**	**End: 31/07/2012**	

Source, develop and characterise project materials

- Successful development setup of simple model based on IU
- Successful development of complex cell mix model combining different defined proportions of distinctive cell types

2	**Start: 01/01/2012**	**End: 28/02/2013**	

Evaluate project materials using existing methodologies (preliminary NMI inter-comparison)

• Development and characterisation of methodologies for measuring model target samples using quantitative PCR • Develop and describe approaches for performing calibration/standardisation using existing approaches (reference materials, reference genes, external controls, sample quality metrics etc.) • Distribute material for preliminary inter -comparison			
3	**Start: 01/03/2012**	**End: 31/08/2013**	
Evaluate project materials using new methodologies such as NGS and/or digital RT PCR • Development and characterisation of at least two higher order methodologies • Perform analysis on model target samples and describe the uncertainties therein • Develop and describe mechanisms to apply findings			
4	**Start: 01/09/2012**	**End: 31/05/2013**	
Real sample evaluation • Evaluation of real samples and testing scenarios			
5	**Start: 01/09/2012**	**End: 31/03/2014**	
Knowledge Transfer • Stakeholder workshop/event (co)-hosted • Peer review publication on enumeration approaches for higher order molecular measurements • Inform CCQM of the study findings with the potential to form the basis of a pilot study			
6	**Start: 01/10/2011**	**End: 31/03/2014**	
Project Management • Project delivered on time and to budget			

Proposal No.	BA28	Price to NMO	£332k
Proposal Title	Measurement needs for using cell free nucleic acids as diagnostic targets	Stage Start Date	Oct 2011
		Est Final Stage End Date	Sep 2014

Summary
The discovery of cell free nucleic acid (cfNA) in blood has provided a potential minimally-invasive source of genetic material for pre-natal or tumour diagnostics. However, as only a small fraction of the cfNA in the sample is derived from the tumour, identification of a genetic mutation represents a difficult analytical challenge given that the target NA is effectively 'diluted' in a background of normal NA. Cell free nucleic acid (cfNA) testing therefore offers considerable potential advantages to conventional diagnostic techniques due to the minimally invasive nature of the sampling. Despite this, many of the key metrology questions associated with measuring cfNA remain unanswered. Addressing these questions will be essential if the true diagnostic potential of this nucleic acid fraction is to be realised. This project will build on existing studies to address the diagnostic measurement issues when measuring cfNA.

The Need & Current State of the Art
cfNA is an ideal diagnostic target as sampling is considerably simpler and less invasive than the alternative approaches and molecular methods can offer rapid and effective diagnoses. Furthermore targeting cfNA when screening for mutations for cancer diagnosis and prognosis could be performed without the need for taking invasive and uncomfortable biopsies. There is a plethora of literature defining the potential diagnostic and prognostic monitoring significance of cfNA but it has suffered poor translation from basic research into clinical practice. One of the main challenges with this field is the very small quantities of nucleic acids available for analysis within this fraction. To combat this cell free NA isolation procedures, targeted enrichment and the introduction of newer more sensitive methods like digital PCR and next generation sequencing offer potential, but the measurement challenges like bias need to be addressed. To realise this, efforts are needed to describe and address the associated measurement challenges that will be required to translate cfNA analysis into routine clinical diagnostics.

The Solution & Metrology Capability to be Delivered
To investigate cfNA detection this project will take advantage of a number of newer extraction procedures that specialise in purification of the cell free nucleic acids and digital technologies that afford absolute molecular measurement. We will evaluate different purification methods and potential enrichment procedures tailored to this fraction of nucleic acids. We will also evaluate how novel technologies like digital PCR and/or next generation sequencing can contribute to two of the most challenging measurement approaches when targeting this fraction; trace molecule detection and minority target assessment. Minority target assessment is an essential area when measuring rare autosomal mutations that might provide prognostic indication of tumour progression. Current technologies like quantitative PCR and conventional sequencing have had some success in these areas but the newer instruments described above coupled with the knowledge generated from the purification and enrichment assessment will provide a description of where the technical challenges lie and possible solutions. Furthermore, this project will also use a clinical scenario to also consider issues that will be met when translating these findings to *in-vitro* diagnostic tests.

Impact and Benefits
In-vitro diagnostics is also one of the largest segments within the UK's Bioscience & Health Technology industry with a turnover for 2009-2010 in excess £1.4bn, employing over 4,000 individuals and which grew by 4% from the previous year. To keep the UK at the forefront of this market it is therefore important to support new innovations. This project facilitates the improvement of clinical diagnosis/prognosis by solving some of the measurement challenges encountered when targeting cfNA. By investigating methods for performing trace detection and minority target assessment this work impacts the two key areas where cfNA analysis can revolutionise diagnostic medicine. Method users will benefit from the evaluation of purification and enrichment procedures enabling identification of potential causes of variation within laboratory measurements and leading to improved standardisation of procedures.
Transfer of project findings from the laboratory to a real clinical scenario will identify the challenges associated with technology translation, directly assisting manufacturers and test developers. Overall improvements in the molecular detection of cfNA will provide diagnostic devices that offer simplified testing regimes and better patient access yielding high economic and quality of life impact.

Support for Programme Challenge, Roadmaps, Government Strategies
Healthcare - Evaluation of new technologies for diagnostics. This project supports the NMO Draft Strategy relating to Healthcare.

Knowledge Transfer and Exploitation Plan
Key peer review publication(s) will be produced as well as method dissemination via the CBM website.

Deliverables

1	**Start: 01/10/2011**	**End: 30/12/2012**	

Definition of study plan and preparation of materials for study based on models such as foetal/cancer

- Definition of experimental project plan defined following consultation and literature review, assisted by findings from previous studies (DX3)
- Materials sourced/prepared for project

2	**Start: 01/01/2012**	**End: 31/03/2013**	

Evaluation of methods for extraction and enrichment of cell free nucleic acids

• Characterise the efficacy of selected cell free NA extraction methods based on % recoveries. • Assess methods for the targeted enrichment of small fragmented DNA for precision and bias			
3	**Start: 01/08/2012**	**End: 31/12/2013**	
Evaluation of methods for measurement of cell free nucleic acid targets to include • An assessment of the ability to measure trace target molecules (low copy number nucleic acid targets) in cfNA and the practical limitations established. • Approaches to detect minority targets (e.g. rare mutations present in a background of wild type targets) from cell free NA will be investigated to define molecular sensitivity and specificity			
4	**Start: 01/11/2012**	**End: 31/12/2013**	
Translational research • Knowledge generated from deliverables 2 and 3 will be used to develop best practice approaches • Identify the most clinically relevant model and establish collaboration with appropriate clinical colleagues • Perform preliminary translational research to evaluate best practice approach			
5	**Start: 01/01/2013**	**End: 31/09/2014**	
Knowledge Transfer • Peer review publication(s) describing cfNA detection techniques and methods for ensuring robust measurement. • Presentation of findings at conference/workshops			
6	**Start: 01/10/2011**	**End: 31/09/2014**	
Project Management • Project managed on time and to budget			

Proposal No.	BA29	**Price to NMO**	£56K
Proposal Title	Validation of an immunoassay method for the detection and quantification of food allergens	**Co-funding target**	
		Start Date	Jul 2011
		End Date	Sep 2013

Summary
Measurement tools are required for the detection and quantitation of food allergens to minimise the use of precautionary labelling and reduce product recalls in the food industry. This project aims to validate an ELISA-based method for the measurement of nut allergens in complex food matrix materials through determination of relevant performance characteristics.

The Need & Current State of the Art
For an estimated 2% of adults and 5-8% of children suffering from food allergy (e.g. nut allergy) in industrialised countries there is currently no cure, avoidance is the primary protective strategy. Loss in quality of life, mortality, food recalls, and associated costs to the UK economy ensue. Food containing certain allergenic ingredients must be clearly labelled but regulatory clarity is lacking as regulatory threshold limits remain to be established for allergens other than gluten and SO_2. Development and efficient deployment of reliable analytical techniques and data interpretation for the determination and quantification of food allergens are key to the resolution and avoidance of technical disputes. In turn this will support sound evidence for public policy development and be crucial to the success of regulatory and food industry allergen management strategies.

The Solution & Metrology Capability to be Delivered
The project will provide food manufacturers and testing laboratories with an effective tool for detection and quantitation of allergens in foods.

Impact and Benefits
The availability of a validated method will improve allergen detection for food manufacturers and testing laboratories and improve inter-laboratory comparability across the industry. In addition, an improved detection method will enable future development of QC/RM materials which would allow food manufacturers and testing laboratories to monitor the performance of their allergen testing methods on an ongoing basis. These benefits will help food manufacturers with allergen labelling regulations and reduce product recalls and, ultimately, contribute to improved quality of life for allergen sufferers.

Support for Programme Challenge, Roadmaps, Government Strategies
Supports the CB Chemical Measurement and Calibration theme, and the Long-term metrology sub-theme.

Knowledge Transfer and Exploitation Plan
Project outputs will be discussed with, and fed into, the allergen community including food retailers, food manufacturers (including several global manufacturers), the UK food research associations, analytical service companies and manufacturers of diagnostic kits ensuring effective integration of new methods into allergen management.

Deliverables

1	**Start: 01/10/12**	**End: 30/09/13**	

Validation of an ELISA kit for the detection of peanut protein
CEW performance characteristics determined of an ELISA method for the analysis of a peanut allergen in a matrix material.

2	**Start: 01/09/11**	**End: 30/09/13**	

Project planning meetings and management
CEW project delivered to time and budget.

3	**Start: 01/10/12**	**End: 30/09/13**	

Knowledge transfer
CEW project results will be disseminated to relevant stakeholders from the Food Industry through various fora and the validated method will be fed into a TSB study to enable production of a well-characterised quality control (QC) material for food allergen testing.

Project No.	CB/2012/BA31	Price to NMO	£297k
Project Title	Strategies for traceable quantification of proteins in biological fluids	Stage Start Date	1 April 2012
		Est Final Stage End Date	31 March 2014

Summary

The development of reference methods and materials for the analysis of proteins and peptides is a recognised requirement for the global harmonisation of clinical laboratory testing. However, a robust approach capable of providing SI traceable results for the quantification of target proteins, in biological fluids, has yet to be fully established. Previous CBM projects have enabled LGC to emerge as a word leader in developing methods for the quantification of standard proteins and peptides with measurement results having low uncertainties and SI traceability, to qualify as "higher order" methods. The current approach is based on the quantification of unique peptides via isotope dilution mass spectrometry (IDMS) that can be formed on digestion of the protein. This approach relies on the complete digestion of the target protein to its constituent peptides. It has been suggested that many of the concerns surrounding total digestion could be remedied by the use of labelled proteins. However, the equilibration of the natural and labelled protein will rely not only on its primary sequence but on its folding (i.e. secondary and tertiary structure) and protein-protein interaction quaternary structure. Recent studies at LGC have suggested that the structure of the protein in biological fluids is an important factor for consideration when quantifying using this approach. This project continues the work carried out within the CBM project BA5 and the iMERA-Plus "ClinBioTrace" project for the quantification of human growth hormone (hGH) in serum. It aims to investigate the impact of the structural differences between the protein to be quantified and its internal standard and to evaluate the implications of those differences in protein quantification In biological matrices.

The Need

The field of clinical proteomics is rapidly expanding the search for candidate protein biomarkers as they can provide a wealth of information on the development and state of disease. Both the International Federation of Clinical Chemistry (IFCC) and the International Joint Committee for Traceability in Laboratory Medicine (JCTLM) recognise the needs for the development of robust quantitative reference methods and reference materials for clinically relevant proteins and other biomolecules to ensure accuracy and comparability of the results obtained from clinical laboratories tests. In recent years the uptake of new protein biomarkers in clinical practice has not kept pace with the hype the "omics" industries promised. Between 2003 and 2008 only 8 new protein biomarkers were approved by the FDA. Experts believe one of the biggest bottlenecks is in the development of screening strategies for the newly discovered biomarkers. While many reviews have been published on quantification of proteins in biological matrices, their chemical and structural heterogeneity renders the development of traceable reference methods and materials and the definition of their requirements difficult. The development of "fit for purpose" reference methods capable of providing reference materials would be beneficial for the validation of new biomarkers and for the harmonisation of existing protein diagnostic markers.

The Solution

IDMS has the potential to be a primary ratio method, whereby results generated can be related directly to the SI with small measurement uncertainties. This method has been successfully applied to produce certified reference materials in biological fluids and has been used by LGC to quantify standard proteins using isotopically labelled peptides as internal standards. When moving from simplistic solutions to serum, the use of peptide internal standards pose some limitations. Labelled peptides do not account for protein/peptide losses or modifications introduced during the complex sample preparation procedure (i.e. digestion and pre-digestion clean up strategies). Isotopically labelled proteins are believed to act as more effective internal standards as, once fully equilibrated, they match the biochemical properties of the analyte of interest. However, the applicability of labelled proteins must first be assessed before they can be used confidently as internal standards for traceable quantification by IDMS. Previous work carried out within the "ClinBioTrace" project, has suggested that different conformations of hGH lead to different ELISA responses and behaviour in serum. This ultimately affects quantification of the protein by IDMS if the protein and its labelled internal standard are present in different conformations. A better understanding of both the process of equilibration of recombinant proteins in serum and their behaviour upon denaturation has to therefore be achieved if recombinant proteins are to be used as internal standards for traceable quantification of biomarkers in serum.

Impact and Benefits

The benefits of traceability for the area of clinical diagnosis are already well documented. The setting up of the JCTLM and the inclusion of traceability terms in such important directives as the EU IVDD is testament to this. However, the current low number of JCTLM reference materials and reference measurement services highlights the need for greater effort in the provision of reference measurements in the protein/peptide areas. This project will contribute to increase the understanding of the challenges related to quantification of proteins in serum and the selection of the appropriate internal standards. The discovery that isotopically labelled proteins are not fully mimicking the behaviour of unlabelled proteins in biological fluids is vital for the scientific community and will be disseminated fully and appropriately, given that the currently held assumption is that isotopically labelled proteins are the ideal standards for quantification of proteins in complex matrices.

Support for Programme Challenge, Roadmaps, Government Strategies

Healthcare - Evaluation of new technologies for diagnostics. This project supports the NMO Draft Strategy relating to Healthcare. It also fits with the TSB Healthcare, Medicines and Bioscience Technology Areas.

Synergies with other projects / programmes

This project continues the work carried out within the CBM BA5 project on traceable quantification of structurally different proteins providing fundamental understanding of the challenges faced when isotopically labelled standards are selected for quantification of proteins in biological fluids. The findings within this project will also support the delivery of project BA26 on clinical relevant protein metrology.			
Knowledge Transfer and Exploitation Key peer-reviewed publications and conference presentations will be produced. Links with the Medicines and Healthcare and Bioscience KTNs, clinical reference materials working group and JCTLM committee will be exploited in parallel with stakeholder events to ensure wider industry uptake of project outputs.			
Deliverables			
1	**Start: 01/05/12**	**End: 01/01/13**	
Assessment of isotopically labelled hGH preparations as internal standards for the quantification of hGH in serum When sample clean up procedures have been optimised and equilibration/denaturation strategies to reduce the structural differences of labelled and unlabelled hGH in serum have been fully evaluated.			
2	**Start: 01/07/12**	**End: 01/03/13**	
Development of a total digestion method for the analysis of hGH in serum When hGH has been quantified in serum via a total digestion methods.			
3	**Start: 01/03/13**	**End: 01/04/13**	
Inter-laboratory comparison of a serum spiked sample When an inter-laboratory comparison, including different digestion strategies and analytical technologies has been completed.			
4	**Start: 01/04/13**	**End: 01/05/13**	
Assessment of the applicability of the method to clinical samples When a number of real patient samples have been quantified using the reference method, including the use of peptide and protein standards. Results compared with results obtained via ELISA.			
5	**Start: 01/04/12**	**End: 31/03/14**	
Preliminary evaluation of the impact of hGH structural difference in clinical measurements When a comparison of the different structural forms of hGH have been made via the use of ion mobility MS and an investigation into the utility of other structural methods (e.g. HDX) has been completed.			
6	**Start: 01/04/12**	**End: 31/03/14**	
Knowledge transfer When two peer-reviewed publications have been prepared and presentations given at 2 international conferences.			
7	**Start: 01/04/12**	**End: 31/03/14**	
Project Management Project managed on time and to budget			

Project No.	CB/2012/BA32 + BA32b	Price to NMO	£129K +£11k
Project Title	Novel mathematical and statistical approaches to uncertainty evaluation	Stage Start Date	1 June 2012
		Est Final Stage End Date	30 June 2015

Summary

This project matches LGC's contribution to EMRP JRP NEW04, which aims to develop novel approaches to measurement uncertainty evaluation and to enable their consistent application, illustrated by appropriate case studies. LGC will apply advanced measurement uncertainty evaluation techniques to emerging problems in chemical and biological measurement, providing case studies for the EMRP project and, by developing appropriate measurement uncertainty evaluation methods, enable the application of new measurement technologies for high level reference measurements in chemical and biological measurement. The project additionally includes the development of guidance on methods for conformity assessment and reliable decision making that incorporate knowledge of the measurement uncertainty.

The Need

Reference measurements in chemical and biological measurement require reliable uncertainty estimates and are using increasingly sophisticated experimental approaches and (particularly in biological measurement) highly replicated observations with non-normal output distributions. These changes are driving the use of more advanced data treatment and evaluation methods, including iterative numerical solutions and novel regression approaches. These in turn change the nature of uncertainty evaluation, from the comparatively simple 'first order' approximation used in current international guidance to computational methods that use highly replicated simulation approaches to obtain reliable uncertainty intervals. This is particularly true of Bayesian methods, which form the basis of most recent developments in uncertainty evaluation. These approaches are, however, substantially under-developed in chemical and biological measurement, limiting the application of new measurement technologies for reference measurement. In short, new measurement technologies offer improved measurement capability but introduce a need for matching uncertainty evaluation techniques. Without reliable uncertainty estimates these newer technologies cannot be applied to high level reference measurement.

The Solution

This project will study novel approaches to measurement uncertainty evaluation and apply them to relevant case studies in (among others) chemical and biological measurement. Project results will contribute to the development of future guidance on uncertainty evaluation (both within and beyond chemical and biological measurement). The methods developed by LGC during the project will additionally be disseminated through open source software, allowing other laboratories to apply them as needed.

Impact and Benefits

The EMRP project benefits are expected to be: Dissemination of methods, software and guidelines for reliable measurement uncertainty evaluation will strengthen UK and European capability for innovation by allowing the use of advanced measurement technologies for reference biological and chemical measurement (economic, social and environmental). Reliable uncertainty evaluation is expected to allow accurate identification of factors affecting agreement between laboratories, reducing unnecessary refinement of the measurement methods and reducing overall measurement costs. Harmonized evaluation of uncertainty evaluation methods will lead to improved safety regulation decisions and conformity assessment for products based on measurements (economic, social and environmental). In applications where the solution of the measurement model is computationally expensive, methods developed in this project will allow a realistic statement of uncertainty, fostering new industrial developments based on traceable measurements (economic). Successful dissemination of the outputs of the proposed project will improve individual engineering and measurement practice, facilitate the transferability of results from NMIs to industry, and reduce barriers to trade (economic). Within the UK, successful participation will improve capabilities for reference measurement in chemical and biochemical measurement. This will allow the production of reference materials for method validation and calibration and the delivery of reference values for inter-laboratory comparisons across a wide range of health, environment and industrial sectors. This in turn will improve agreement in measurements of known analytes and enable measurements of new analytes and products.

Support for Programme Challenge, Roadmaps, Government Strategies

Supports CBM strategic priority themes of Bioanalysis, Chemical Measurement and Calibration; roadmap theme of Genes (through choice of case studies). Provides wider general support for UK Chem/Bio measurement capability at the NMI via the development of methodology for uncertainty evaluation that can be applied to a wide range of applications

Synergies with other projects / programmes

EMRP JRP NEW04 "Novel mathematical and statistical approaches to uncertainty evaluation" this will bring world-leading expertise in advanced uncertainty evaluation methodologies from other measurement sectors to the work, and ensure that outputs are relevant across the wider chemical and biological metrology programme themes.

Knowledge Transfer and Exploitation

To ensure wide dissemination, a stakeholder group will be formed, initially of experimentalists from partner NMIs, regulators and industrial end users in target application areas. Regular interaction with this group via meetings and a JRP website will ensure project focus and external awareness of outputs. Metrology standards groups, particularly Joint Committee for Guides in Metrology (JCGM), will be accessed via the stakeholder group. Case study materials will

be used in subsequent training events and national and international workshops and made available via the JRP website. Software developed will be made available free of charge via the website. Code developed will also provide software and algorithms written in 'R' and distributed as an extension to the metrology package, an existing open source library produced by LGC. Additional dissemination will be via the package repository network for the R project, which currently includes mirrored repositories in over 100 locations worldwide. Peer review publications will result from technical work.			
Deliverables			
1	**Start: 01/06/12**	**End: 31/03/13**	
Statistical models: Description of statistical models appropriate for digital PCR and real-time PCR regression completed and passed to EMRP project leader			
2	**Start: 31/03/13**	**End: 31/07/14**	
Case study on biochemical concentration: Manuscript submitted to an appropriate peer reviewed journal, describing the application of advanced uncertainty evaluation methods to at least one chemical or biochemical measurement problem			
3	**Start: 1/08/14**	**End: 30/06/15**	
Open source software implementation available: Advanced uncertainty evaluation methodology available in a widely available open source package			
4	**Start: 1/06/12**	**End: 30/06/15**	
Project Management			

Project No.	CB/2013/BA33	Price to NMO	£358k
Project Title	Capability building in protein modification and folding to underpin the development of biological reference materials	Stage Start Date	Jun 13
		Stage End Date	Dec 14
Sector	Underpinning metrology	Activity	Methodology for new capabilities

Summary

This project is the first of a series of projects which aims to expand LGC protein measurement capabilities to support the development of reference methods and biological certified reference materials (CRM) across a number of sectors where standardisation is an urgent requirement (e.g. clinical, food and bio-pharma). These capabilities include the analysis of post-translational modifications (PTM) such as glycosylation and the evaluation of the tertiary/quaternary structure of proteins.

In this project, a number of separation and mass spectrometry platforms for the analysis of at least one PTM such as glycosylation will be assessed and the use of ion mobility mass spectrometry based methods for the analysis of the tertiary and quaternary structure of a protein will be evaluated.

The Need

Over the past decade LGC, independently as the first National Measurement Institute (NMI) and then more recently in collaboration with other NMIs, has developed methods to quantify the primary structure of a protein in aqueous solutions and in complex matrices with the final aim to produce biological reference materials and reference methods. These methods have been validated through participation in CCQM studies and inter-laboratories comparisons. However, it is recognised that while quantification of the primary structure of proteins ensures traceability to the International System of Units, additional protein characterisation is necessary to correlate the amount of a protein to its biological function (e.g. whether the protein is glycosylated, phosphorylated, deamidated, oxidated or folded appropriately).

The Solution

In order to produce fit for purpose biological reference materials, there is a requirement to identify PTMs and to ensure PTM homogeneity within and between batches of the same material. In addition, the tertiary structure of the protein also needs to be considered, since changes in the tertiary structure may cause changes in protein activity and stability. Furthermore, if the reference material is intended to standardise ELISA kits, changes to protein tertiary structure induced by storage conditions may affect antibody binding and therefore the analytical measurement.

A review of current methods for the analysis of PTM and protein tertiary/quaternary structure will identify the most appropriate methods to be applied to support protein metrology for biological measurements.

Impact and Benefits

The capabilities developed within this project are essential to underpin the development of protein reference materials for the clinical and food sector and will be transferable to applications in other areas such as the biopharmaceutical industry. It will also extend the UK's metrological capabilities through the development of a set of measurement tools for protein characterisation.

Support for Programme Challenge, Roadmaps, Government Strategies

Aligns with CBM Strategic Theme 'Chemical Measurement and Calibration'.

Synergies with other projects / programmes

Synergy with other contracted protein mass spectrometry projects (BA26, BA31) to develop accurate traceable measurements for protein biomarkers.

Knowledge Transfer and Exploitation

The results of the project will be disseminated at conferences, through peer review papers (if appropriate) and through discussion at a new protein measurement stakeholder user group forum set up via project KT2e.

Deliverables

1	**Start: 01/06/13**	**End: 31/12/14**	

Development of capabilities for the analysis post-translational modifications

When analysis of the glycosylation profile of a clinical relevant protein (e.g. NT-proBNP) is performed and preliminary experiments are carried out to evaluate the measurement requirements for the analysis of other relevant post-translational modifications e.g. phosphorylation and oxidation

2	**Start: 01/07/13**	**End: 01/06/14**	

Development of ion mobility mass spectrometry methods for structural analysis of proteins

When ion mobility mass spectrometry based methods for the analysis of the tertiary structure of proteins have been established

3	**Start: 01/06/14**	**End: 31/12/14**	

Knowledge transfer

When the findings/methods of this project will be disseminated through attendance at conferences, peer review papers or reports as appropriate.

4	**Start: 01/06/14**	**End: 31/12/14**	

Project management

Project delivered in a cost effective manner. Customer reporting requirements fulfilled.

Project No.	CB/2013/BA35	**Price to NMO**	£639k
Project Title	Bio-SITrace - Traceability for biologically relevant molecules and entities	**Stage Start Date**	Jun 13
		Stage End Date	May 16
Sector	Diagnostics, Regulatory frameworks, Traceability & uncertainty, Extension of SI	**Activity**	Methodology for new capabilities

Summary
This project provides matching funding for LGC's contribution to the EMRP project JRP SIB54 (Bio-SITrace); A large European consortium project coordinated by LGC. The overall aim is to progress the state of the art for biomeasurement comparability by developing internationally agreed guidance on achieving metrological traceability to the Systeme International (SI) and assigning measurement uncertainty values for nucleic acid and cell-based measurements.

The Need
Accurate measurement of biological analytes underpins many sectors including healthcare, security, environment, biotechnology, and food. Examples include circulating tumour cells in cancer, viral load monitoring in patients, presence of GMOs, allergens and pathogens in foods, host cell contamination in vaccines and biopharmaceuticals, QC of tissue engineered products etc. However, a lack of higher order reference methods and materials is a major hindrance for deriving traceability and measurement comparability, and impacts upon accreditation and regulatory compliance.
The importance of measurement comparability in the field of Laboratory Medicine, and the need for fundamental scientifically valid measurements based on traceability to SI units, is clearly emphasised under EU Directive 98/79/EC which states that "The traceability of values assigned to calibrators and (trueness) control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order". In ISO 17511:2003 it is explained that standardisation among different routine measurement procedures should ideally be achieved according to fundamental metrological principles with full traceability to SI units, supported with higher order reference measurement procedures and reference materials. In addition, a 2011 BIPM report entitled "Study of Measurement Service and Comparison Needs for an International Measurement Infrastructure for the Biosciences and Biotechnology" also highlighted the key requirement of "Support for fundamental metrology, aimed at making biomeasurements traceable to the SI".

The Solution
Biomeasurements lend themselves to description in terms of number of discrete entities such as DNA copies or number of cells. Technologies such as digital PCR, Next Generation Sequencing, as well as flow cytometry and other cell-based imaging methods are capable of measuring or 'counting' individual molecules, a concept known as 'enumeration'. These methods, in combination with reference materials (characterised for purity of measurand e.g. presence/absence of sequence mutations in a DNA reference material), have the potential to address stakeholder needs through the development of SI-traceable biomeasurements. This will provide the basis for a substantial increase in the range of biological measurements that can rely on traceability to the SI.

Impact and Benefits
Success in this research project will reduce one of the most important barriers to adoption of SI traceability for biological measurements. This will help to widen the applicability of SI traceability for a wide range of biological measurements undertaken within and outside NMIs. Wider application of the SI will in turn; Reduce reliance on consensus values for primary certified materials, improve the long term consistency of biological measurements; Enable the production of a wider range of SI-traceable reference materials for calibration and validation of biological measurement systems in the field; Allow NMIs to provide more reliable reference values for proficiency schemes, in the long term reducing disagreements between assay kit manufacturers and improving agreement between different laboratories worldwide; Simplify approval of reference measurement systems and reference materials by JCTLM (Joint Committee for Traceability in Laboratory Medicine) by providing clear traceability to the SI; Facilitate conversion of relevant values from International Units (IU) to SI. Accurate counting of biological entities, including both molecular and cell targets, underpins many sectors including healthcare, security, environment, biotechnology, and food. In all of these sectors an ability to identify and count individual biological entities is essential. Improvements in understanding of enumeration will therefore have wide applicability across many priority areas of measurement.

Support for Programme Challenge, Roadmaps, Government Strategies
Aligns with CBM Strategic Theme 'Bioanalysis' and sub-theme 'Diagnostics – Development of quantitative reference methods and standards traceable to higher order required by EU IVD Directive'.

Synergies with other projects / programmes
JRP SIB54: "Traceability for biologically relevant molecules and entities"; BA27: "Mechanisms for SI traceable bio molecular metrology".

Knowledge Transfer and Exploitation
Technical outputs from this project will be used to directly inform standards /guidance/recommendations by appropriate bodies (including ISO TC212 WG2, CLSI, IFCC Scientific Division and Molecular Standards WG, Eurachem, JCTLM, CCQM). Dissemination will be achieved through direct collaborative interaction with relevant instrument manufacturers, reference laboratories, and relevant professional interest bodies. Further dissemination will be by focused stakeholder workshops and a series of publications and conference presentations to the wider community.

Deliverables			
1	**Start: 01/06/13**	**End: 30/11/13**	
Project and concept definition: Development of a conceptual framework for achieving traceability of bio-molecules (nucleic acids and cells).			
2	**Start: 01/06/13**	**End: 28/02/16**	
Enumeration methods for nucleic acids: Procedures and uncertainty budgets suitable for primary reference measurements of amount of nucleic acid based on single-molecule detection and counting (enumeration) established.			
3	**Start: 01/06/13**	**End: 31/03/16**	
Enumeration methods for cells: Development and evaluation of reference measurement procedures for the enumeration of cell-based entities and determination of their concentrations.			
4	**Start: 01/01/14**	**End: 28/02/16**	
Protocol for the characterisation of purity of nucleic acid and cell-based calibration materials: Development of measurement methods for the characterisation of the purity of biological materials.			
5	**Start: 01/06/2013**	**End: 31/05/16**	
Creating Impact: Production of a project website, peer review publications and organisation of workshops.			
6	**Start: 01/06/2013**	**End: 31/05/16**	
JRP Management and Coordination of consortium: Project Management.			

Proposal No.	IM1c	Price to NMO	£668k
Proposal Title	International Chemical and BioMetrology	Stage Start Date	April 2013
		Est Final Stage End Date	March 2014

Summary

The continued provision of a chemical and biomeasurement system for the UK linked internationally through a developed infrastructure and calibration and measurement capability (CMC) needed to fulfil UK obligations under the CIPM MRA, such that calibration services are provided to UK organisations and UK chemical and bioscience standards are recognised globally.

The Need & Current State of the Art

The CIPM Mutual Recognition Arrangement (MRA) requires LGC's participation in international comparisons of chemical and biomeasurements (pilot and key comparisons), maintenance of quality systems and demonstration of competence in related calibration and measurement activities.

These obligations require significant commitment to infrastructure development and the development of personnel, quality systems and processes.

LGC's national measurement institute (NMI) designation supports UK industry trading activities and compliance with legislation. Provision of high-accuracy reference methods and materials improves data comparability and supports new measurement technologies.

In comparison to physical metrology, there is a paucity of higher order reference standards and materials maintained by the NMIs for the chemical and biosciences.

By ensuring awareness and accessibility of this reference measurement provision through its calibration services, LGC leads improvements in chemical and biometrology traceability and hence measurement quality and practice of routine laboratories.

The Solution & Metrology Capability to be Delivered

To maintain a leading presence internationally, the UK needs to develop key reference measurement systems with fit-for-purpose uncertainties relevant to UK industry priorities, and participate actively in the work of CCQM. Active participation will discharge the UK's responsibilities in maintaining the SI and assist in validating reference measurement methods for use in the UK NMS.

This project therefore focuses on the maintenance and development of chemical and bioreference methods and materials and their validation via international comparisons.

Impact and Benefits

The project supports measurements of importance to existing and emerging regulation and to trade through international acceptance of high-accuracy measurement capability and certified reference materials, and provision of calibration services. Its outputs feed directly into the development of standards and support innovation and underpin competitiveness of UK industry.

Successful participation in the studies under discussion for 2011-13 will help guard against contamination in the food chain, deliver safer consumer products and more sustainable chemicals, underpin a diversified energy strategy and foster innovation for improved healthcare.

Participation by LGC in international comparison studies ensures the UK remains at the forefront of chemical and biomeasurement science, contributes effectively to international discussions, addresses key measurement issues relevant to its priorities and maintains development of a centre of excellence able to support the UK measurement infrastructure.

Support for Programme Challenge, Roadmaps, Government Strategies

Strategic priority relating to (Primary) Reference Methods, Higher Order Reference Standards/ Calibrants and Traceability.

Supports the CBKB Organic, Inorganic and Bio-Analysis themes.

Relevance to UK Economic Impact; UK Quality of Life; UK NMS Science and Innovation and calibration services capability.

Supports NMO Draft Strategy through delivery of world-class science important for the development of international metrology. Supports NMS intervention by underpinning metrology relevant to the UK economy and society.

Synergies with other projects / programmes

This project relates to Metrology for cell imaging (BA25), Chromium Speciation (IS9), Mechanisms for SI traceable bio molecular metrology (BA27), Clinically Relevant Protein Metrology (BA26) and Nucleic Acid Metrology (BA4).

Technical Risks

Risk is low due to the inherent function and capability of the NMI.

Knowledge Transfer and Exploitation Plan

Knowledge transfer of the developed reference strategies and products to parties in the relevant sectors and academia

will be achieved through peer-reviewed publications and presentations at scientific meetings. Moreover, methodology transfer through publication in the UK NMS web-site will be undertaken. Exploitation directly to other NMIs at CCQM, and to the wider measurement and research communities through provision of reference methods and certified reference materials, and calibration services.			
Deliverables			
1	**Start: 01/04/13**	**End: 31/03/14**	
CEW: UK CMC claims have been established and maintained through participation in/organisation of at least 4 CCQM chemical (OAWG/IAWG) key comparisons or pilot studies and regional EURAMET comparisons			
2	**Start: 01/04/13**	**End: 31/03/14**	
CEW: UK CMC claims have been established and maintained through participation in/organisation of at least 4 CCQM bioscience (BAWG) key comparisons or pilot studies and regional EURAMET comparisons			
3	**Start: 01/04/13**	**End: 31/03/14**	
CEW: EURAMET TC-Q Annual Reports have been prepared and submitted; LGC CMC claims reviewed and submitted to relevant the BIPM and JCTLM databases; CMCs of other NMIs evaluated as required by EURAMET; CRM data input to the COMAR database			
4	**Start: 01/04/13**	**End: 31/03/14**	
CEW: At least 3 calibration and reference measurement services to be delivered to UK organisations annually with direct costs paid for by customers have been delivered (zero cost to NMS).			
5	**Start: 01/04/13**	**End: 31/03/14**	
CEW: Project management activities completed. CEW articles prepared, describing progress and outputs of the project.			

Project No.	CB/2012/IM1d	Price to NMO	£668k
Project Title	International Chemical and BioMetrology	Stage Start Date	1 April 2014
		Est Final Stage End Date	31 March 2015
Sector	Health, Environmental sustainability, Underpinning metrology	Activity	Development of existing capabilities; International obligations

Summary

The continued provision of a chemical and biomeasurement system for the UK linked internationally through a developed infrastructure and calibration and measurement capability (CMC) needed to fulfil UK obligations under the CIPM MRA, such that calibration services are provided to UK organisations and UK chemical and bioscience standards are recognised globally.

The Need

The CIPM Mutual Recognition Arrangement (MRA) requires LGC's participation in international comparisons of chemical and biomeasurements (pilot and key comparisons), maintenance of quality systems and demonstration of competence in related calibration and measurement activities.

These obligations require significant commitment to infrastructure development (participation in comparisons and representation of chemical and biometrology interests in CCQM and EUROMET), and the development of personnel, quality systems and processes.

LGC's national measurement institute (NMI) designation supports UK industry trading activities and compliance with legislation. Provision of high-accuracy reference methods and materials improves data comparability and supports new measurement technologies.

In comparison to physical metrology, there is a paucity of higher order reference standards and materials maintained by the NMIs for the chemical and biosciences.

By ensuring awareness and accessibility of this reference measurement provision through its calibration services, LGC leads improvements in chemical and biometrology traceability and hence measurement quality and practice of routine laboratories.

The Solution

To maintain a leading presence internationally, the UK needs to develop key reference measurement systems with fit-for-purpose uncertainties relevant to UK industry priorities, and participate actively in the work of CCQM. Active participation will discharge the UK's responsibilities in maintaining the SI and assist in validating reference measurement methods for use in the UK NMS.

This project therefore focuses on the maintenance and development of chemical and bioreference methods and materials and their validation via international comparisons.

Impact and Benefits

The project supports measurements of importance to existing and emerging regulation and to trade through international acceptance of high-accuracy measurement capability and certified reference materials, and provision of calibration services. Its outputs feed directly into the development of standards and support innovation and underpin competitiveness of UK industry.

Coordination of, and participation in, international comparison studies (e.g. CCQM and EUROMET) by LGC ensures the UK remains at the forefront of chemical and biomeasurement science, contributes effectively to international discussions, addresses key measurement issues relevant to its priorities and maintains development of a centre of excellence able to support the UK measurement infrastructure.

Support for Programme Challenge, Roadmaps, Government Strategies

Strategic priority relating to (Primary) Reference Methods, Higher Order Reference Standards/ Calibrants and Traceability.

Supports the CBKB Organic, Inorganic and Bio-Analysis themes.

Relevance to UK Economic Impact; UK Quality of Life; UK NMS Science and Innovation and calibration services capability.

Supports NMO Draft Strategy through delivery of world-class science important for the development of international metrology. Supports NMS intervention by underpinning metrology relevant to the UK economy and society.

Synergies with other projects / programmes

This project relates to OA1 (Chemical metrology), IM1 (International CBM), IM1c (International Chemical and BioMetrology), Cell Phenotype authentication (BA2), Metrology for cell imaging (BA25), Chromium Speciation (IS9), Mechanisms for SI traceable bio molecular metrology (BA27), Clinically Relevant Protein Metrology (BA26) and Nucleic Acid Metrology (BA4).

Knowledge Transfer and Exploitation

Knowledge transfer of the developed reference strategies and products to parties in the relevant sectors and academia will be achieved through peer-reviewed publications and presentations at scientific meetings. Moreover, methodology

transfer through publication on the UK NMS website will be undertaken. Exploitation is directly to other NMIs at CCQM, and to the wider measurement and research communities through provision of reference methods and certified reference materials, and calibration services.			
Deliverables			
1	**Start: 01/04/14**	**End: 31/03/15**	
CEW UK CMC claims have been established and maintained through participation in/organisation of at least 4 CCQM chemical (OAWG/IAWG) key comparisons or pilot studies and regional EURAMET comparisons			
2	**Start: 01/04/14**	**End: 31/03/15**	
CEW UK CMC claims have been established and maintained through participation in/organisation of at least 4 CCQM bioscience (BAWG) key comparisons or pilot studies and regional EURAMET comparisons			
3	**Start: 01/04/14**	**End: 31/03/15**	
CEW EURAMET TC-Q Annual Reports have been prepared and submitted; LGC CMC claims reviewed and submitted to the BIPM and JCTLM databases; CMCs of other NMI's evaluated as required by EURAMET; CRM data input to the COMAR database			
4	**Start: 01/04/14**	**End: 31/03/15**	
CEW at least 3 calibration and reference measurement services to be delivered to UK organisations annually with direct costs paid for by customers have been delivered (zero cost to NMS).			
5	**Start: 01/04/14**	**End: 31/03/15**	
CEW project management activities completed. CEW articles prepared, describing progress and outputs of the project.			

Project No.	CB/2013/IM1e	**Price to NMO**	£668k
Project Title	International Chemical and BioMetrology	**Stage Start Date**	Apr 15
Project Lead	Julian Braybrook	**Stage End Date**	Mar 16
Sector	Underpinning Metrology	**Activity**	Development of existing capabilities

Summary
The continued provision of a chemical and biomeasurement system for the UK linked internationally through a developed infrastructure and calibration and measurement capability (CMC) needed to fulfil UK obligations under the CIPM MRA, such that calibration services are provided to UK organisations and UK chemical and bioscience standards are recognised globally.

The Need
The CIPM Mutual Recognition Arrangement (MRA) requires LGC's participation in international comparisons of chemical and biomeasurements (pilot and key comparisons), maintenance of quality systems and demonstration of competence in related calibration and measurement activities.
These obligations require significant commitment to infrastructure development (participation in comparisons and representation of chemical and biometrology interests in CCQM and EUROMET), and the development of personnel, quality systems and processes.
LGC's national measurement institute (NMI) designation supports UK industry trading activities and compliance with legislation. Provision of high-accuracy reference methods and materials improves data comparability and supports new measurement technologies.
In comparison to physical metrology, there is a paucity of higher order reference standards and materials maintained by the NMIs for the chemical and biosciences.
By ensuring awareness and accessibility of this reference measurement provision through its calibration services, LGC leads improvements in chemical and biometrology traceability and hence measurement quality and practice of routine laboratories.

The Solution
To maintain a leading presence internationally, the UK needs to develop key reference measurement systems with fit-for-purpose uncertainties relevant to UK industry priorities, and participate actively in the work of CCQM. Active participation will discharge the UK's responsibilities in maintaining the SI and assist in validating reference measurement methods for use in the UK NMS.
This project therefore focuses on the maintenance and development of chemical and bioreference methods and materials and their validation via international comparisons.

Impact and Benefits
The project supports measurements of importance to existing and emerging regulation and to trade through international acceptance of high-accuracy measurement capability and certified reference materials, and provision of calibration services. Its outputs feed directly into the development of standards and support innovation and underpin competitiveness of UK industry.
Successful participation in the studies under discussion for 2012-15 will help guard against contamination in the food chain, deliver safer consumer products and more sustainable chemicals, underpin a diversified energy strategy and foster innovation for improved healthcare.
Participation by LGC in international comparison studies (e.g. CCQM and EUROMET) ensures the UK remains at the forefront of chemical and biomeasurement science, contributes effectively to international discussions, addresses key measurement issues relevant to its priorities and maintains development of a centre of excellence able to support the UK measurement infrastructure.

Support for Programme Challenge, Roadmaps, Government Strategies
Strategic priority relating to (Primary) Reference Methods, Higher Order Reference Standards/ Calibrants and Traceability.
Supports the CBM Strategic Themes 'Chemical Measurement and Calibrations' and 'Bioanalysis'.
Relevance to UK Economic Impact; UK Quality of Life; UK NMS Science and Innovation and calibration services capability.
Supports NMO Strategy through delivery of world-class science important for the development of international metrology. Supports NMS intervention by underpinning metrology relevant to the UK economy and society.

Synergies with other projects / programmes
Synergistic work to develop reference methods and SI traceable methods for biological measurements (i.e. nucleic acids and cells) include BA25 (Metrology for cell imaging), BA27 (Biomolecular metrology), BA35 (BioSITrace) and BA28 (Cell Free Nucleic Acids). Development of improved methods for purity assessments relates to OA13 (Direct analysis for organic purity measurements), and for elemental inorganic analysis relates to IS13 (Elements).

Knowledge Transfer and Exploitation Plan
Knowledge transfer of the developed reference strategies and products to parties in the relevant sectors and academia will be achieved through peer-reviewed publications and presentations at scientific meetings. Moreover, methodology transfer through publication in the UK NMS web-site will be undertaken.

Exploitation is directly to other NMIs at CCQM, and to the wider measurement and research communities through provision of reference methods and certified reference materials, and calibration services.			
Deliverables			
1	**Start: 01/04/14**	**End: 31/03/15**	
CEW UK CMC claims have been established and maintained through participation in/organisation of at least 4 CCQM chemical (OAWG/IAWG) key comparisons or pilot studies and regional EURAMET comparisons			
2	**Start: 01/04/14**	**End: 31/03/15**	
CEW UK CMC claims have been established and maintained through participation in/organisation of at least 4 CCQM bioscience (BAWG) key comparisons or pilot studies and regional EURAMET comparisons			
3	**Start: 01/04/14**	**End: 31/03/15**	
CEW EURAMET TC-Q Annual Reports have been prepared and submitted; LGC CMC claims reviewed and submitted to the BIPM and JCTLM databases; CMCs of other NMI's evaluated as required by EURAMET; CRM data input to the COMAR database			
4	**Start: 01/04/14**	**End: 31/03/15**	
CEW at least 3 calibration and reference measurement services to be delivered to UK organisations annually with direct costs paid for by customers have been delivered (zero cost to NMS).			
5	**Start: 01/04/14**	**End: 31/03/15**	
CEW project management activities completed. CEW articles prepared, describing progress and outputs of the project.			

Proposal No.	IM2c	Price to NMO	£450k
Proposal Title	International and national representation	Stage Start Date	April 2011
		Est Final Stage End Date	March 2014

Summary

To represent UK NMS interests on key national, European and international metrology organisations, as needed, to maintain and develop the infrastructure and competencies required to fulfil UK obligations under the CIPM MRA, such that the UK NMS for chemical and biological measurements is recognised globally.

To collaborate with other countries to develop best practice and to harmonise standards and guidance concerned with improving the quality and comparability of chemical and biological measurements.

To provide UK stakeholders with the opportunity to comment on significant international developments.

The Need & Current State of the Art

The UK's obligations under the CIPM MRA require a significant commitment to infrastructure development (participation in comparisons, representation of chemical metrology interests in CCQM and EUROMET), the development of personnel and quality systems and processes.

Collaboration provides a mechanism for gaining international acceptance of outputs from the programme. Input into ISO and IUPAC activities is essential for the UK to maintain a position of influence and credibility, and therefore help ensure that international guides and standards meet the requirements of the UK measurement community.

Lead and active representation for UK NMI chemical and biological metrology interests on key national, European and international organisations and committees.

Lead and active contribution to international harmonisation of standards and guidance aimed at accurate and comparable chemical and bio-analytical measurement.

The Solution & Metrology Capability to be Delivered

Maintain current international and national commitments and representation, reviewing contribution in light of international developments to ensure UK position maintained or developed as required.

Supports the three CBKB themes of Bioanalysis, and Chemical Measurement and Calibration (Organic Analysis and Inorganic Analysis).

Supports the related CBKB sub-themes through underpinning metrology.

This project will support national representation/networking activities to ensure a representative UK input into international organisations and committees, and to obtain stakeholders' input into programme requirements on generic measurement topics at meetings organised by professional bodies and standards organisations in NMS priority areas.

Impact and Benefits

Participation in CCQM ensures that UK obligations under the CIPM MRA are met and that UK chemical and biological measurement capability is recognised globally.

Proactive participation in international organisations ensures UK credibility and influence on strategic metrology and analytical measurement issues.

International collaboration delivers improved value for money through securing wide expert input to tasks and sharing the cost of activities.

International harmonisation reduces transaction costs and increases productivity for UK business via provision of a level playing field and common requirements for calibration and testing laboratories.

Prompt communication of international developments to UK stakeholders helps maintain awareness of key topics and provides competitive advantage.

Support for Programme Challenge, Roadmaps, Government Strategies

Strategic priority relating to pro-active UK lead in Underpinning Metrology.

Synergies with other projects / programmes

Provides cross programme synergy via support for the three main themes of Bioanalysis, Organic Analysis and Inorganic Analysis and providing underpinning metrology for the six related CBKB sub-themes.

Knowledge Transfer and Exploitation Plan

Prompt communication of international developments to UK stakeholders will maintain awareness of key topics and provides competitive advantage. The outputs of the project will feed directly into CMCs, CRMs and documentary standards preparation and revision, and back into the CBKB sub-themes to ensure transfer within and out from the programme.

The outputs of the project will feed directly into CMCs, certified reference materials and documentary standards preparation and revision.

Deliverables

1	**Start: 01/04/13**	**End: 31/03/14**	

Core NMI international representation

CEW: UK NMS interests represented on CIPM, CCQM and EUROMET and their sub-committees and working groups

relevant to chemical and biological metrology (e.g. IAWG, BAWG, OAWG, JCTLM, MetChem).			
2	**Start: 01/04/11**	**End: 31/03/14**	
National representation and networking CEW: LGC's metrology experts have attended relevant national committee meetings to brief, and be briefed by, UK stakeholders on metrology activities, and resulting actions have been completed.			
3	**Start: 01/04/13**	**End: 31/03/14**	
International representation CEW: Pro-active input has been made to Eurachem, CITAC, EA, EUROLAB, ISO-REMCO and COMAR.			

Project No.	CB/2012/IM2d	**Price to NMO**	£350k
Project Title	International and national representation	**Stage Start Date**	1 April 2014
		Est Final Stage End Date	31 March 2015
Sector	Health, Environmental sustainability, Underpinning metrology	**Activity**	International obligations; Statutory and policy obligations; Provision of stds and maintenance of capabilities

Summary

To represent UK NMS interests on key national, European and international metrology organisations, as needed, to maintain and develop the infrastructure and competencies required to fulfil UK obligations under the CIPM MRA, such that the UK NMS for chemical and biological measurements is recognised globally.

To collaborate with other countries to develop best practice and to harmonise standards and guidance concerned with improving the quality and comparability of chemical and biological measurements.

To provide UK stakeholders with the opportunity to comment on significant international developments.

The Need

The UK's obligations under the CIPM MRA require a significant commitment to infrastructure development (participation in comparisons, representation of chemical metrology interests in CCQM and EUROMET), the development of personnel and quality systems and processes.

Collaboration through organisations such as Eurachem and CITAC provides a mechanism for gaining international acceptance of outputs from the programme. Input into ISO and IUPAC activities is essential for the UK to maintain a position of influence and credibility, and therefore help ensure that international guides and standards meet the requirements of the UK measurement community.

Lead and active representation for UK NMI chemical and biological metrology interests on key national, European and international organisations and committees.

Lead and active contribution to international harmonisation of standards and guidance aimed at accurate and comparable chemical and bio-analytical measurement.

The Solution

Maintain current international and national commitments and representation, reviewing contribution in light of international developments to ensure UK position maintained or developed as required.

Supports the CBKB themes of Bioanalysis, and Chemical Measurement and Calibration (Organic Analysis and Inorganic Analysis).

Supports the related CBKB sub-themes through underpinning metrology.

This project will support national representation/networking activities to ensure a representative UK input into international organisations and committees, and to obtain stakeholders' input into programme requirements on generic measurement topics (e.g. Reference Materials Working Group and Proficiency Testing Working Group) at meetings organised by professional bodies and standards organisations (e.g. RSC AMC and relevant sub-committees, BSI, CEN and ISO technical committees) in NMS priority areas.

Impact and Benefits

Participation in CCQM ensures that UK obligations under the CIPM MRA are met and that UK chemical and biological measurement capability is recognised globally.

Proactive participation in international organisations ensures UK credibility and influence on strategic metrology and analytical measurement issues.

International collaboration delivers improved value for money through securing wide expert input to tasks and sharing the cost of activities.

International harmonisation reduces transaction costs and increases productivity for UK business via provision of a level playing field and common requirements for calibration and testing laboratories.

Prompt communication of international developments to UK stakeholders helps maintain awareness of key topics and provides competitive advantage.

Support for Programme Challenge, Roadmaps, Government Strategies

Strategic priority relating to pro-active UK lead in Underpinning Metrology.

Synergies with other projects / programmes

Provides cross programme synergy via support for the main themes of Bioanalysis, Organic Analysis and Inorganic Analysis and providing underpinning metrology for the six related CBKB sub-themes.

Knowledge Transfer and Exploitation

Prompt communication of international developments to UK stakeholders will maintain awareness of key topics and provides competitive advantage. The outputs of the project will feed directly into CMCs, CRMs and documentary standards preparation and revision, and back into the CBKB sub-themes to ensure transfer within and out from the

programme. The outputs of the project will feed directly into CMCs, certified reference materials and documentary standards preparation and revision.			
Deliverables			
1	**Start: 01/04/14**	**End: 31/03/15**	
Core NMI international representation: CEW UK NMS interests represented on CIPM, CCQM and EUROMET and their sub-committees and working groups relevant to chemical and biological metrology (e.g. IAWG, BAWG, OAWG, JCTLM, MetChem).			
2	**Start: 01/04/14**	**End: 31/03/15**	
National representation and networking: CEW LGC's metrology experts have attended relevant national committee meetings to brief, and be briefed by, UK stakeholders on metrology activities, and resulting actions have been completed.			
3	**Start: 01/04/14**	**End: 31/03/15**	
International representation: CEW pro-active input has been made to Eurachem, CITAC, EA, EUROLAB, ISO-REMCO and COMAR.			

Project No.	CB/2013/IM2e	**Price to NMO**	£350k
Project Title	International and national representation	**Stage Start Date**	Apr 15
		Stage End Date	Mar 16
Sector	Health, Environmental sustainability, Underpinning metrology	**Activity**	International obligations; Statutory and policy obligations; Provision of stds and maintenance of capabilities

Summary

To represent UK NMS interests on key national, European and international metrology organisations, as needed, to maintain and develop the infrastructure and competencies required to fulfil UK obligations under the CIPM MRA, such that the UK NMS for chemical and biological measurements is recognised globally.
To collaborate with other countries to develop best practice and to harmonise standards and guidance concerned with improving the quality and comparability of chemical and biological measurements.
To provide UK stakeholders with the opportunity to comment on significant international developments.

The Need

The UK's obligations under the CIPM MRA require a significant commitment to infrastructure development (participation in comparisons, representation of chemical metrology interests in CCQM and EUROMET), the development of personnel and quality systems and processes.
Collaboration through organisations such as Eurachem and CITAC provides a mechanism for gaining international acceptance of outputs from the programme. Input into ISO and IUPAC activities is essential for the UK to maintain a position of influence and credibility, and therefore help ensure that international guides and standards meet the requirements of the UK measurement community.
Lead and active representation for UK NMI chemical and biological metrology interests on key national, European and international organisations and committees.
Lead and active contribution to international harmonisation of standards and guidance aimed at accurate and comparable chemical and bio-analytical measurement.

The Solution

Maintain current international and national commitments and representation, reviewing contribution in light of international developments to ensure UK position maintained or developed as required.
Supports the CBM Strategic themes of Bioanalysis, and Chemical Measurement and Calibration (Organic Analysis and Inorganic Analysis).
Supports the related CBM sub-themes through underpinning metrology.
This project will support national representation/networking activities to ensure a representative UK input into international organisations and committees, and to obtain stakeholders' input into programme requirements on generic measurement topics (e.g. Reference Materials Working Group and Proficiency Testing Working Group) at meetings organised by professional bodies and standards organisations (e.g. RSC AMC and relevant sub-committees, BSI, CEN and ISO technical committees) in NMS priority areas.

Impact and Benefits

Participation in CCQM ensures that UK obligations under the CIPM MRA are met and that UK chemical and biological measurement capability is recognised globally.
Proactive participation in international organisations ensures UK credibility and influence on strategic metrology and analytical measurement issues.
International collaboration delivers improved value for money through securing wide expert input to tasks and sharing the cost of activities.
International harmonisation reduces transaction costs and increases productivity for UK business via provision of a level playing field and common requirements for calibration and testing laboratories.
Prompt communication of international developments to UK stakeholders helps maintain awareness of key topics and provides competitive advantage.

Support for Programme Challenge, Roadmaps, Government Strategies

Strategic priority relating to pro-active UK lead in Underpinning Metrology.

Synergies with other projects / programmes

Provides cross programme synergy via support for the main themes of Bioanalysis, Organic Analysis and Inorganic Analysis and providing underpinning metrology for the six related CBM sub-themes.

Knowledge Transfer and Exploitation

Prompt communication of international developments to UK stakeholders will maintain awareness of key topics and provides competitive advantage. The outputs of the project will feed directly into CMCs, CRMs and documentary standards preparation and revision, and back into the CBM sub-themes to ensure transfer within and out from the programme.

Deliverables

1	**Start: 01/04/15**	**End: 31/03/16**	

Core NMI international representation: CEW UK NMS interests represented on CIPM, CCQM and EUROMET and their sub-committees and working groups relevant to chemical and biological metrology (e.g. IAWG, BAWG, OAWG, JCTLM, MetChem).

2	**Start: 01/04/15**	**End: 31/03/16**	
National representation and networking: CEW LGC's metrology experts have attended relevant national committee meetings to brief, and be briefed by, UK stakeholders on metrology activities, and resulting actions have been completed.			
3	**Start: 01/04/15**	**End: 31/03/16**	
International representation: CEW pro-active input has been made to Eurachem, CITAC, EA, EUROLAB, ISO-REMCO and COMAR.			

Project IS1	Certification of Reference Standards for Absolute Carbon Isotope Ratios Traceable to the SI

Project Objectives

- To produce the first material certified for carbon isotope ratios traceable to the SI.
- To develop a liquid chromatography (LC) method for the analysis of a compound of interest using mobile phases compatible with carbon isotope ratio measurements and to evaluate coupling LC to multicollector inductively coupled mass spectrometer (MC-ICP-MS).
- To provide high accuracy carbon isotope ratio values for organic compounds of metrology interest to industry and forensic laboratories. This will include the evaluation of a compound/s of interest to produce a carbon isotopic CRM (certified for isotope ratios rather than relative differences in VPDB scale).

Background and Rationale

The most common technique to measure carbon isotopic abundance variations is gas source isotope ratio mass spectrometry (GS-IRMS) where carbon is measured as CO_2. CO_2 isotope ratio amounts are then measured monitoring molecular ion masses 44, 45 and 46. IRMS measurements are made against a reference gas and values are expressed as differences in % in the VPDB scale. The $^{13}C/^{12}C$ information becomes available through measurement of ion-currents at m/z 44 and 45 and application of an 'oxygen' correction to the measured ion-current ratios.

SI traceable carbon isotope ratio amounts can be measured using a MC-ICP-MS. The advantage of the method over conventional GS-IRMS measurements is that carbon isotope amount ratios are measured as C^+ instead of CO_2^+ and 'oxygen correction' is not required. In addition, despite the recent efforts of instrument manufacturers, there has not, to date, been a successful commercial coupling of LC to an IRMS for measurement of high accuracy carbon isotope ratios in complex mixtures. The main constraints are related to the use of aqueous mobile phases thus limiting the chromatographic separation mechanism. This project will develop non-organic mobile phases for the analysis of a compound of interest and the coupling of LC to a MC-ICP-MS for the measurement of carbon isotope ratios evaluated.

Reference standards for carbon isotope ratio values are unavailable and existing materials are certified for ^{13}C value relative to a reference standard that defines the VPDB scale. This project will provide, for the first time, absolute carbon isotope ratios traceable to the SI.

Research carried out by LGC under NMS project I3 has established capabilities to measure traceable sulphur[1] and carbon[2] isotope ratios in pharmaceuticals and shown applicability of the method for counterfeit detection and forensic evidence[3,4]. Stakeholders will again benefit from the knowledge transfer of the developed strategy through publication of peer-reviewed scientific papers and presentations at scientific meetings.

Impact

Economic: The validation of IRMS methods to measure SI traceable absolute carbon isotope ratios and the certification of reference standards underpin important industrial sectors (pharmaceutical, food/feed and fuel), analytical/forensic laboratories, and law/order forces, where individual and collective economic consequences are substantial when measurement (e.g. authenticity, fraud and safety) is incorrect or goes un-noticed.

Quality of Life: Societal health, environment and security resulting from improper measurements, either affect many in a minor manner (e.g. pharmaceutical), several in a moderate manner (e.g. food/feed) or a few in a substantial manner (forensic). In particular, this project assists food/drug testing laboratories, law and order forces and forensic analysts to gain traceable, comparable and reliable information from forensic evidence, to identify drug misuse, detect fraud and enhance national security and consumer safety.

Innovation: Improved methodology for the measurement of absolute carbon isotope ratios in complex liquid samples is necessary to quantify small compound specific isotopic variations. The developed CRM will have a metrological impact enabling isotope ratio experts to compare absolute values and be able to perform traceable measurements in a wide range of compounds. The project is aligned, longer-term, to the Technology Strategy Board priorities of Healthcare, Bioscience and Energy, and the RSC Chemical Roadmap priority, Building a more secure environment.

Science Value: Provision of reference standards with assigned absolute carbon isotope ratios for the first time. Gaining traceability to the SI of those measurements is a priority and by doing so we will help interested parties improve their methods and accuracy and validate their findings.

NMS Capability: The validation of methodologies for absolute carbon isotope ratio measurements builds on a growing key platform capability established within LGC through previous NMS CBM Programmes and establishes the basis for calibration procedures that meet the needs of UK industry and law enforcement bodies. The assignment of traceable carbon isotopic ratios to materials of interest allows assessment of measurement accuracy and helps the interested parties gain traceability to the SI for these measurands.

Deliverables				
No.	**Deliverable**	**Start**	**End**	**Cost**
1	CEW consultation with FIRMS, anti-doping agencies (NADO, WADA) & instrument manufacturers etc has been completed. CEW a literature review has identified candidate compound/s. CEW preliminary carbon isotope ratio values for a target analyte in the candidate material has been completed.	Apr 10	Jul 10	
2	CEW candidate material to be certified for carbon isotope ratios has been evaluated. CEW best approaches for certifying isotope ratio values by MC-ICPMS inc. bulk analysis, laser ablation, etc have been identified.	Aug 10	Dec 10	
3	CEW coupling LC to the MC-ICPMS has been evaluated. CEW a LC method for analysis of the candidate compound using non-organic mobile phases compatible with carbon isotope ratio measurements has been developed. CEW the coupling of LC separations with MC-ICPMS (inc. the effect on measurement uncertainty) has been assessed.	Jan 11	Dec 11	
4	CEW a FIRMS inter-laboratory exercise establishes confirmation values for candidate reference material.	Jan 12	Mar 12	
5	CEW carbon isotope ratio values have been certified for the chosen material.	Jan 12	Dec 13	
6	CEW project management activities completed. CEW articles prepared for CBM website, describing progress and outputs of the project. CEW project findings disseminated at relevant conferences/ FIRMS Steering Group meetings and through at least 2 peer-review publications.	Apr 10	Dec 13	

Proposal No.	IS11+ IS11b	Price to NMO	£355K + £49k
Proposal Title	Traceable measurements and partitioning platforms for monitoring critical pollutants under the European Water Framework Directive (WFD-2000/60/EC)	Stage Start Date	01/09/2011
		Est Final Stage End Date	31/08/2014

Summary

This EMRP matched project will develop underpinning metrology in support of the implementation of the European Water Framework Directive (WFD, Directive 2000/60/EC). By developing traceable methods for the accurate determination of the total concentration and partitioning of WFD listed pollutants (e.g. polybrominated flame retardants (PBDEs) and/or tributyltin (TBT), which have been shown to be carcinogenic in animal studies) at the required levels in natural waters, this project the will help accomplish the final objective of WFD, namely good quality of surface, ground and coastal water in the EU by 2015.

The Need & Current State of the Art

The implementation of the WFD essentially depends on the availability of analytical reference methods and materials for the priority substances specified in the directive (e.g. maximum allowable concentrations equivalent to European Quality Standards (EQS) for TBT and ∑PBDE of 0.2 and 0.5 ng/L, respectively). For reliable measurements of contaminants at EQS level, the WFD daughter directive 2009/90/EC demands analytical methods for test laboratories which have a limit of quantification (LOQ) equal to or lower than 30% of the EQS and a measurement uncertainty (95% confidence) of 50% or less. Therefore, primary methods of measurement, which should be the reference for those of the test laboratories, should have a considerably lower LOQ. Such methods are not available yet. EQS values refer to the whole water body, i.e. include contaminants, which are associated to suspended solids or colloids present in the natural water. Contaminant species such as PBDEs and TBT have been shown to be distributed among different fractions of environmental waters (Anal. Bioanal. Chem., 2008, 390, 1805-13; Env. Sci. Techn., 2005, 39, 3521-27). Within the “dissolved” fraction they appear to be present in organic and inorganic-rich colloid fractions of different size (1 nm - 1 □m). They also appear to be associated with suspended particulate matter. Considering the maximum target levels of such species as specified by the WFD (low ng/L), achieving maximum extraction efficiency of such compounds from the whole water sample becomes essential. However, the interactions of such contaminants with other contaminants or ligands present in the different aquatic compartments have been shown to have a different nature, often affecting their quantitative release from the matrix using conventional extraction procedures. The development and validation of fractionation techniques, which in combination with IDMS speciation methodologies for total species determination, will help determine the partitioning of the target species or measurands in compartments of aquatic samples. Such analytical platforms, which are not yet available, will also be invaluable tools to provide mass balance quantitative data and also relevant information on the interactions, bioavailability and mobility of such contaminants.

The Solution & Metrology Capability to be Delivered

The project will build up on previous experience on the determination of PBDEs acquired under a previous CBM project (VAMR7). It will develop/validate species-specific IDMS methodologies for the accurate quantification of PBDES in whole water with element-specific detection by interference-reducing ICP-MS (double focusing or collision reaction cell ICP-MS) using spike materials and novel preparation/preconcentration methods provided.

Impact and Benefits

The WFD requires comparable measurement of priority hazardous substances for the assessment of the chemical status of waters in the EU to ensure reliable decision making and appropriate measures for the protection of the EU population. TBT and PBDEs, listed as current WFD priority substances, are considered as endocrine disruptors. Such pollutants can also cause cancer in the population. According to the WHO, 2.4 Million people developed cancer in the EU in 2008 with annual costs to the UK healthcare system of approximately £26.3 Billion. By providing validated reference (primary) methods for pollutants such as PBDEs and TBT’s, this project will help reduce these compounds to below harmful levels bringing quality of life benefits to the UK population via reduced associated cancer incidence and economic benefit to the UK economy via reduced healthcare costs. The proposed work will also enhance LGC’s measurement capability by improving the quality of measurements performed via participation in international inter-comparison studies.

Support for Programme Challenge, Roadmaps, Government Strategies

Supports NMO Draft Strategy through NMS interventions related to Environment. Supports Government priority area of Environmental sustainability. Supports the CBKB Inorganic Analysis theme, and the CBKB Speciation sub-theme.

Knowledge Transfer and Exploitation Plan

Knowledge transfer to the scientific community and potential users will primarily be achieved by publication of the outcome of the work in peer-reviewed scientific literature and participation at international conferences. Methodologies developed will be disseminated using key KT channels such as the CBM website.

Deliverables			
1	**Start: 01/09/2011**	**End: 31/05/2013**	
Reference method for quantification of PBDEs in whole water CEW: Reference methodology for the accurate determination of PBDEs at the required WFD levels in whole water using chromatography combined with interference-reducing ICP-MS and species-specific IDMS calibration.			
2	**Start: 01/09/2011**	**End: 31/05/2013**	
Methodology for PBDEs monitoring in water fractions by FFF-ICP-MS CEW: Validated methodology for monitoring fractionation of WFD-listed PBDs in water fractions of different size and nature (e.g. suspended organic matter, organic and inorganic-rich colloids) using FFF-ICP-MS			
3	**Start: 01/06/2013**	**End: 31/05/2014**	
Application of developed combined methodology to analysis of environmental waters CEW: Feasibility evaluation and application of the combined FFF fractionation and metrological IDMS speciation procedures to determine quantitative partitioning (e.g. size distribution) and thus, mass balance for PBDEs in environmental natural waters.			
4	**Start: 01/06/2013**	**End: 31/05/2014**	
Knowledge Transfer: Validated methods reported. A peer reviewed scientific paper published. Presentation at an international conference.			
5	**Start: 01/06/2013**	**End: 31/05/2014**	
Project Management: Project delivered on time and to budget			

Project No.	CB/2012/IS12	**Price to NMO**	£300k
Project Title	Improved calibration strategies and candidate standards for traceable quantitative elemental tissue imaging	**Stage Start Date**	01 August 2013
		Est Final Stage End Date	31 July 2015
Sector	Diagnostics	**Activity**	Development of existing capabilities; Provision of standards

Summary
Traceable methods for the determination of total metal concentrations, as well as the regional spatial distribution of trace metals (quantitative imaging), in diseased tissues compared to normal tissues is important to understand the pathogenesis and potential treatment of diseases such as Alzheimer's disease (AD), Age-related Macular Degeneration (AMD), cell-based therapy for organ rejection following transplantation, and tumour targeting of Pt-based chemotherapy.
The objective of this project is to develop internal standardisation calibration strategies and candidate standards for traceable quantitative elemental imaging of soft tissues (Fe for clinical diagnosis and monitoring progression of AD and for Zn in AMD). It proposes a traceable infrastructure to correlate quantitative elemental mapping data with that from semi-quantitative x-ray fluorescence (XRF), secondary ion mass spectrometry (SIMS) and non-invasive magnetic resonance imaging (MRI).

The Need
The impact of neurodegenerative diseases, and predominantly AD, is increasing rapidly with the changing demographics of our societies. Current clinical confidence in diagnosis of AD is typically 70-80%. This uncertainty can lead to mis-information with respect to likelihood of disease development and associated anxiety for 2-4y. Early recognition is the bottleneck for identification of more preventive measures and development of efficacious therapies by neurological and psychiatric clinics on a patient-group (stratified) basis. A characteristic feature of AD is amyloidosis, due to the accumulation of mis-folded ß-amyloid (Aβ). This has a propensity to bind and accumulate transition metals, e.g. iron (Fe). The ability to assess Fe is vital for predicting clinical outcome.
AMD is the cause of 20-30% of visual impairment in Developed countries, reflecting their older populations and greater life expectancy. Zn is found in high concentrations in the principal lesion (drusen) associated with AMD and is active in causing oligomerisation of complement factor H (CFH) which forms a significant component of plaque. There is a need to map Zn in the sub-cellular spaces in the retina and in cells associated with the retinal pigment epithelium (RPE).
Currently there are no traceable methods able to achieve relative limits of quantitation at the ppb level in such complex materials. Laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) and SIMS are sensitive surface analytical techniques that posses the capability to determine the distribution of metals and metalloids in biological tissues in a selected area of interest or in a complete thin tissue section, although the inherent matrix effects (up to 6 orders of magnitude) for SIMS significantly affects quantification. The spatial resolution provided by LA-ICP-MS at the µm scale is sufficient to image metals, metalloids and some non-metals at ppb levels in biological tissues. However, LA-ICP-MS lacks suitable calibration strategies and candidate standards for traceable quantitative elemental imaging.

The Solution
This project will develop calibration strategies for elemental quantitative bio-imaging at low ng/g levels in tissue sections by LA-ICP-MS based on *in house* prepared and well characterised matrix-matched calibration standards and internal standard normalisation. The standards will be characterised for total content, homogeneity and stability using complementary ICP-MS analysis after microwave acid digestion. An IDMS procedure with an associated measurement uncertainty budget will be developed in parallel to validate an external calibration methodology most convenient for high throughput analysis of multiple samples. Elemental imaging data obtained on the same samples by XRF will be used for confirmation of the LA-ICP-MS data.

Impact and Benefits
The increasing number of people suffering from AD (7.3 million in the EU, 2009) "poses important challenges for all European healthcare systems, since the oldest old [age >84y] is one of the fastest growing sectors of our European societies" [www.medicalnewstoday.com/articles/157422.php]. The total cost for their treatment in 2008 was €160bn [www.alzheimer-europe.org/EN/Research/ European-Collaboration-on-Dementia/Cost-of-dementia/Cost-of-illness-and-burden-of-dementia]. In the UK, an estimated 750,000 people suffer from Alzheimer's and other dementia disorders. Should prevalence rates remain unchanged, and as the population ages, the total number of dementia cases could more than double (Government Actuary & ONS Series PP2 No 25 2006) with associated economic costs of approximately £7 to £15 billion.
AMD is the most common cause of vision loss in the developed world for those >50y and it is estimated that there are >20m cases in the US and Europe. In the UK the disease affects around 420,000 people and an estimated 214,000 people have registered vision impairment secondary to AMD. Currently there is no available treatment.
The development and validation of traceable methods for the determination of total metal concentrations as well as the regional spatial distribution of trace metals (quantitative imaging) in diseased tissues compared to normal tissues will be important to understand the pathogenesis and potential treatment of diseases such as AD and AMD. The establishment of robust, quantitative chemical measurements to support the validation, traceability and comparability of clinical imaging data and demonstration of the proof of principle for tissue standards will underpin a metrological infrastructure for early diagnosis and enable development of more efficacious therapies, benefitting patients and healthcare providers alike.

Support for Programme Challenge, Roadmaps, Government Strategies

Strategic priority related to Healthcare. Supports NMO Draft Strategy through NMS interventions related to Healthcare - Diagnostics. Underpins the draft Technology Strategy Board Healthcare strategy.

Synergies with other projects / programmes

This project relates to other CBM and IRD projects (e.g. IRD HO7 on metallomic approaches for Se, CBM IS9 on methods for V biomolecules, CBM IS7 on methods for Pt-DNA adducts) dealing with the development of analytical methods to quantify metal-containing biomarkers for disease diagnosis and treatment. It builds on the capability developed under finalising IRD H09 on novel metal mapping.

Knowledge Transfer and Exploitation

The proposed translation of accurate quantitative metal imaging capability for AD studies is timely & highly relevant to society.

Knowledge transfer of the developed strategies to active parties in the healthcare sector and academia will be achieved through peer-reviewed publications, presentations at scientific meetings and clinical workshops. Also, through secondment between collaborators. Moreover, methodology transfer through publication in the UK NMS web-site will be undertaken.

Deliverables

1	**Start: 01/08/2013**	**End: 31/11/2013**	

Feasibility study to investigate production of matrix-matched standards:

CEW the feasibility of producing well characterised matrix-matched standards, in terms of homogeneity and stability, for quantitative tissue imaging has been investigated.

2	**Start: 01/12/2013**	**End: 31/09/2014**	

Method validation for quantitative determination of Fe and Zn spatial distribution:

CEW validated methodology based on the combination of laser ablation with double focusing magnetic sector ICP-MS and internal standardisation for the quantitative determination of Fe and Zn spatial distribution in tissue sections has been established.

3	**Start: 01/10/2014**	**End: 31/07/2015**	

Application of developed methodology:

CEW the feasibility of application of the developed methodology to quantitative Fe and Zn imaging in an AD model versus normal brain samples and human brain and eye bank has been established and the degree of correlation of metal mapping with novel MRI has been assessed.

4	**Start: 01/04/2013**	**End: 31/07/2015**	

Project management:

CEW project delivered on time and on budget

Project No.	CB/2012/IS13 +IS13b	**Price to NMO**	£340K +£37k
Project Title	Improved methodology for elemental and isotopic characterisation of primary elemental standards	**Stage Start Date**	1 July 2012
		Stage End Date	31 March 2015
		Est Final Stage End Date	30 June 2015
Sector	Health, Environmental sustainability, Underpinning metrology	**Activity**	Provision of stds and maintenance of capabilities

Summary

This project matches LGC's contribution to EMRP JRP S08 (Primary standards for challenging elements) and will develop and validate new and improved methods for determination of the elemental and isotopic composition of primary elemental standards. The realisation and dissemination of primary standards is of fundamental importance for comparability of measurement results through traceability in all fields of chemical analysis. The accurate determination of isotope abundance ratios is urgently needed in establishing traceability in quantitative elemental analysis because they play a fundamental role in two aspects of the traceability chain including: (i) measuring the isotope composition of primary and secondary calibration standards and of the analyte in matrix reference materials or other samples and (ii) application of isotope dilution mass spectrometry (IDMS) for transfer of calibrations between primary and secondary standards and reference measurements

The Need

Realisation and dissemination of primary standards is of fundamental importance for comparability of measurement results through traceability in all fields of chemical analysis. Primary standards in chemistry are usually materials known for their total purity and therefore appropriate for realising the link with the SI. However, due to the complexity and effort required for their characterisation, there are hardly any demonstrated primary standards in this field. The lack of comparability of measurement results in time and space has a direct impact on quality of life whenever measurement results are compared with other data, e.g. other measurement results, legal limit values or product specifications. Without primary standards, important European directives such as the In Vitro Diagnostics Directive (IVDD) and the Water Framework Directive (WFD) would not be able to be implemented.

Top level traceability is realised by primary calibration standards for the determination of element concentrations but these high purity substances may undergo isotope fractionation processes during production. Additionally, for many elements isotopic variations occur in nature. Therefore, the isotope composition may differ between primary calibration and secondary calibration standards and certainly differ from that of the analyte in many samples. Many measurement principles in chemical analysis are on a molar basis or are isotope selective and therefore a difference in the isotope composition between sample and calibration standard will lead to result bias. In addition, the conversion from mass fraction (e.g. mg/kg) to amount content (e.g. mol/kg) and vice versa leads to biased results unless the isotopic composition is also considered. Most determinations of isotope abundance ratios are based on mass spectrometry, which offers the potential for measuring the ratios with very small uncertainties. However, instruments are subject to mass discrimination effects which require mass calibration or correction of the spectrometer. The more fundamental approach, with potential for smallest uncertainties, is based on mass bias calibration of the spectrometer for a specific application using isotope mixtures of known composition prepared gravimetrically from certified pure isotopes of the target element. However, such pure isotopes are rarely available and their synthesis is time consuming and expensive. Therefore, there is a growing need for the investigation of alternative approaches.

The Solution

To develop and evaluate approaches for mass bias correction with sufficiently small uncertainty for measuring the isotope composition of primary calibration standards. These approaches will include mass bias calibration with mixtures of commercially available "pure" isotopes, mass bias correction using a nearby isotope of another element and mass bias correction using the "isotopic double spiking" technique. The elements selected as models for development and optimisation of new isotopic measurement procedures are Mg and Mo. Mg will be used to evaluate procedures for ultra-high purification of single isotopes and gravimetric preparation of isotopic calibration mixtures for mass bias correction of Mg isotope ratio measurements. Mo is an element for which isotopes of reasonable purity are available commercially but for which ultra-high purification would present much greater challenges. Unlike Mg, it also has sufficient isotopes to allow evaluation of the "isotopic double spiking" technique. The deliverables include well characterised isotopic materials for each element with uncertainties < 0.01 % for Mg and < 0.05 % for Mo. Both elements show significant isotopic variation in nature. Hence the availability of these materials will also improve the uncertainties achievable by IDMS measurements for applications in the biological, clinical, environmental and materials science sectors.

Impact and Benefits

Through development of the measurement platform required to generate demanded primary elemental standards, indispensible for providing traceability and thereby comparability of measurement results as an essential requirement of European directives in several fields of chemical analysis (e.g. WFD, IVD). The project will also contribute to a reduction in costs resulting from disputes and unnecessary repeat measurements. In health care, for example, a significant fraction of all measurements could be avoided by an improvement in the confidence of results and in Europe this is estimated to be ca several €Billion per year.

Support for Programme Challenge, Roadmaps, Government Strategies

Supports CB Strategic Priority Themes- Standards and Regulation and Metrology and SI and CBM Inorganic Analysis roadmap. BSI strategic plan for development of new and improved calibration standards to support food industry,

healthcare, environmental sustainability**.**

Synergies with other projects / programmes

EMRP JRP S08: “Primary standards for challenging elements”. Relates in general to all inorganic and speciation projects conducted under NMS programmes but more specifically CBM IS1 (Certification of Reference Standards for Absolute Carbon Isotope Ratios Traceable to the SI).

Knowledge Transfer and Exploitation

Knowledge transfer within the immediate metrological community will be realised by reporting at the regular EURAMET and CCQM meetings and through secondments between collaborators. Wider knowledge transfer of the developed strategies will be achieved through peer-reviewed publications and presentations at scientific meetings.

Within the frame of the EMRP JRP S08 project two workshops for stakeholders will be held, specifically focused on producers of calibration solutions and reference materials to disseminate primary standards via secondary standards to field laboratories. Also as part of the EMRP project, a practical guide for field laboratories on how to judge the quality of a calibration material or standard will be prepared in collaboration with EURACHEM.

Deliverables

1	**Start: 01/07/2012**	**End: 01/06/2014**	
Develop approaches without the use of pure isotopes CEW Comparison of approaches to mass bias correction for isotopic measurements of Mg and Mo by MC-ICP-MS without use of pure isotopes of the same element (e.g. multiple isotopic spiking techniques, internal normalisation to another element and use of synthetic mixtures of commercially available enriched isotopes) has been established			
2	**Start: 01/12/2013**	**End: 01/12/2014**	
Develop approaches with the use of pure isotopes CEW Validated methodology for mass bias correction for Mg isotopic measurements by multicollector ICP-MS using gravimetrically prepared mixtures of purified isotopes has been established.			
3	**Start: 01/06/2014**	**End: 30/06/2015**	
Determination of the natural isotopic composition of Mo and Mg primary calibration standards CEW Optimal mass bias correction approach has been applied to accurately determine the natural isotopic composition of Mo and Mg primary calibration standards.			
4	**Start: 01/07/2012**	**End: 30/06/2015**	
Project Management: Project delivered on time and to budget			

Project No.	CB/2013/IS14	Price to NMO	£377k
Project Title	Novel chromium speciation methods and reference materials to support Healthcare	Stage Start Date	Jun 13
		Stage End Date	Mar 16
Sector	Health and Safety	Activity	Methodology for new capabilities; provision of standards and maintenance of capabilities

Summary
The role and levels of chromium (Cr) and its variant forms in human physiology are not well understood; Both the beneficial role of trivalent chromium in human metabolism as well as the carcinogenic role of hexavalent chromium is under critical review by several health related organisations. This project will extend current NMS capabilities to measure relevant Cr species in clinical samples from patients supplemented with a Cr supplemented diet. In addition, a reference material certified for total Cr and Cr(III) in a food/food supplement matrix will be produced for the first time.

The Need
Cr food supplements are increasingly popular, making up approximately 6% of all mineral supplements sold today. However, the physiological effects of Cr on human health remain unclear, and are the subject of discussion by various health agencies (http://www.environment-agency.gov.uk/static/documents/Research/chromium_old_approach_2028660.pdf). There is evidence to suggest that the different speciated forms perform very different functions. Trivalent Cr (CrIII) may improve glucose and fat metabolism whereas hexavalent Cr (CrVI) is carcinogenic.
Food and food supplements are the main source of Cr intake by man, with CrIII thought to be the most prevalent form in foods. However, there is no available data to demonstrate that CrIII is the only form present in high content Cr foods such as fruits, sugars, fish, meat and food supplements. In response to this, the Scientific Panel on Contaminants in the Food Chain (CONTAM – part of the European Food Safety Authority [EFSA]) wished to assess the dietary exposure to Cr, and, in particular, to the carcinogenic form CrVI. In addressing exposure, they have expressed the need to collect additional data on Cr and Cr species levels in dietary sources of Cr (http://www.efsa.europa.eu/en/data/call/datex101217.htm).
To understand the levels of dietary Cr uptake but also accumulation, mobility and toxicity in the body, it requires a method that can reliably quantify Cr species not only in food and food supplements but also in clinical samples. Reference materials are also required to validate existing speciation methods, which are currently lacking inorganic Cr species for foods/food supplements. Such reference materials are essential for quality control of existing food products and to support forthcoming regulations by the EFSA to set maximum limits of CrVI in food/food supplements.

The Solution
Work under a related CBM project (IS9) developed methods to measure Cr species (including CrIII and CrVI) in food/food supplements using inductively coupled plasma mass spectrometry (ICPMS). These methods will be further developed and applied to measure Cr species in clinical samples (e.g. urine or plasma from patients supplemented with Cr-enriched yeast). Clinical samples will be obtained from a clinical trial run by a food supplement manufacturer, Pharma Nord, in association with a Professional Health Organisation to international standards. These methods will provide tools to investigate the hypothesised mechanism that the human body detoxifies Cr by reduction of CrVI to CrIII. Finally, a reference material certified for total Cr and CrIII content will be produced from a food / food supplement.

Impact and Benefits
Food/food supplement reference materials for inorganic Cr species are essential to the development of safe and effective dietary sources of high Cr content, enabling UK industry to enter new economies/markets.
EFSA has requested supplement manufacturers provide specification requirements for the detection of inorganic CrVI during the manufacturing process and in the final product. In response to this, industrial collaborators such as Pharma Nord have expressed the urgent need for reference methods and materials for Cr speciation to enable more efficient production and quality control processes.
The development of these analytical techniques for Cr speciation will support industry's compliance with emerging regulation and enabling regulators to discriminate between conforming and non-conforming Cr enriched foods and supplements. In turn, this provides consumers with increased confidence as to the nature of the product they are purchasing.
The beneficial/toxic effects of Cr are species-dependent and reference methods for clinical samples will help understand the quality of life effects of Cr supplementation and of the uptake of high Cr dietary sources.
The analytical advances driven by this project, supported by LGC's expertise in producing CRMs for determining selenium species in complex matrices, will retain LGC's position as a leading NMI in clinical speciation. Improvements in the quality of measurement science will enable the UK to actively contribute to international collaborations in this area, for example, international inter-comparison studies on Cr speciation.

Support for Programme Challenge, Roadmaps, Government Strategies
Aligns with CBM Strategy Theme 'Chemical Measurement and Calibration', sub-theme 'Food and Feed Manufacture'. Also BSI strategic plan re: development of new and improved calibration standards and reference materials to support food industry, healthcare, energy sustainability, etc.

Synergies with other projects / programmes
This project relates to other CBM and IRD speciation projects (CBM IS11: Metrology for WFD pollutants; IRD Metrology for metalloproteins; IRD H09: Novel metallomic approaches for Se speciation). It builds on the capability developed under CBM IS9 (Methodologies for the traceable quantification and identification of chromium species to

support new food supplements & disease prevention).			
Knowledge Transfer and Exploitation Knowledge transfer of the developed strategies to UK stakeholders will be achieved through peer-reviewed publication(s), presentations at scientific meetings and through discussion at a new Speciation user group to be set up as part of CBM project KT2e. Moreover, methodology transfer will be achieved through visits to industrial manufacturers of Cr supplements.			
Deliverables			
1	**Start: 01/06/13**	**End: 30/09/13**	
IDMS methodology for inorganic Cr in urine: CEW Methodology based on species-specific IDMS quantitation for inorganic Cr species in urine has been developed.			
2	**Start: 01/10/13**	**End: 30/09/14**	
Methodology for Cr associated to Cr-albumin/transferring: CEW methodology based on the combination of off line fractionation (using cut off centrifugal devices) and on-line separation techniques (e.g. FFF or FPLC) for the quantification of Cr associated with the albumin/transferrin fraction has been developed.			
3	**Start: 01/10/14**	**End: 31/03/16**	
Feasibility of application to clinical samples from a clinical trial: CEW Speciation methodologies developed earlier and mass balance approach (sum of isotopes 50, 52 and 53 and percentage determination of ^{52}Cr from the total using double focusing magnetic sector ICP-MS after microwave acid digestion) have been applied to selected samples from the human Cr supplementation trial and results have been reported.			
4	**Start: 01/06/13**	**End: 31/03/16**	
Reference material production: CEW a food/supplement reference material certified for total Cr and CrIII has been produced and become available for sale			
5	**Start: 01/06/13**	**End: 31/03/16**	
Knowledge Transfer: When a peer-reviewed publication has been prepared and a conference presentation has been made.			
6	**Start: 01/06/13**	**End: 31/03/16**	
Project Management: Project delivered in a cost effective manner. Customer reporting requirements fulfilled.			

Project No.	CB/2013/IS15	Price to NMO	£155k
Project Title	A metrology platform for isotope ratio mass spectrometry (IRMS) standards	Stage Start Date	May 13
		Stage End Date	Mar 15
Sector	Underpinning metrology, measurement infrastructure	Activity	Methodology for new capabilities

Summary
There is an urgent need to support stable isotope ratio measurements with matrix matched biological reference materials. The portfolio of such materials is very limited and, more importantly, falling ever further behind the needs of the rapidly expanding range and number of key regulatory, health and forensic applications. Certification of those that do exist, mainly for geochemical applications, has been based on consensus values from a few routine laboratories (although this also includes some very old materials still available through NIST). LGC has expertise unavailable in other NMIs or established CRM producers. This project will establish UK leadership in an expanding field delivering improved methodology which will facilitate future production and characterisation of matrix-matched reference materials for bulk (H, O) and compound-specific (C) isotope ratio measurements. Initial focus will be given towards identified priority materials for the food sector.

The Need
IRMS measurements of light elements are widely applied in the fields of geochemistry (e.g. various proxies for past sea surface temperatures are based upon oxygen isotope ratios), forensic science (e.g. identification of murder victims via bulk multi-isotopic analyses, or exposure of testosterone doping in athletes), food or drug authenticity and origin (e.g. detection of honey adulteration with high fructose corn syrup using C isotope ratio or counterfeit whiskeys using H and O isotope ratios), food and environment (e.g. investigation of food chain and cycling of nutrients within soils) and fingerprinting of substances (e.g. linking precursors to products during the synthesis of mephedrone).

Stable isotope ratio measurements for these light elements are reported relative to international standards, which have no SI traceability and some of which are 'virtual' materials. Calibration with matrix matched reference materials is required to minimize the effects of isotopic fractionation during the procedures used to determine stable isotopes for real samples. The simple gases to be measured in the mass spectrometer must first be generated from these samples. Hence, it is desirable to have a reference material with composition as similar as possible to the sample and to have isotope ratios of the standard close to (ideally bracketing) those of the sample. The portfolio of available materials is extremely limited and becoming even more so with time. Where such materials do exist, they tend not to comply with current requirements, such as certification in accordance with ISO Guide 34 and use of accredited measurement laboratories for provision of data. It is therefore common practice for laboratories to prepare their own 'tertiary' (or in-house, etc) calibration materials derived from the commercially available 'primary' or 'secondary' sources. These act as matrix-matched standards with the use of secondary reference materials for normalisation to the international scale. As instrumental techniques have refined over the years, this limitation has made an increasingly large contribution to the error of relative isotope ratio determinations.

The International Atomic Energy Agency (IAEA) and the National Institute of Standards and Technology (NIST) have a small range of secondary reference materials, which have been calibrated against the 'primary' standards. However, normalisation of measured compound-specific $\delta^{13}C$ values to the current VPDB scale is not straightforward. For example, none of the carbon isotope reference materials distributed by the IAEA or NIST are amenable to GC analyses, so alternative methods for normalisation of results to the VPDB scale are required.
The Technical strategy of the UK Forensic Isotope Ratio Mass Spectrometry (FIRMS) network (DSTL/STR08207, 2003-present) emphasises the urgent need for the development and appropriate use of reference materials to facilitate good practice and to enhance the traceability of IRMS measurements, especially for forensic purposes.

The Solution
The development of new UK NMI capabilities based on isotope ratio measurements of H and O in bulk materials with complex matrices. The development of improved methodology for compound-specific C IRMS (e.g. for which the calibrant and sample undergo the same steps of IRMS analysis). By having a ^{13}C-enriched calibrant, this approach will enable performing on-line isotope dilution analysis. This represents a breakthrough in IRMS measurements with potential application to purity measurement of organic calibrants.
Such measurement capabilities will be essential to the future development of IRMS reference materials, which are urgently needed to facilitate good practice and the traceability.

Impact and Benefits
The project will contribute to more robust IRMS measurements leading to a reduction of costs derived from industrial dispute cases and unnecessarily repeated measurements. For example, in the food industry, estimations indicate that a significant proportion of all measurements could be avoided by an improvement of confidence in IRMS measurements, resulting in savings for Europe of several billion Euro per year (FIRMS technical strategy document; Vinci et al (2013) J. Sci. Food Agric. 3:439-448). Reference materials for light element isotope ratio measurements are essential to the development of safe food and sustainable and authentic sources of biofuels, enabling UK industry to enter new economies/markets. Similar situations arise in other fields (such as forensics and geochemistry) where stable isotope measurements play a major role.
The project will also improve UK NMI capability for isotope ratio measurements and create impact by developing the measurement platform necessary to produce reference materials, essential for traceability and comparability of results.

Support for Programme Challenge, Roadmaps, Government Strategies Supports NMO Strategic Priority Themes Standards and Regulation and Metrology. Supports the CBM Inorganic/Organic Analysis theme. Also BSI strategic plan re. development of new and improved calibration standards and reference materials to support food industry, healthcare, energy sustainability etc..			
Synergies with other projects / programmes This project relates to other CBM projects (e.g. CBM IS1: Absolute C isotope ratio measurements and CBM IS13: Improved methodology for elemental and isotopic characterisation of primary elemental standards) dealing with the development of analytical methods for accurate isotope ratio measurements and reference material certification. It builds on the capability developed under the IRD-matched EMRP project Metrology for Biofuels.			
Knowledge Transfer and Exploitation Knowledge transfer of the developed strategies will be achieved through peer-reviewed publication and presentation at scientific meeting(s). Also, through active participation at FIRMS meetings and inter-laboratory comparison studies. Also, through secondment to/from other NMIs.			
Deliverables			
1	**Start: 01/05/13**	**End: 30/06/13**	
Material and compound selection: CEW Selection of matrix materials and compounds with partners have been established.			
2	**Start: 01/07/13**	**End: 30/11/13**	
Improved compound-specific C IR methodology: CEW improved methodology for compound-specific C isotope ratio measurements has been developed and its feasibility for fatty acid characterisation has been investigated.			
3	**Start: 01/12/13**	**End: 01/11/14**	
New H and O bulk IR methodology: CEW capability for H and O IRMS has been established and methodology for bulk H and O isotope ratio measurement in matrix materials using TC/EA-IRMS has been developed and validated.			
4	**Start: 01/05/14**	**End: 31/03/15**	
Knowledge Transfer: CEW a scientific paper has been published in a peer-reviewed journal and results have been presented at a scientific meeting.			
5	**Start: 01/05/13**	**End: 31/03/15**	
Project Management: CEW project delivered in a cost effective manner. Customer reporting requirements fulfilled.			

Project No.	CB/2013/IS16	Price to NMO	£160k
Project Title	Production of a Certified Reference Material for Toxic Metals in Blood	Stage Start Date	May 13
		Stage End Date	Mar 15
Sector	Drugs & therapies; Traceability & uncertainty	Activity	Provision of stds and maintenance of capabilities

Summary
Production of a certified reference material (CRM) for Co & Cr to improve health monitoring of patients with hip replacements.

The Need
There are currently about 80,000 (National Joint Registry, 2012) hip replacement operations performed per year in the UK alone and with an ageing population, this figure is likely to increase. About 35% of these operations involve the use of metal-on-metal (MoM) hip joints. Evidence suggests that these types of joints are robust and well-suited to young, active patients. However, there is growing concern that patients may develop progressive soft tissue reactions due to metal ions associated with wear debris entering the bloodstream. These concerns led to the MHRA issuing a Medical Devices Alert (MDA/2012/036) in June 2012 providing recommendations for patient follow-up which includes the analysis of Co & Cr in blood. Moreover, the FDA[1] have decided to gather further information about MoM systems in order to understand the significance of increased levels of Co & Cr in the bloodstream.
A proficiency test (PT) is available in the UK for these analyses which gives an indication of comparability of laboratories performing these tests. However, there is often significant variation (>20%) among the participant results and since there is no available CRM at appropriate concentrations, there is no measure of the accuracy of the results nor any traceability to international agreed units.

The Solution
Production of a CRM for Co & Cr will provide a new calibration tool for improving the accuracy and consistency of results within and between laboratories that monitor patients with MoM hip replacements.

Impact and Benefits
MDA guidance recommends that if Co and Cr levels in blood are of >7ng/ml, further analysis and possible clinical intervention are recommended. Hence, if the analytical laboratories report erroneous results, as the PT scheme would suggest, then significant and expensive intervention may be occurring unnecessarily. Equally, if laboratories are reporting erroneously low results, then joint erosion may be occurring without diagnosis. 13% of MOM hip replacements require revision after seven years (National Joint Registry Annual Report 2011). By improved measurement of Cr and Co in patient's blood through the provision of a CRM, it is anticipated that this will lead to a reduction in the variability of PT results, providing improved patient care.

Support for Programme Challenge, Roadmaps, Government Strategies
NHS drives, to reduce costs & improvement patient management, will be supported by more accurate analysis of blood samples. An improvement in the reliability of this analytical service should also assist in the development and application of current implant strategies.

Synergies with other projects / programmes
Exact matching IDMS methods previously developed for CCQM studies P106 and K87 will be used. This project is also linked to CCQM key comparison K107 and other activities related to low level elements & species in clinical sample matrices.

Knowledge Transfer and Exploitation
It is expected that routine laboratories who participate in the PT scheme will use the candidate CRM to further validate the ongoing performance of their methods. We will also highlight the availability and application of the CRM through dissemination in relevant trade journal(s) and/or clinical literature as well as through liaison with relevant Trade Bodies. In addition, we will lobby accreditation assessors to encourage the use of this material. Comparison of the certified value with that PT scheme consensus value will also give an indication of any method biases and, if necessary, could lead to the provision of reference values to this and other similar schemes.

Deliverables

1	**Start: 01/05/13**	**End: 01/10/14**	
Completion of analysis: Analysis of Co & Cr for characterisation, homogeneity & stability in candidate blood CRM is reported.			
2	**Start: 01/06/14**	**End: 01/12/14**	
Commutability study: Analysis of real patient samples is completed and reported using the certification method. Also, analysis of the candidate material is reported by routine laboratories.			
3	**Start: 01/12/14**	**End: 01/03/15**	
Certification of CRM: Certified reference material is released for sale with certified values for Co & Cr as well as indicative values for other relevant metals.			
4	**Start: 01/01/15**	**End: 31/03/15**	
Knowledge Transfer: Publication of an application note and/or other reports in relevant trade journals/clinical literature and engagement with trade bodies, regulators and legislators to encourage use of CRM.			

5	**Start: 01/05/13**	**End: 31/03/15**	
Project Management: Delivery of project in a cost effective manner. Customer reporting requirements fulfilled.			

Project No.	CB/2013/KT1e	Price to NMO	£130k
Project Title	Increasing stakeholder engagement and awareness	Stage Start Date	Apr 13
		Stage End Date	Mar 14
Sector	Health, Underpinning metrology	Activity	Knowledge transfer

Summary

This project will provide effective and efficient mechanisms for disseminating the outputs of the programme to the measurement community and for engaging with stakeholders. The project will increase awareness of the measurement issues being addressed and the capabilities and applications of the measurement techniques used. The project will also assess the impact of ChemBio projects on the measurement community. These outcomes will be achieved through the continued provision of a web-presence which will provide a focus for the dissemination of programme information and outputs, production of case studies demonstrating how the programme has benefited UK stakeholders, and participation in relevant technical events and conferences organised by intermediaries. Through provision of a 'helpdesk' service the project will also provide access to expertise on quality assurance issues and on chemical and bioanalytical measurements.

The Need

To maximise the benefits and impact of the scientific outputs of the programme, and improve the level of awareness of the importance of valid measurements, effective mechanisms for transferring the knowledge and expertise generated within the technical projects to stakeholders are required. Each technical project has a 'knowledge transfer plan' to ensure that the outputs are disseminated to the relevant measurement communities through, for example, the publication of peer-reviewed papers and presentation of results at scientific conferences. To realise the full benefit of NMO investment in LGC's NMI function there is a need to ensure that the technical outputs are easily accessible and also to raise awareness of the aims and benefits of the programme beyond those who are already actively engaged. Stakeholders also need to be able to access the measurement expertise contained within the programme. In previous programmes these issues have been addressed through the provision of a dedicated programme website, development of awareness raising materials such as case studies and providing access to technical advice.

The Solution

This project will support the day-to-day activities required to effectively disseminate programme outputs and knowledge. The web is a key source of information on the technical work carried out under LGC's NMI role and contains a significant amount of freely available training materials and guidance documents produced under previous programmes. A new LGC corporate website is expected to be launched in early 2013 and content will be migrated from the current ChemBio website to a dedicated area of the corporate site. This will lead to cost savings by removing the need for hosting and licensing of a separate website. It is also anticipated that traffic to the programme-relevant pages will increase due to the higher visitor numbers for the LGC corporate site. This project will support the continued provision of a web-presence which will allow information on programme outputs and activities, papers, reports and training materials produced under the programme to be disseminated quickly and cost effectively. Regular 'e-alerts' will notify website users of new content and production of the 'Catalyst' e-newsletter will demonstrate the range and impact of the technical projects. Production of a series of case studies and 'feature articles' will demonstrate the benefits and impact of the programme, while working with intermediaries such as KTNs, Sector Skills Councils, professional bodies, government departments, standards organisations and regulatory bodies, will help to increase engagement with the programme and minimise costs associated with dissemination of information. The project will also utilise the cross NMS Measurement Network web space established on the Technology Strategy Board _connect portal as a dissemination channel. Providing access to expert technical advice and training materials will help UK industry to solve measurement and quality assurance issues.

Impact and Benefits

This project will maximise the benefits of the programme to the measurement community by improving awareness and uptake of the programme outputs and assisting organisations with solving measurement issues. Provision of technical advice will benefit organisations by assisting them in ensuring the quality of their measurements, enabling them to meet regulatory requirements and maintaining market acceptance.

Support for Programme Challenge, Roadmaps, Government Strategies

This project supports the wider CBM themes of chemical measurement and calibration, and bioanalysis by providing mechanisms for effectively disseminating the outputs of the associated technical projects and providing access to measurement expertise.

Synergies with other projects / programmes

This project is essential for the effective dissemination of the outputs, knowledge and expertise from the technical projects, and to maximise the benefits of BIS investment in measurement research. While each technical project has specific deliverables to address effective knowledge transfer, this project will provide a central focus for the knowledge originating from the programme. The web-presence provides a dedicated contact point for individuals to access the programme. It is also the primary route for disseminating the technical training resources produced under the 'Improving measurement knowledge and skills' project. In addition, value for users is maximised by signposting the lists of, and providing access points to, the good practice guides produced across all four UK National Measurement Institutes. Production of case studies and participation in technical events allows the benefits of the programme to be communicated to, and taken up by, new and existing stakeholders.

Knowledge Transfer and Exploitation

The project is composed of knowledge transfer activities which will enhance the uptake of outputs from the technical projects and raise awareness of key measurement issues. The dissemination/engagement routes described (website, NMS Measurement Network, case studies, feature articles, working with intermediaries) will provide effective mechanisms for disseminating the outputs and knowledge from the programme. Costs are minimised through the use of electronic media and key intermediaries to disseminate information.			
Deliverables			
1	**Start: 01/04/13**	**End: 31/03/14**	
Website: CEW a website containing up to date information on programme activities and technical outputs has been hosted and managed, material has been migrated from the current CBM website to the new LGC platform, quarterly email alerts have been distributed to registered website users and two issues of the 'Catalyst' e-newsletter has been prepared and disseminated.			
2	**Start: 01/04/13**	**End: 31/03/14**	
Disseminating programme benefits: CEW activities to demonstrate the benefits and impact of the programme, and increase engagement with UK industry have been completed. Activities will include the production of at least four case studies (including two detailed 'impact' studies, and a possible subcontract to develop an impact model for early stage disruptive technologies) and four feature articles, collation of information for the annual NMS portfolio Value Scorecard, and partnering with intermediaries to deliver effective knowledge transfer and ensure cost efficiencies.			
3	**Start: 01/04/13**	**End: 31/03/14**	
Technical advice: CEW technical enquiries on measurement and quality assurance issues have been answered and information on programme outputs, and products and resources produced under the programme has been provided.			

Project KT2	Exploiting NMI capability to improve knowledge and skills

Project Objectives

- To exploit LGC's NMI expertise and capabilities to raise awareness of chemical and biochemical measurement issues and improve the quality of measurements made within the UK.
- To improve skills and knowledge of key metrology principles and practices (e.g. method validation) and application of key measurement techniques (e.g. mass spectrometry) to deliver accurate and reliable chemical and biochemical measurements.

Background and Rationale

In order to make accurate and reliable measurements, organisations require a skilled workforce that is knowledgeable in key underpinning measurement and quality assurance principles and practices. The expertise and measurement capabilities developed within LGC's NMI function must be effectively transferred to stakeholders in order to maximise the benefit of BIS investment.

National networking activities provide an effective mechanism for disseminating the outputs of the programme and to securing collaboration and co-funding of tasks. They also ensure stakeholder input to requirements and are essential to formulating a representative UK input to international organisations and committees.

Mass spectrometry is one of the most widely used analytical techniques which has moved from 'specialist' laboratories into routine use. Many analysts now have access to mass spectrometry instruments on a daily basis, but often lack formal training or knowledge on how to ensure the quality of data produced. The need for guidance in two key areas has been identified: quantitative analysis by LC-MS and isotope ratio mass spectrometry (IRMS).

Implementing suitable quality assurance procedures can be a significant burden for laboratories in terms of the time and effort involved. Method validation is one of the key areas that is relevant to all measurement sectors. Feedback from training courses and seminars indicates that there is a need for worked examples which illustrate the complete validation process, from planning experiments to processing and interpreting the data. This project will also continue to support laboratories in carrying out suitable QA activities through the provision of training material and the organisation of seminars and workshops.

To help ensure that future scientists have the necessary analytical skills, it is essential that the principles of metrology and valid measurements are introduced and reinforced during undergraduate and postgraduate study. The projects proposed in this area will give a context to measurement and quality issues by producing educational materials and organising events that focus on key QA activities.

Impact

- Dissemination and adoption of internationally recognised metrology principles and practices provides confidence and credibility in results generated by UK laboratories.
- Raising awareness of the role of the NMI for chemical and biochemical measurement will improve analysts' understanding of the need for standardisation and the importance of reference materials.
- National networking activities help disseminate programme outputs, engage stakeholder participation / co-funding for tasks and enable UK organisations to input to the direction of the programme.
- Guidance on application of mass spectrometry will enable laboratories across a wide range of sectors to improve and ensure the reliability of their measurement results.
- New method validation tools will simplify implementation and reduce the burden/cost of quality assurance across a wide range of measurement sectors.
- The projects supporting the education and training of future scientists will enhance the teaching of measurement and quality assurance issues to improve the skills of those entering scientific careers.

Deliverables

No.	Deliverable	Start	End	Cost
1	CEW national networking activities on generic topics which cross technical project areas (e.g. RSC AMC, PTWG, RMWG, MSWG) have been reported.	Oct 09	Mar 11	
2	CEW a web-based resource has been developed describing the key techniques used within the NMI, their applications and capabilities.	Oct 09	Mar 11	
3	CEW a best practice guide on quantitative analysis by LC-MS has been published.	Oct 09	Dec 13	
4	CEW a workshop on key issues relating to the production of valid measurements by IRMS has been organised and a best practice	Oct 09	Mar 11	

	guide on producing reliable measurements using IRMS has been published.			
5	CEW an ‘e-book’ to assist laboratories with the planning and execution of validation studies has been developed, and a seminar organised to disseminate the resource.	Oct 09	Mar 11	deleted
6	CEW the web-based QA resource has been extended to include biomeasurement issues.	Oct 09	Sep 12	
7	CEW resources and activities to improve the skills of graduates and postgraduate students have been developed. Proposed activities include: Development of case studies on quality assurance and metrology issues to enhance the teaching university courses; delivery of a 1 day ‘Introduction to quality assurance’ workshop for postgraduates; delivery of presentations and workshops on measurement and QA topics to a range of university courses.	Oct 09	Mar 11	
			Total cost	**£205K**

Proposal No.	KT2c	Price to NMO	£120k
Proposal Title	Improving measurement knowledge and skills	Stage Start Date	1 April 2011
		Est Final Stage End Date	31 Dec 2013

Summary

This project will help to improve the quality and reliability of measurement results by improving the skills and knowledge of UK stakeholders involved in making chemical and bioanalytical measurements. This will be achieved through the production of cost-effective and targeted training resources which are easily accessible to the measurement community.

The Need & Current State of the Art

Chemical and bioanalytical measurements impact on many areas of government, industry and society. These measurements underpin regulatory controls, support commercial activities and enable innovation in industry and protect the public. It is therefore essential that measurement results are reliable and sufficiently accurate for their required purpose. In order to make valid measurements, organisations require a skilled workforce that has knowledge of relevant measurement techniques and key quality assurance principles. The increasing sophistication and automation of analytical instrumentation means it can be relatively easy for users to generate data without necessarily having a detailed understanding of the principles underpinning the measurement techniques. This can make it difficult for analysts to develop suitable protocols to ensure the validity of results, and also to identify poor quality data. There is an ongoing need for accessible guidance and training on generic quality/metrology issues, especially for those starting their scientific careers. LGC has an established track record in the production and dissemination of training resources. The best practice guides and other resources produced under previous programme are well regarded by stakeholders and recognised as authoritative sources of information. The materials produced under the knowledge transfer projects assist organisations in making measurements competently and accurately, therefore reducing the costs associated with implementing robust quality procedures and meeting regulatory requirements.

The Solution & Metrology Capability to be Delivered

The knowledge and expertise generated through NMO investment in LGC's NMI function must be disseminated effectively to stakeholders to maximise the impact of that investment. The production and dissemination of training resources is a cost effective way of using NMI expertise to support UK organisations in making valid measurements. A number of key areas have been identified. Training resources will be developed to assist laboratories in obtaining valid results using qPCR. This is a widely used technique but users require guidance on key aspects such as standardisation and method validation. The materials will be disseminated via the website and also form the basis of a training course (at zero cost to the project).

Best practice guidance on the combined use of elemental and molecular mass spectrometry for elemental speciation analysis will also be developed. There is a need for disseminating essential information on good laboratory practice when performing quantitation and identification of ultratrace elemental species in complex samples by using chromatography with ICPMS and ESI MS/MS. After a brief introduction of the techniques, the advantages and pitfalls of using ICP-MS in parallel with molecular mass spectrometry will be described. The quality control aspects of speciation measurements using this parallel approach will also be discussed.

There is an ongoing need for accessible and user-friendly resources covering general quality and measurement related issues such as the correct use of reference materials, method validation and quality control. Training materials will continue to be developed to assist with improving skills in the workplace. A 'mapping exercise' will also be undertaken to identify where existing resources developed under previous and future VAM/CBM programmes can be used to support implementation of relevant National Occupational Standards (NOS) developed by the Sector Skills Councils. These standards provide a framework for training and development, support the delivery of apprenticeships (an area of government priority) and form the basis of National Vocational Qualifications (NVQs).

Impact and Benefits

The technical training resources produced under this project will benefit individuals and organisations by supporting skills development and reducing the burdens associated with implementing quality assurance procedures. Effective quality assurance also reduces the costs associated with poor quality data such as the need to repeat measurements and the potential issues associated with incorrect decisions based on erroneous results. The resources covering specific measurement techniques will enable laboratories across a wide range of sectors to improve the reliability of their measurements.

Support for Programme Challenge, Roadmaps, Government Strategies

This project supports the CBM themes of chemical measurement and calibration, and bioanalysis by providing stakeholders with resources which will allow them to improve and ensure the quality of their measurement results. Such measurements will impact a wide range of sectors including the priority areas of healthcare, sustainability and security.

Knowledge Transfer and Exploitation Plan

This project comprises knowledge transfer activities which will assist organisations in ensuring the quality of measurement results. Cost are minimised by distributing training resources via the electronic media supported under

the 'Increasing stakeholder engagement and awareness' project, and through using intermediaries (e.g. professional bodies such as Royal Society of Chemistry, and Association for Clinical Biochemistry, Sector Skills Councils).			
Deliverables			
1	**Start: 01/04/11**	**End: 31/12/2013**	
Training resources on qPCR: CEW when training resources have been prepared, reviewed by stakeholders and disseminated via a training course and the Chemical and Biological Metrology website (organisation and delivery of training course at zero cost to project).			
2	**Start: 01/04/11**	**End: 31/12/2013**	
Best practice guidance on combined use of elemental and molecular mass spectrometry for elemental speciation analysis: CEW best practice guidance has been prepared, reviewed by stakeholders and disseminated via the Chemical and Biological Metrology website.			
3	**Start: 01/04/11**	**End: 30/09/2012**	
Interactive training resources: CEW when training resources have been developed, evaluated by laboratory staff and disseminated via the Chemical and Biological Metrology website.			
4	**Start: 01/04/11**	**End: 30/09/2012**	
Case studies demonstrating the practical implementation of QA: CEW when at least two case studies have been developed and disseminated via the Chemical and Biological Metrology website.			
5	**Start: 01/04/11**	**End: 30/09/2012**	
Resource mapping exercise: CEW when VAM/CBM programme resources have been mapped against NOS requirement and a summary has been disseminated via the Chemical and Biological Metrology website and relevant Sector Skills Councils.			

Project No.	CB/2012/KT2d	Price to NMO	£85k
Project Title	Improving knowledge and skills	Stage Start Date	1 April 2012
		Stage End Date	30 June 2013

Summary

This project will help to improve the quality and reliability of measurement results by improving the skills and knowledge of UK stakeholders involved in making chemical and bioanalytical measurements. This will be achieved through the production of cost-effective and targeted training resources which are easily accessible to the measurement community and through engagement with key organisations such as the Sector Skills Councils (SSCs).

The Need

Chemical and bioanalytical measurements impact on many areas of society, government and industry. These measurements underpin regulatory controls, support commercial activities, enable innovation in industry and protect the public. It is therefore essential that measurement results are reliable and sufficiently accurate for their required purpose. In order to make valid measurements, organisations require a skilled workforce that has knowledge of relevant analytical techniques and quality assurance principles. There is therefore an ongoing requirement for training in basic laboratory skills and for resources illustrating the practical implementation of quality assurance in the laboratory. In particular, the 'resource mapping' exercise carried out during 2011 at LGC has identified a need for materials to support skills training in cell and molecular biology.

The Solution

The knowledge and expertise generated through NMO investment in LGC's NMI function must be disseminated effectively to stakeholders to maximise the impact of that investment. The production and dissemination of training resources is a cost effective way of using NMI expertise to support UK organisations in making valid measurements. A number of key areas have been identified. Training resources will be developed to enhance skills training in basic laboratory techniques for molecular and cell biology. This will build upon the successful 'Laboratory Skills Handbook' for chemical analysis developed under a previous programme. LGC will continue to work with the SSCs and other providers of higher level skills training, to enhance uptake of training resources developed under the programme and to identify future opportunities for collaboration and resource development.

There is an ongoing need for accessible and user-friendly resources covering general quality and measurement related issues such as the correct use of reference materials, method validation, quality control and continuous improvement in the laboratory. Case studies will continue to be developed to illustrate the effective implementation of quality assurance.

Impact and Benefits

The training resources produced under this project will benefit individuals and organisations by supporting skills development and reducing the burdens associated with implementing quality assurance procedures. Effective quality assurance also reduces the costs associated with poor quality data such as the need to repeat measurements and the potential issues associated with incorrect decisions based on erroneous results. Collaboration with SSCs will help to ensure that suitable resources are developed and reach their target audience.

Support for Programme Challenge, Roadmaps, Government Strategies

This project supports the CBM themes of chemical measurement and calibration, and bioanalysis by providing stakeholders with resources which will allow them to improve and ensure the quality of their measurement results. Such measurements will impact a wide range of sectors including the priority areas of healthcare, sustainability and security.

Synergies with other projects / programmes

The activities in this project provide the opportunity to disseminate the broader technical knowledge from across the CBM programme. The development of technical training resources will support the NMS skills strategy and maximise and extend the portfolio of materials produced under previous programmes and builds on LGC's successful track record in training and education.

Knowledge Transfer and Exploitation

This project comprises knowledge transfer activities which will assist organisations in ensuring the quality of measurement results. Cost are minimised by distributing training resources via electronic media supported under the 'Increasing stakeholder engagement and awareness' project, and through using appropriate intermediaries (e.g. professional bodies, SSCs).

Deliverables

1	**Start: 01/04/12**	**End: 31/06/13**	

Training resources on laboratory skills for cell biology:

CEW best practice guidance has been prepared, reviewed by stakeholders and disseminated via the Chemical and

Biological Metrology website.			
2	**Start: 01/04/12**	**End: 31/06/13**	
Training resources on laboratory skills for molecular biology: CEW best practice guidance has been prepared, reviewed by stakeholders and disseminated via the Chemical and Biological Metrology website.			
3	**Start: 01/04/12**	**End: 31/03/13**	
Case studies demonstrating the practical implementation of QA: CEW at least two case studies have been developed and disseminated via the Chemical and Biological Metrology website.			
4	**Start: 01/04/12**	**End: 31/03/13**	
Working with intermediaries: CEW at least five meetings/other engagement activities completed to support delivery of work-based training programmes.			

Project No.	CB/2013/KT2e	Price to NMO	£90k
Project Title	Improving knowledge and skills	Stage Start Date	Apr 13
		Stage End Date	Mar 14
Sector	Health, Underpinning metrology	Activity	Knowledge Transfer

Summary
This project will help to improve the quality and reliability of measurement results by improving the skills and knowledge of UK stakeholders involved in making chemical and bioanalytical measurements. This will be achieved through the production of cost-effective and targeted training resources which are easily accessible to the measurement community. The project will also support the establishment of user groups which will provide an effective mechanism for knowledge transfer and stakeholder engagement.

The Need
Chemical and bioanalytical measurements impact on many areas of society, government and industry. These measurements underpin regulatory controls, support commercial activities, enable innovation in industry and protect the public. It is therefore essential that measurement results are reliable and sufficiently accurate for their required purpose. This requires an understanding of method validation and uncertainty estimation. In order to make valid measurements, organisations therefore require a skilled workforce that has knowledge of relevant analytical techniques and quality assurance principles. There is an ongoing requirement for training in key laboratory techniques and for resources to support the practical implementation of quality assurance in the laboratory. In addition, to carry out effective method development and validation, analysts require an understanding of experimental design techniques. Evaluation of measurement uncertainty is a requirement of the ISO/IEC 17025 standard. The principles of uncertainty evaluation for the results from chemical analysis are relatively well established and a number of guides have been published. In the field of microbiological testing, however, the principles are less well understood. Feedback from participants in LGC Proficiency Testing schemes has indicated a need for guidance on uncertainty estimation for microbiological testing.
There is also a need for greater engagement with stakeholders to allow effective knowledge transfer and to ensure that future projects meet the needs of the measurement community.

The Solution
The knowledge and expertise generated through NMO investment in LGC's NMI function must be transferred effectively to stakeholders to maximise the impact of that investment. The production and provision of training resources is a cost effective way of using NMI expertise to support UK organisations in making valid measurements. A number of key areas have been identified. A review of approaches for uncertainty estimation in microbiological testing will be carried out and a guidance document produced. The approaches proposed in the guidance will be evaluated through a proficiency testing scheme.
Training resources will be developed to support laboratories in planning effective experiments ('experimental design') and in making valid measurements in the field of molecular biology. The materials will be provided via the web and also form the basis of training courses (delivered at zero cost to the project).
LGC is an active member of the Eurachem network and staff have contributed to the production of a number of successful and highly-regarded guides. The revision of two Eurachem guides is planned – 'The Fitness for Purpose of Analytical Methods: A Laboratory Guide to Method Validation and Related Topics' and 'Guide to Quality in Analytical Chemistry: An Aid to Accreditation'. This project will support the UK contribution to the revision of these important guides.
Finally, the project will support the establishment of 'user groups' to provide an effective mechanism for greater stakeholder engagement. Key areas identified include peptide/protein measurements, quantitative nucleic acid measurements, and speciation analysis, but these may be adapted or changed to reflect more explicit user requirements and feedback.

Impact and Benefits
The training resources produced under this project will benefit individuals and organisations by supporting skills development and reducing the burdens associated with implementing quality assurance procedures. Effective quality assurance also reduces the costs associated with poor quality data such as the need to repeat measurements and the potential issues associated with incorrect decisions based on erroneous results. Collaboration with Eurachem will ensure that guidance documents have international recognition. The user groups will provide an effective knowledge transfer mechanism and a forum for discussing the direction of future projects.

Support for Programme Challenge, Roadmaps, Government Strategies
This project supports the CBM themes of chemical measurement and calibration, and bioanalysis by providing stakeholders with resources which will allow them to improve and ensure the quality of their measurement results. Such measurements will impact a wide range of sectors including the priority areas of healthcare, sustainability and security.

Synergies with other projects / programmes
The activities in this project provide the opportunity to disseminate the broader technical knowledge from across the CBM programme. The development of technical training resources will support the NMS skills strategy and maximise and extend the portfolio of materials produced under previous programmes and builds on LGC's successful track record in training and education.

Knowledge Transfer and Exploitation This project comprises knowledge transfer activities which will assist organisations in ensuring the quality of measurement results. Cost are minimised by providing training resources via electronic media supported under the 'Increasing stakeholder engagement and awareness' project, and through using appropriate intermediaries (e.g. Eurachem, stakeholder user groups).			
Deliverables			
1	**Start: 01/04/13**	**End: 31/03/14**	
Evaluation and recommendations on approaches to estimating measurement uncertainty in microbiological testing: CEW approaches have been reviewed and evaluated, guidance document prepared and recommended approaches assessed via a PT scheme.			
2	**Start: 01/04/13**	**End: 31/03/14**	
Development of training material on experimental design and achieving valid measurements in molecular biology: CEW training resources have been prepared, reviewed by stakeholders and disseminated via training courses and the web (organisation and delivery of training courses at zero cost to project).			
3	**Start: 01/04/13**	**End: 31/03/14**	
Production of guidance on method validation and achieving accreditation: CEW required sections of the relevant Eurachem guides have been revised and endorsed by Eurachem members.			
4	**Start: 01/04/13**	**End: 31/03/14**	
Establishment of user groups: CEW at least three user groups have been established and have met at least once during the project. Target areas are peptide/protein measurements, quantitative nucleic acid measurements, and speciation analysis.			

Project No.	CB/2013/MD3e	**Price to NMO**	£135K
Project Title	Programme Management	**Stage Start Date**	Apr 13
		Stage End Date	Mar 14
Sector	N/A	**Activity**	Programme Management

Summary

This project supports the LGC management and co-ordination activities that are necessary to ensure that the Chemical and Biological Metrology (CBM) programme is delivered effectively.

- To provide co-ordinated management and reporting on all CBM projects contracted to LGC and to ensure the delivery of this work to quality, time and budget
- To enable effective co-ordination and collaboration with NPL in order to deliver a seamless CBM programme.

The Need

The CBM programme is one of a portfolio of programmes within the National Measurement System. Effective programme management and liaison with NMO and other NMS contractors (NPL, NEL) is essential to ensure the programme is delivered to quality, time and budget and co-ordinated with other NMS initiatives and programmes.

Impact and Benefits

This project ensures that work contracted to LGC is delivered to quality, time and budget. Provision of timely and accurate information helps NMO to manage the overall NMS programme portfolio effectively and ensure that NMO delivery targets are achieved.

Support for Programme Challenge, Roadmaps, Government Strategies

N/A

Synergies with other projects / programmes

N/A

Risks

Loss of key staff (medium) offset by the bringing through of new individuals.

Knowledge Transfer and Exploitation

N/A

Deliverables

1	**Start: 01/04/13**	**End: 31/03/14**	

Programme Management including:

- **Monthly Reporting:** Monthly reports and invoices, submitted to NMO within one month of period end.
- **Contract Review Meetings:** Quarterly meetings between LGC (Programme Manager) and NMO (Programme Supervisor) to review contract delivery.
- **Annual Report:** Annual report, produced in collaboration with NPL, submitted to NMO within two months of year end.
- **Progress Review and Decision Conference:** Annual progress review meeting and Decision conference, organised with NPL, held to the satisfaction of NMO and CBM WG.

Project No.	CB/2012/MD4d	Price to NMO	£349K
Project Title	Programme Formulation & Strategy	Stage Start Date	1 April 2012
		Stage End Date	30 September 2013

Summary

This project underpins the strategic development of the Chemical and Biological Metrology (CBM) Programme. It supports the formulation of future project work to be delivered under the programme and enables LGC to proactively contribute to NMS policy initiatives and activities.

The Need

Programme formulation requires close liaison with NMO and their expert advisors and collaboration with other NMIs (both in UK and overseas) to ensure that the technical specifications reflect stakeholder needs, and also to ensure that project proposals are prepared in accordance with NMO strategy and policy. Proactive input to the formulation of EMRP projects is vital in order to influence and secure strong involvement and payback for UK plc.

The Solution

Impact and Benefits

Effective programme formulation enables NMO to identify and procure the most effective work for the available budget, consistent with BIS policy objectives. Well-founded project specifications that are representative of requirements and address priority needs are essential to maximising the future impact of the NMS. Proactive involvement of LGC in NMS policy initiatives helps NMO to develop and implement NMS strategy and thus achieve BIS policy objectives.

Support for Programme Challenge, Roadmaps, Government Strategies

This project directly supports the development and updating of programme roadmaps.

Synergies with other projects / programmes

Knowledge Transfer and Exploitation Plan

Deliverables

1	Start: 01/04/2012	End: 30/09/2013	

- Preparing for and attending strategy and policy meetings (e.g. Programme Board, KT Forum, International Forum)
- Drafting and commenting on strategy papers (e.g. programme roadmaps, stakeholder engagement, impact assessment)
- Providing briefing material for NMO (e.g. for Measurement Board and Ministerial submissions)
- Consulting and disseminating NMS policy amongst NMI staff
- Hosting senior level visits to LGC (Ministers, HQ staff) to provide briefing on NMS activities and NMI function
- Production of CBM project proposals and specifications
- Preparing for and attending EMRP formulation meetings and producing EMRP project proposals with other EMRP partners
- Production of a report outlining the measurement requirements currently facing the biopharmaceutical industry.

Project No.	CB/2013/MD4e	**Price to NMO**	£305k
Project Title	Programme Formulation & Strategy	**Stage Start Date**	Apr 13
		Stage End Date	Mar 14
Sector	N/A	**Activity**	Programme Management

Summary

This project underpins the strategic development of the Chemical and Biological Metrology (CBM) Programme. It supports the formulation of future project work to be delivered under the programme and enables LGC to proactively contribute to NMS policy initiatives and activities.

The Need

Programme formulation requires close liaison with NMO and their expert advisors and collaboration with other NMIs (both in UK and overseas) to ensure that the technical specifications reflect stakeholder needs, and also to ensure that project proposals are prepared in accordance with NMO strategy and policy. Proactive input to the formulation of EMRP projects is vital in order to influence and secure strong involvement and payback for UK plc.

The Solution

N/A

Impact and Benefits

Effective programme formulation enables NMO to identify and procure the most effective work for the available budget, consistent with BIS policy objectives. Well-founded project specifications that are representative of requirements and address priority needs are essential to maximising the future impact of the NMS. Proactive involvement of LGC in NMS policy initiatives helps NMO to develop and implement NMS strategy and thus achieve BIS policy objectives.

Support for Programme Challenge, Roadmaps, Government Strategies

This project directly supports the development and updating of programme roadmaps.

Synergies with other projects / programmes

N/A

Knowledge Transfer and Exploitation

N/A

Deliverables

1	**Start: 01/04/13**	**End: 31/03/14**	

- Preparing for and attending strategy and policy meetings (e.g. Programme Board, KT Forum, International Forum)
- Drafting and commenting on strategy papers (e.g. programme roadmaps, stakeholder engagement)
- Providing briefing material for NMO (e.g. for Measurement Board and Ministerial submissions)
- Consulting and disseminating NMS policy amongst NMI staff
- Hosting senior level visits to LGC (Ministers, HQ staff) to provide briefing on NMS activities and NMI function
- Production of CBM project proposals and specifications
- Preparing for and attending EMRP formulation meetings and producing EMRP project proposals with other EMRP partners.
- Preparing for and organisation of EURAMET TC MC 2014 meeting.

Proposal No.	NB10	Price to NMO	£502k
Proposal Title	*In vitro* nanotoxicology	Stage Start Date	1st June 2011
		Est Final Stage End Date	31st July 2013

Summary

This project will produce a prototype panel of reference materials characterised for their chemical and biological properties to allow the development of traceable methods for *in vitro* safety assessment. The materials will be characterised in physiologically relevant biological media so they can be applied as calibration standards in routine testing procedures.

The Need & Current State of the Art

Nanoparticles have been incorporated into more than 800 commercial products and now account for over £104 billion in sales worldwide (Lux Research Inc, 2008). These products impact on all areas of human life, ranging from coatings that stop corrosion, nano-catalysts for fuel cells, imaging agents for medical research, sun creams and cosmetics. However, alongside the growing applications for nanoparticles, reports that nanoparticles can cross cellular barriers as a result of their small size and unusual properties have raised safety concerns. Moreover, reports from the UK government highlight that in order to take full advantage of the technological benefits of nanotechnology and to sustain competitive economic growth in the UK, it is becoming increasingly necessary to ensure that nanoproducts are safe at all stages of their life-cycle and that the public and the environment is adequately protected from any adverse effects.

One of the fastest methods to measure the potential toxicity of nanoparticles is through the use of high throughput *in vitro* screens which mimic the physiological environment that nanoparticles encounter within the body. However, comparability of *in vitro* data between laboratories is poor, with a number of reports identifying the key contributor to this variability as being the lack of characterised reference materials. In the UK, the Nanotechnology Research Coordination Group (NRCG) in its key report [Development of testing strategies and methods for human health hazard assessment of nanoparticles] identified the development of a bank of reference materials for toxicology and metrology as a critical objective. This was mirrored in later reports by DEFRA [Characterising the potential risks posed by engineered nanoparticles] and through the conclusions of the REFNANO project [Reference materials for engineered nanoparticle toxicology and metrology]. Outside the UK a number of international reports: authored by the NNI, (2009) [Strategy for Nanotechnology Related Environmental, Health and Safety Research] and, OECD, (2010) [Publications in the Series on the Safety of Manufactured Nanomaterials] and the World Technology Evaluation Centre (draft report, 2010) have similarly highlighted the urgent requirement for suitable nanoparticle reference materials as well as standardised *in vitro* assay protocols.

The Solution & Metrology Capability to be Delivered

To develop a panel of prototype reference materials characterised for their chemical and biological properties to be used to assess measurement uncertainty and variability in high throughput *in vitro* nanotoxicity screens.

Impact and Benefits

Economic impact: The development of reference materials to support nanoparticle safety assessment will have an economic impact through support of the UK nanotechnology market which is worth >£5bn and incorporates >600 companies which are developing products that impact on almost all areas of human life from computing to medicine. This will also support the increasing production demands in the UK, which is estimated to increase from 2500 tons/y to 58000 tons/y by 2020.

Quality of life, Science and innovation impact: The potential for nanotechnology to improve human health and aid diagnostic and medical procedures can only be realised if nanomaterials are shown to be non-hazardous to human health, particularly those for use in nanomedicine applications and consumer products. This project will impact across the sector by providing reference materials which can be incorporated into testing regimes for regulatory processes and public acceptance of nanomaterial safety. Maintaining close links with key stakeholders will ensure knowledge transfer through industry trade associations and peer-reviewed scientific posters and publications.

Support for Programme Challenge, Roadmaps, Government Strategies

Supports CBM roadmap 'Pollution: particulates' as well as 'Risks from new technologies': work-place and environmental stress' and CBM nanotechnologies roadmap: Nanoparticle risk assessment. Also supports the UK strategy for nanotechnology, 2007, 2010: 'Health and Safety of nanoparticles'.

Knowledge Transfer and Exploitation Plan

Scientific findings of the project will be disseminated through peer review publications, presentations at relevant scientific conferences and via the CBM website.

1	Start: 01/06/11	End: 30/09/2012	

Size characterisation and cytotoxicity of reference nanoparticles

CEW: A panel of reference nanoparticles have been selected and characterised for size in biological media and toxicity in physiologically relevant *in vitro* models.

2	Start: 01/01/12	End: 31/03/14	

Quantification of intracellular nanoparticle uptake and activity

CEW**:** The biological impact of the selected nanoparticles including uptake, distribution and mode of toxicity has been measured in the physiologically relevant *in vitro* models from deliverable 1.

3	**Start: 01/04/12**	**End: 31/03/13**	
Characterisation of nanoparticle suspensions and elemental composition CEW**:** Methods for the use of FFF coupled to ICP-MS have been developed to characterise the size distribution and sized based elemental composition of nanoparticle suspensions in biological media.			
4	**Start: 01/04/13**	**End: 31/03/13**	
Feasibility evaluation of FFF coupled to ICP-MS for the characterisation of intracellular dose CEW: FFF coupled ICP-MS has been examined to determine the distribution elemental composition of intra-cellular nanoparticles.			
5	**Start: 01/06/11**	**End: 31/07/13**	
Knowledge Transfer: Disseminated through peer reviewed publications and presentations. Methodology and updates will also be published on the UK NMS website			
6	**Start: 01/06/11**	**End: 31/07/13**	
Project Management: Project managed on time and to budget			

Project No.	CB/2012/NB11 + NB11b	Price to NMO	£537K +£48k
Project Title	Nano ChOp-Chemical and optical characterisation of nanomaterials in biological systems	Stage Start Date	01 June 2012
		Est Final Stage End Date	30 June 2015

Summary

This project matches LGC's contribution to EMRP JRP New003 (Nano ChOp) which will develop and validate methods for the physical, chemical and optical characterisation of nanomaterials in biological matrices. As the use of nanotechnologies continues to grow it is becoming increasingly important to be able to accurately characterise their potential effects when they come into contact with biological systems. Current techniques largely focus on determining physical properties in monodispersed powdered or simple matrices necessitating the development of new measurement techniques which can be used in a range of increasingly complex biological matrices.

The Need

Nanotechnologies are increasingly being used to overcome scientific, commercial and industrial challenges through the engineering of application specific nanoscale materials. This has led to nanotechnologies being incorporated into over 1300 commercial products in a global market currently worth €9.6 billion and expected to reach €16.6 billion by 2015. As the impact of nanotechnologies on human life becomes more prevalent it is becoming increasingly important to be able to characterise nanomaterials for their potential effects when they contact biological systems, whether through accidental exposure or through nano-medical applications. To achieve this, characterisation techniques must go beyond the current methods for measuring physical properties such as size, charge and shape in idealised matrices to allow characterisation in appropriate biological milieu. This is critical as the physical and chemical properties of nanomaterials frequently change in biological systems, altering their functional properties.

Europe enjoys a strong position in the development and commercialisation of nanotechnologies and is currently the second strongest region globally in terms of nanotechnology companies, patents and commercialised products. This position is supported by both sector and product specific legislation which has so far supported innovation in this rapidly expanding sector. However as nanotechnology use has increased there have been a number of reports which have concluded that amendments to the current regulatory frameworks are crucial to ensuring the safety of nanotechnologies, with particular concern about a lack of suitable measurement techniques. A scoping study conducted for the UK Defra identified a number of regulatory gaps originating from exemptions under legislative frameworks set out in European Directives such as REACH (EC1907/2006) or from a lack of information, or uncertainties over reliable and validated methods for measurement and characterization that can be used in monitoring potential risks associated with nanomaterials. Similarly, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) acknowledged major gaps in the knowledge necessary for risk assessment and hazard evaluation of manufactured nanotechnologies, such as nanomaterial characterisation and the dose-response/fate and persistence of nanomaterials in humans. It concluded that current risk assessment methodologies require some modifications in order to deal with the hazards associated with nanotechnology, and in particular that methodologies are required for characterisation in biological systems.

The Solution

The EMRP funded JRP (New03) to which this CBM project aligns will address these issues by developing a European measurement infrastructure to characterise nanomaterials for their physical, chemical and optical properties in a range of complex biological matrices from serum to cell based systems.

Impact and Benefits

Benefits will accrue via: Nanobiotechnology and nano-medicine organisations being provided with validated protocols with which to perform their analysis; Regulatory bodies and legislators obtaining coherent and comparable data recommendations from which to formulate policy; Manufacturers of nanomaterials being able to operate under a reasonable, rather than overly stringent, regulatory framework. Proportionate measures to regulate the use of such materials will also allay public concern over the use of nanomaterials and regulation of those nanomaterials that are of particular concern (such as nano-drug delivery systems) would lead to the established, sustainable development of innovative nanomaterial industries.

Support for Programme Challenge, Roadmaps, Government Strategies

Supports: CBM Strategic Priority Theme 6: Nanobiotechnology. CBM Theme roadmaps: 'Nanobiotechnology','Cells & Tissues', 'Inorganic' 'Particles'; UK strategy for nanotechnology, 2007, 2010 'Health and Safety of nanoparticles'; European Commission mandate to CEN, CENELEC and ETSI [M/461 EN, 2 February 2010] to provide methodologies for nanomaterials characterisation in the manufactured form.

Synergies with other projects / programmes

EMRP JRP n11:"Nano ChOp-Chemical and optical characterisation of nanomaterials in biological systems", CBM project NB10 "*In vitro* nanotoxicology", IRD project 2010_09 "Nanoparticle characterisation methods for food security", CBM proposal CB/2012/P13 "Measuring the dynamics of nanomaterials in the environment".

Knowledge Transfer and Exploitation

Outputs will be disseminated through representation on the BSI committee for characterisation and measurement techniques in nanotechnologies (NT1), the OECD committee for the safety of manufactured nanomaterials (OECD/WPMN) and to UK industry through established links with the Nanotechnologies Industry Association (NIA), Nano KTN and CIKTN. Dissemination will also be via workshops planned as part of the aligned EMRP project and feed into a range of European standardisation activities via the wider EMRP partner organisations.

Deliverables			
1	**Start: 01/06/12**	**End: 01/09/12**	
Selection of suitable nanoparticles to become reference materials			
2	**Start: 01/09/12**	**End: 01/01/14**	
Optimisation of cell based model(s) as a biological matrix and characterisation of the bio-interaction of the reference materials.			
3	**Start: 01/12/12**	**End: 01/06/14**	
Development of methods for the chemical characterisation of nanomaterials in serum based matrices using ICP-MS and physical characterisation using nanoparticle tracking analysis and zeta-potential.			
4	**Start: 01/10/13**	**End: 01/06/15**	
Development of methods for the simultaneous physical and chemical characterisation of nanomaterials in serum and cells based matrices using FFF/MALS/ICP-MS.			
5	**Start: 01/06/12**	**End: 01/06/15**	
Management of the impact workpackage of JRP New03 overseeing production of a project website, peer review publications and organisation of workshops.			
6	**Start: 01/06/12**	**End: 30/06/15**	
Project Management			

Project Ref:	OA7				
Title:	Improved Certified Reference Materials for Food Analysis				
Start Date:	April 2010	End Date:	June 2014	Price:	£274K

Vision
The increased availability of 'true-to-life' wet materials which are homogenous, stable and can be transported to the user at minimum cost.
Cross-sector impact on the basis of support for Standards and Regulation; International Leadership; Metrology.

Impact & Benefits
UK consumer expenditure on basic food items was £54.6bn (2006). Spending on fish and fish products showed the strongest growth, but all core sectors increased in value over the period. Meat is an integral part of the UK diet, consistently accounting for ~25% household food expenditure.
Reference materials support regulation by improving agreement between producers and regulators, and removing barriers to trade.
Food and diet continue to preoccupy UK citizens. To enable informed consumer choice, accurate food composition data is needed.

Support for Programme Challenge
Strategic priority relating to Underpinning Metrology.

Support for Government Strategies
Supports NMO Draft Strategy through NMS interventions related to Healthcare and Food security.
Supports Government priority area of Food security.

The Need
There are few fresh meat and fresh fish matrix reference materials, despite their importance for nutritional and contaminant interest. Most currently available fish reference materials are freeze-dried and characterised for organic contaminants, but do not represent materials under test in routine laboratories. 'Wet' fish materials (NIST), characterised for organic analytes, proximates and some elements, are sold as frozen samples (-80 °C during transport, storage and sampling), making them expensive to distribute and difficult to work with in most routine laboratories.
1. Evaluation of production and packaging options that ensure good homogeneity and stability for 'wet' food products.
2. Development of a traceable measurement method for hydroxyproline in food products and preparation of appropriate calibration standards.
3. Preparation of one meat reference material in appropriate packaging for hydroxyproline, with additional characterisation through inter-laboratory studies.
4. Preparation and certification of one fish reference material, in appropriate packaging, for selected elements of contaminant interest, with additional characterisation through inter-laboratory studies.

The investigation of packaging options and production of the final materials will be subcontracted.

Exploitation/Spin Offs
New (realistic) reference materials are required that are sufficiently homogeneous and stable to ensure fit-for-purpose uncertainties of their certified values.

Current State of the Art
Traceable measurement methods are not available for the main constituents of food materials, although for some, traceability is not applicable, e.g. fat and dietary fibre (defined by measurement procedure).
However, hydroxyproline is a well defined measurand and traceability is possible. Two meat-based RMs certified for hydroxyproline content are available (ERM-BB501a and SMRD 2000-6). However, SMRD 2000-6 will sell out shortly, leaving ERM-BB501a at the high end of the expected range. A gap will then exist in the AOAC food triangle.
Previous wet fish reference materials (LGC 7101 mackerel paste and LGC 7160 crab paste), sealed in cans, were withdrawn from sale due to failure of the packaging.
Certain metallic contaminants can cause a risk to public health either at low or high levels and consequently are regulated [Regulation (EC) 1881/2006 of Dec 2006]. Traceable methods have been developed under previous NMS Programmes for elements such as Pb, Cd, Sn and Hg.

The Solution
1) To develop a traceable method for hydroxyproline
2) To develop preparation and packaging strategies to allow certification and sale of realistic materials
3) To use these technologies to prepare, package and certify new, realistic food reference materials.

Metrology Capability to be Delivered
Supports the two CBKB Organic Analysis and Inorganic Analysis themes.
Supports the two CBKB Organic and Inorganic sub-themes and the Roadmap – Improved food safety.

Project Description
The outputs of the project will feed directly to improved packaging for reference materials across all sectors.

Synergy with Other Projects
This project will use capabilities developed under previous 'VAM' programmes to characterise the fish-based material for elements of contaminant interest.
Fast LC and IDMS methods are currently being evaluated and this project will benefit from the methods developed in these.

Knowledge Transfer Plan
Knowledge transfer of the development of a traceable method for hydroxyproline will be achieved through publication of the developed methodology.
The availability of two new reference materials will be publicised as the materials are released.

Updates will be posted on the CBM website.

Deliverables		Start	End	Price
1.	**Investigation of packaging options for wet food matrices.** Evidence: Report on the options investigated and the results obtained published on the CBM website	**Apr 10**	**Mar 11**	
2.	**Development of a traceable measurement method for hydroxyproline in food products.** Evidence: Peer reviewed scientific paper and validated method	**Apr 10**	**Dec 13**	
3.	**Production and characterisation of an appropriate calibration standard.** Evidence: Availability of calibration standard		**deleted**	
4.	**Production and certification of a meat reference material for proximates, elements and hydroxyproline.** Evidence: Release of certified reference material for sale	**Apr 11**	**Dec 13**	
5.	**Production and certification of a fish reference material for proximates and elements.** Evidence: Release of certified reference material for sale	**Apr 11**	**Jun 14**	
6.	**Project Management & Dissemination** Evidence: When an article on the production of the materials has been published in a peer reviewed journal.	**Apr 10**	**Jun 14**	

Proposal No.	OA12c	Price to NMO	£270K
Proposal Title	Reference Material Certification & Support	Stage Start Date	April 2012
		Est Final Stage End Date	April 2014

Summary

An extension (2 additional years) to current projects OA12 and OA12b that finish in March 2012.

This project underpins the maintenance of the infrastructure needed to ensure continuity of supply of NMS funded RMs and the ongoing development of improved procedures for reference material characterisation and certification. It supports a proactive involvement of the UK NMI in RM standardisation activities, primarily REMCO and the ERM initiative, and enables the UK NMI to fulfil its obligations as an accredited RM producer in accordance with the requirements of ISO Guide 34.

The Need & Current State of the Art

ISO Guide 34 (General requirements for the competency of RM producers) requires RM producers to provide a post distribution service to the customers and users of their materials. This includes on-going monitoring of the stability of reference materials and the provision of guidance and technical services.

The National Measurement Office is encouraging UK NMIs to increase collaboration with other European metrology institutes in order to improve the scope and value for money of NMS output. LGC has a responsibility under the ERM co-operation to undertake peer review of CRMs produced (15 materials were submitted to LGC for peer-review in the year to September 2010.)

LGC is the UK's national Coding Centre for the international reference materials database (COMAR). As such LGC is responsible for managing the input and continuous update of national CRM data into COMAR according to the procedures laid down by the COMAR Council. LGC's attendance at COMAR meetings is funded under Project IM2, but co-ordination of COMAR related matters within the UK is supported under this project. Historically, LGC performed CRM data input and update of the COMAR database on behalf of UK RM producers. Although in the future it is expected that RM producers will enter and update their own CRM data, LGC will retain responsibility for interfacing with COMAR and co-ordinating the activities of UK RM producers.

The Solution & Metrology Capability to be Delivered

The project extends the scope of current work underpinning the production and continued supply of NMS funded reference materials.

Impact and Benefits

A 2004 survey carried out on behalf of the NMS identified 73 UK organisations with the capability to produce or arrange production of RMs. The value of the RM market in the UK (2005) was estimated to be £7.5m. NMS funded RMs are relevant to all areas of analytical measurement supporting sectors such as law enforcement, protection of the environment and protection of public health. International collaboration delivers improved value for money by securing wide expert input to tasks and sharing the cost of RM production activities between NMIs. Provision of advice and guidance to users of RMs, for example, through publication of application notes, improves awareness of the role of RMs in achieving helping laboratories to perform accurate and reliable measurements.

Support for Programme Challenge, Roadmaps, Government Strategies

The project supports the infrastructure for production and certification of reference materials within the UK NMI.

Knowledge Transfer and Exploitation Plan

The project directly supports knowledge transfer through production of ERM application notes that will be published on the ERM website and dissemination of information on NMS funded RMs via COMAR and JCTLM databases which are publicly available. The knowledge developed under this project will also be disseminated to UK stakeholders via the UK RMWG and the CBM website.

Deliverables

1	**Start: 01/04/2012**	**End: 31/03/2014**	
Support for RM standardisation Proactive involvement of UK NMI staff in ISO REMCO tasks concerned with the development and harmonisation of improved reference material characterisation and certification procedures.			
2	**Start: 01/04/2012**	**End: 31/03/2014**	
Representation of UK NMI interests on ERM co-operation Attendance at ERM management meetings; peer review of CRMs produced by partner institutes; and drafting of ERM application notes.			
3	**Start: 01/04/2012**	**End: 31/03/2014**	
Maintenance of RM producer accreditation within NMI capability at LGC			
4	**Start: 01/04/2012**	**End: 31/03/2014**	

Provision of advice, support and technical services to users of NMS CBM reference materials			
5	**Start: 01/04/2012**	**End: 31/03/2014**	
Co-ordination and updating of UK produced RMs on international COMAR and JCTLM databases			
6	**Start: 01/04/2012**	**End: 31/03/2014**	
Project Management Project managed on time and to budget			

Project No.	CB/2012/OA12d	Price to NMO	£135K
Project Title	Reference Material and Certification and Support	Stage Start Date	April 2014
		Est Final Stage End Date	March 2015
Sector	Standards and Regulation	Activity	Provision of stds and maintenance of capabilities

Summary

An extension (additional year) to current projects OA12, OA12b and OA12c that finish in March 2013.

This project underpins the maintenance of the infrastructure needed to ensure continuity of supply of NMS funded RMs and the ongoing development of improved procedures for reference material characterisation and certification. It supports a proactive involvement of the UK NMI in RM standardisation activities, primarily REMCO and the ERM initiative, and enables the UK NMI to fulfil its obligations as an accredited RM producer in accordance with the requirements of ISO Guide 34.

The Need

ISO Guide 34 (General requirements for the competency of RM producers) requires RM producers to provide a post distribution service to the customers and users of their materials. This includes on-going monitoring of the stability of reference materials and the provision of guidance and technical services.
The National Measurement Office is encouraging UK NMIs to increase collaboration with other European metrology institutes in order to improve the scope and value for money of NMS output. LGC has a responsibility under the ERM co-operation to undertake peer review of CRMs produced by IRMM and BAM.
LGC is the UK's national Coding Centre for the international reference materials database (COMAR). As such LGC is responsible for managing the input and continuous update of national CRM data into COMAR according to the procedures laid down by the COMAR Council. LGC's attendance at COMAR meetings is funded under Project IM2, but co-ordination of COMAR related matters within the UK is supported under this project. Historically, LGC performed CRM data input and update of the COMAR database on behalf of UK RM producers. Although in the future it is expected that RM producers will enter and update their own CRM data, LGC will retain responsibility for interfacing with COMAR and co-ordinating the activities of UK RM producers. LGC is also required to submit data on NMS funded RMs for consideration for inclusion in the JCTLM database.

The Solution

N/A.

Impact and Benefits

A 2004 survey carried out on behalf of the NMS identified 73 UK organisations with the capability to produce or arrange production of RMs. The value of the RM market in the UK (2005) was estimated to be £7.5m. NMS funded RMs are relevant to all areas of analytical measurement supporting sectors such as law enforcement, protection of the environment and protection of public health. International collaboration, for example, through the European Reference Materials (ERM) co-operation, delivers improved value for money by securing wide expert input to tasks and sharing the cost of RM production activities between NMIs. Provision of advice and guidance to users of RMs, for example, through publication of ERM application notes, improves awareness of the role of RMs in achieving helping laboratories to perform accurate and reliable measurements.

Support for Programme Challenge, Roadmaps, Government Strategies

The project supports the infrastructure for production and certification of reference materials within the UK NMI.

Synergies with other projects / programmes

The project underpins technical research and development projects that deliver specific CRMs.

Knowledge Transfer and Exploitation

The project directly supports knowledge transfer through production of ERM application notes that will be published on the ERM website and dissemination of information on NMS funded RMs via COMAR and JCTLM databases which are publicly available. The knowledge developed under this project will also be disseminated to UK stakeholders via the UK RMWG and the CBM website.

Deliverables

1	**Start: 01/04/2014**	**End: 31/03/2015**	
Support for RM standardisation: Proactive involvement of UK NMI staff in ISO REMCO tasks concerned with the development and harmonisation of improved reference material characterisation and certification procedures.			
2	**Start: 01/04/2014**	**End: 31/03/2015**	
Representation of UK NMI interests on ERM co-operation: Attendance at ERM management meetings; peer review of CRMs produced by partner institutes; and drafting of ERM application notes.			
3	**Start: 01/04/2014**	**End: 31/03/2015**	
Maintenance of RM producer accreditation within NMI capability at LGC			
4	**Start: 01/04/2014**	**End: 31/03/2015**	
Provision of advice, support and technical services to users of NMS CBM reference materials			

5	**Start: 01/04/2014**	**End: 31/03/2015**	
Co-ordination and updating of UK produced RMs on COMAR and JCTLM databases			
6	**Start: 01/04/2014**	**End: 31/03/2015**	
Project Management			

Project No.	CB/2013/OA12e	**Price to NMO**	£135k
Project Title	Reference Material Certification and Support	**Stage Start Date**	Apr 15
		Stage End Date	Mar 16
Sector	Standards and Regulation	**Activity**	Provision of stds and maintenance of capabilities

Summary
An extension (additional year) to projects OA12C and OA12D that finish in March 2014 and March 2015 respectively. This project underpins the maintenance of the infrastructure needed to ensure continuity of supply of NMS funded reference materials (RMs) and the ongoing development of improved procedures for reference material characterisation and certification. It supports a proactive involvement of the UK NMI in RM standardisation activities, primarily ISO-REMCO (International Organization for Standardization - Committee for Reference materials) and the ERM (European Reference Material) initiative, and enables the UK NMI to fulfill its obligations as an accredited RM producer in accordance with the requirements of ISO Guide 34.

The Need
ISO Guide 34 (General requirements for the competency of RM producers) requires RM producers to provide a post distribution service to the customers and users of their materials. This includes on-going monitoring of the stability of reference materials and the provision of guidance and technical services.
The NMO is encouraging UK NMIs to increase collaboration with other European metrology institutes in order to improve the scope and value for money of NMS output. LGC has a responsibility under the ERM co-operation to undertake peer review of CRMs produced by IRMM and BAM.
LGC is the UK's national Coding Centre for the international reference materials database (COMAR). As such LGC is responsible for managing the input and continuous update of national CRM data into COMAR according to the procedures laid down by the COMAR Council. LGC's attendance at COMAR meetings is funded under Project IM2(e), but co-ordination of COMAR related matters within the UK is supported under this project. Historically, LGC performed CRM data input and update of the COMAR database on behalf of UK RM producers. Although in the future it is expected that RM producers will enter and update their own CRM data, LGC will retain responsibility for interfacing with COMAR and co-ordinating the activities of UK RM producers. LGC is also required to submit data on NMS funded RMs for consideration for inclusion in the JCTLM (Joint Committee for Traceability in Laboratory Medicine) database.

The Solution
Maintenance of LGC's infrastructure as an RM producer and to include proactive involvement in international RM standardization activities as well as the maintenance international RM databases.

Impact and Benefits
A 2004 survey carried out on behalf of the NMS identified 73 UK organisations with the capability to produce or arrange production of RMs. The value of the RM market in the UK (2012) was estimated to be £12m. NMS funded RMs are relevant to all areas of analytical measurement supporting sectors such as law enforcement, protection of the environment and protection of public health. International collaboration, for example, through the ERM co-operation, delivers improved value for money by securing wide expert input to tasks and sharing the cost of RM production activities between NMIs. Provision of advice and guidance to users of RMs, for example, through publication of ERM application notes, improves awareness of the role of RMs in achieving helping laboratories to perform accurate and reliable measurements.

Support for Programme Challenge, Roadmaps, Government Strategies
The project supports the infrastructure for production and certification of reference materials within the UK NMI.

Synergies with other projects / programmes
The project underpins technical research and development projects that deliver specific CRMs.

Knowledge Transfer and Exploitation
The project directly supports knowledge transfer through production of ERM application notes that will be published on the ERM website and dissemination of information on NMS funded RMs via COMAR and JCTLM databases which are publicly available. The knowledge developed under this project will also be disseminated to UK stakeholders via the UK RMWG and the CBM website.

Deliverables

1	**Start: 01/04/15**	**End: 31/03/16**	
Support for RM standardisation: Proactive involvement of UK NMI staff in ISO REMCO tasks concerned with the development and harmonisation of improved reference material characterisation and certification procedures.			
2	**Start: 01/04/15**	**End: 31/03/16**	
Representation of UK NMI interests on ERM co-operation: Attendance at ERM management meetings; peer review of CRMs produced by partner institutes (BAM, IRMM); and drafting of ERM application notes.			
3	**Start: 01/04/15**	**End: 31/03/16**	
Maintenance of RM producer accreditation within NMI capability at LGC			
4	**Start: 01/04/15**	**End: 31/03/16**	
Provision of advice, support and technical services to users of NMS CBM reference materials			

5	**Start: 01/04/15**	**End: 31/03/16**	
Co-ordination and updating of UK produced RMs on COMAR and JCTLM databases			
6	**Start: 01/04/15**	**End: 31/03/16**	
Project Management: Project delivered in a cost effective manner. Customer reporting requirements fulfilled.			

Project No.	CB/2012/OA13	Price to NMO	£614k
Project Title	Direct analysis for organic purity assessment	Stage Start Date	01 April 2012
		Stage End Date	31 March 2015
Sector	Traceability & uncertainty	Activity	Methodology for new capabilities

Summary

The ability to characterise “high purity” substances for the mass fraction of an agreed substance in a given sample is essential for a NMI to offer traceability to the SI for organic analysis measurements. Traditional “mass balance” approaches are labour intensive and of limited traceability. For most quantitative measurements, the pinnacle of the traceability chain is to use a pure substance as a primary calibrator to which a high accuracy purity value is assigned. This calibrator is then used to assign values to (matrix) reference materials, with the uncertainty of the primary calibrator being a major component of the overall uncertainty of the analysis. Given the increasing need for NMIs to provide traceability for a broader range of activities and sectors, the primary calibrator approach struggles to provide the range of materials required at an acceptable cost and timescale. The objective of this project is to refine the direct methods for assigning amount of material, thus reducing the uncertainty of these approaches, and extending their application to biological materials. This project relates to CBM project OA11b (‘Purity of low purity substances’) which highlighted the applicability of extending LGC’s capability to perform ‘direct’, SI traceable purity determination through quantitative NMR.

The Need

The Organic Analysis Working Group (OAWG) of CCQM has continually stressed the importance of the purity assessment of all calibrants used for high accuracy measurements to ensure traceability of results. The lack of availability of traceable calibration materials has hampered the acceptance of many proposed matrix CMC (Chemical Measurement and Calibration) claims within the EURAMET framework. Whilst lacking formal guidelines, there is a general consensus amongst qNMR practitioners on appropriate acquisition parameters but there remains a large disparity between users in data processing methodologies. This diversity in processing gives rise to significant inter-lab variation (as recently evidenced in K55c CCQM study) and is a key obstacle in the wider adoption of qNMR as a routine technique for traceable assay. A recent survey of key stakeholders, including NMIs, regulators and industry, conducted for the BIPM entitled “Study of Measurement Service and Comparison Needs for an International Measurement Infrastructure for the Biosciences and Biotechnology” concluded that requirements for underpinning work to assure the traceability of quantitative measurements of proteins to the SI, including the high accuracy purity determinations and analysis of proteins, peptides and amino acids would have a significant strategic impact on the sector. Therefore, extension of the scope of our purity capability to include compounds with a relative molar mass exceeding 800 will be required to address future challenges.

The Solution

The overall objective of the work is to develop capability for the assessment of chemical purity with low uncertainty to ensure traceability to the SI for chemistry and biochemistry. This will include an assessment of appropriate calibration methods, generation of a best practice guide for data processing and a systematic assessment of the uncertainty contributions. Current mass balance approaches will then be extended to include the analysis of molecules with increased molecular mass (>500g/mol) and the provision of sequence and purity information of biopolymers.

Impact and Benefits

A considered estimate of the value of world trade that relies on chemical measurement is > $350bn p.a. The world market for reference materials is >$300mn p.a.. This project would greatly increase our capability to characterise high purity reference materials in the area of organic and bioanalysis to meet the demand arising from increasing regulation and the realisation of the benefits of traceability. The impact of this project will be in the speed by which we can provide primary calibrators in new and emerging areas and in the increasing diverse number of pure chemical substances requested. Through active participation within a forthcoming Track D (pre-pilot) CCQM study and collaboration with the BIPM in analysis of K55c data, LGC will consolidate it’s leading position in application of qNMR for traceable purity assay.

Support for Programme Challenge, Roadmaps, Government Strategies

Strategic priority related to underpinning metrology.

Synergies with other projects / programmes

The proposed project would build on the work carried out under the OA11b project on assessing the utility of qNMR in purity determination. Protein quantification projects including BA26 would benefit from reduced raw material costs and improved accuracy and uncertainties of reference materials.

Knowledge Transfer and Exploitation

Key peer-reviewed publications and conference presentations will be produced. Dissemination through NMR user groups, clinical reference materials working group, OAWG of CCQM and other relevant bodies.

Deliverables

1	**Start: 01/04/12**	**End: 31/12/14**	

qNMR assessment for traceable quantification of peptide purity

When an SOP for the externally standardised assay method has been prepared.

When a report on the applicability of qNMR for peptide purity has been completed. When the feasibility of alternate referencing strategies has been assessed and suitable standards evaluated for use in peptide purity.			
2	**Start: 01/10/12**	**End: 30/11/13**	
Development of purification methods for extraction and purification of organic materials When suitable physical and chromatographic separations enabling the rapid development of potential reference materials from a range of crude starting materials have been investigated. When the developed capability to deliver selected methodologies for reference material generation has been applied to at least 3 relevant materials.			
3	**Start: 01/06/12**	**End: 31/12/14**	
Assessment of methodologies for applicability to peptide and amino acids When purification methodologies developed in D2 have been assessed for their applicability to peptide and amino acids by: • Investigating improved analytical methods related to improve purity determinations in small peptides, compare examples against existing methodology and produce a report on the successes and recommendations. • When a report, including measurement uncertainty estimations, on qNMR methodologies for the non destructive peptide and amino acids has been produced.			
4	**Start: 01/04/12**	**End: 31/07/12**	
DSC optimisation When a report on the revalidation of the DSC and its SOP through a comparative study of old and new materials including the revision of uncertainty calculations has been completed. When a report on the findings of options for screening materials for the suitability of DSC for purity analysis has been generated.			
5	**Start: 01/07/13**	**End: 31/12/13**	
qNMR Best Practice guide When a Best Practice guide has been written and published that focuses on the processing of qNMR data and its impact on the traceability and uncertainty or the technique. When the guide has been publicised via NMR conference(s), NMR resource websites and, if possible, endorsement from instrument vendors.			
6	**Start: 01/07/13**	**End: 31/12/13**	
OAWG Track D CCQM study Participation in NMIJ (NMI Japan) coordinated CCQM Track D study on qNMR to assess NMI capabilities and assessment of potential standards.			
7	**Start: 01/10/12**	**End: 31/03/15**	
Knowledge Transfer When two peer-reviewed publications have been prepared (qNMR & Purification) and two conference presentations at Euromar, BERM or similar have been made.			
6	**Start: 01/04/12**	**End: 31/03/15**	
Project Management Project managed on time and to budget			

Project No.	CB/2012/OA14 + OA14b	Price to NMO	£430k + £190k
Project Title	Universal standards for ion mobility	Stage Start Date	01 April 12
		Est Final Stage End Date	31 March 15

Summary

Ion mobility spectrometry (IMS) is a stand-alone detection technique used extensively in the law enforcement and security sectors for the detection of volatile and semi-volatile species such as drugs-of-abuse, explosives and chemical weapons. Their successful deployment for high throughput screening in some of the most challenging environments has resulted in many new application areas being investigated. Users in these newer fields of application have highlighted several areas of concern with regards to the use of current IMS technology. Chief among these concerns are the influence "external environmental conditions" and "chemical background" play on the detection capability of the instruments. Improvements in IMS instrumentation by different manufacturers have also resulted in multiple approaches to the separation of molecular species, with collision cross sections and reduced mobility measurements made on different IMS instruments giving different results.

This project addresses these issues by working with manufacturers to compare a set of candidate molecules compatible as calibrants within a desired concentration range suitable to each application for the different types of ion mobility instrumentation. Provision of a set of standards will enable the user to correct, or at least assess, when external factors may be having an influence on the results generated and expedite the uptake of this versatile technology in new areas of application.

The Need

IMS is a gas phase electrophoretic separation technique that has seen a recent dramatic increase in its use. The ability to deploy the instruments in often the harshest of environments, including their hand-held use by the military in detecting chemical warfare agents and on-site security services in explosives monitoring, has resulted in ion mobility spectrometers being one of the most ubiquitous analytical instruments. The move from military to civilian monitoring did not happen as smoothly as was first predicted and confusion still remains over their use for screening and/or confirming the presence of particular chemicals. As such the real potential of IMS is thought to far exceed its current uses. In many cases adverse results are caused by the calibrants and calibration procedures used to check instrumentation with calibration and validation of these devices varying greatly depending on their use. For example, in many police forces the use of a single calibration standard containing the compound of interest (i.e. cocaine for DoA, TNT for explosives) generating a single point calibration for both quantification and identification is common practice. This approach requires the use of standards in the field which could potentially result in contamination of protected scenes. Also the influence of environmental conditions, such as background air vapour and its constituents, are known to cause differences in compound drift times and intensity. Compensation for environmental differences on a portable technology are therefore essential and the need for surrogate calibrants (that mimic the compounds of interest) and calibration procedures to check instrument performance is clear as they would increase confidence in results and reduce potential contamination issues.

In addition different IMS instrumentation separates ions by virtue of differences in their movement through a gas using one of two ways either Linear IMS: ions are injected into a drift cell which contains a gas in the case of linear IMS, or differential IMS: Differential IMS (or high-field asymmetric waveform ion mobility spectrometry; FAIMS) uses an asymmetric high-field/low-field square-wave waveform to separate ions passing between two plates in a gas flow. While several manufacturers produce IMS devices there are three technologies which appear to be in widespread use in the UK; two linear IMS instruments from GE Sensing and Smith's Detection and one FAIMS instrument from Owlstone/SelexGalileo. These instruments detect trace analytes at levels lower than the µg/l ranges and their use is widespread. Ideally any standards or solutions developed would be applicable to both types of IMS.

The Solution

The development of standards with known mobility characteristics would be the suggested starting point. A second set of standards, where the influences of external environmental conditions are known will also be developed. These will serve as important indicators for when changes in the background chemical matrix may be impairing or influencing the analytical result. Most importantly the standards would enable the routine recalibration of the instruments

Impact and Benefits

The major impact of the project would be in the improved confidence and reliability of the results obtained from this portable technology. Many initiatives are in place to extend the application base of IMS. The support from industry, both UK-based pharmaceutical and instrumental companies, for IMS is due to the potential they perceive in this technology. Process analytical technology, at line testing, and routine quality/safety measurements have all been suggested as potential application areas. IMS was highlighted in the VAM patent mapping study as an area of particular strength within the UK. This project would undoubtedly help support these innovations. The reduction in "false positives" would lead to a wider acceptance of the technology and its use in our everyday lives.

Support for Programme Challenge, Roadmaps, Government Strategies

Aligns with the aims of the CBM program to improve the accuracy and reliability of chemical and biochemical measurements in support of improving UK competiveness and quality of life.

Synergies with other projects / programmes

Follow on project from old VAM (VAM O1) IMS project looking at the development of IMS standards.

Knowledge Transfer and Exploitation

As the project will be delivered in collaboration with manufactures, academia and end users there will be regular workshop-style meetings to update on the findings of our research. A publication is planned where the finding will be reviewed and disseminated to the wider analytical community.			
Deliverables			
1	**Start: 01/04/12**	**End: 30/09/13**	
Installation and Set up IMS capability at LGC: • When IMS instruments have been installed at LGC and familiarisation with current instruments completed • When meetings with project partners has been held.			
2	**Start: 01/09/12**	**End: 30/04/13**	
Assessment of current calibration strategies: • When the operation of at least two IMS systems have been assessed for specificity based on vendors procedures under different environmental conditions.			
3	**Start: 01/12/12**	**End: 31/01/15**	
Development of IMS standards			
4	**Start: 01/04/13**	**End:31/03/15**	
Knowledge Transfer: • Produce discussion paper on outcomes. Dissemination activities with relevant manufacturers and end users. Final Report.			
5	**Start: 01/04/12**	**End: 31/03/15**	
Project and sub contract management: • Project managed on time and to budget.			

Project No.	CB/2013/OA15	Price to NMO	£600K
Project Title	RMPs & CRMs for Therapeutic Drug Monitoring	Stage Start Date	Jun 13
		Stage End Date	Mar 16
Sector	Drugs and therapies; Traceability and Uncertainty	Activity	Provision of stds and maintenance of capabilities

Summary

An area of clinical chemistry reported as needing urgent standardisation is that of Therapeutic Drug Monitoring (TDM) of immunosuppressant drugs (ISD) for the prevention of organ transplant rejection. LGC has made significant progress over recent years to develop Reference Measurement Procedures (RMPs) and Certified Reference Materials (CRMs) to address this need. Further RMPs & CRMs are required to enable *In vitro* Diagnostic (IVD) kit manufacturers and hospital laboratories to fully assess method accuracy and achieve metrological traceability. Tacrolimus is set to retain its position as the most widely prescribed ISD, currently holding an 80% market share, therefore the primary focus of the project is to complete the work required for tacrolimus standardisation. A pure tacrolimus CRM plus a set of pooled patient blood CRMs will be produced, before progressing to the development of RMPs for another ISD, either everolimus or ciclosporin. In addition, this project will also support the completion of work started under the previous CBM project OA2 to produce a matrix CRM for the ISD sirolimus.

The Need

External Quality Assessment (EQA) schemes for ISDs have demonstrated that there is an unacceptably wide spread of data between different laboratories, and in some cases greater than the ISD's currently accepted therapeutic reference range. This is due to a number of factors including the use of multiple sources of calibrants, multiple assay types and the adjustment of calibrant reference values to take account of previous EQA performance. There are many consequences to this lack of harmonisation, including the inability to pool data from multiple sites to enable more accurate drug dosing strategies to be devised. The adjustment of calibrators to fit previous EQA rounds has meant that the consensus mean value may no longer be an accurate target value for EQA participants. Positive biases are often observed for immunoassay based methodology when compared to LC-MS/MS based methods due to the detection of ISD metabolites as well as the target analyte. However, LC-MS/MS methods are not without their potential pitfalls either, and for example, may under or over estimate drug concentrations in patient samples as they frequently do not employ isotopically labelled internal standards to correct for potential matrix effects. Therefore, there is a need for RMP for all of the currently prescribed ISD in order to provide reference values to EQA schemes and CRMs.

IVD kit manufacturers have requested a high purity (with low measurement uncertainty) tacrolimus 'powder' material as it would enable laboratories to achieve metrological traceability directly. In addition, pooled patient CRMs are required for laboratories to assess the selectivity of their methods to ensure other tacrolimus metabolites are not detected (when not intended) and that any cell lysis step is efficient, reproducible and releases any tacrolimus bound within erythrocytes.

LGC has also received requests for higher order CRMs for other prescribed ISDs, namely, everolimus and ciclosporin. Although ciclosporin is currently being phased out, patients who are currently prescribed it will remain so for the rest of their lifetimes. LGC has developed a candidate RMP for ciclosporin which requires further validation before it can be used to assign reference values to CRMs and EQA schemes. Everolimus is now being used in the USA for transplant rejection purposes. However, in the UK, NICE has only approved its use as an anti-cancer drug. If the drug is granted a license for use as an ISD in the UK, the opportunity to react quickly and standardise the measurement of this compound should be seized.

The Solution

- The production and characterisation of a pure tacrolimus CRM
- The production and characterisation of pooled patient tacrolimus in whole blood CRMs
- The development of RMPs for other TDM measurands (e.g. ciclosporin or everolimus)

The methods and materials will meet the requirements of the IVD Medical Device Directive, IVDD (EC98/79/EC) and comply with the requirements for listing on the database of higher-order reference materials of the Joint Committee for Traceability in Laboratory Medicine (JCTLM). A series of presentations and publications will be given on standardisation concepts (metrological traceability, measurement uncertainty etc.) incorporating knowledge gained from the development of clinical RMPs & CRMs.

Impact and Benefits

Standardisation of TDM of ISD has many significant economic and quality of life benefits. It will enable medical researchers to combine data from independent clinical trials with greater confidence and subsequently provide greater accuracy in the determination of optimal ISD dosing protocols. In addition, clinicians will have greater confidence in lowering doses of ISD, which will reduce the cost of medication and improve patient welfare through reduction of the many adverse side effects associated with ISDs (e.g. the onset of insulin dependent diabetes). TDM, over the life time of a single organ transplant, costs the NHS over £100,000 (NHS 2010 Kidney Care report). With nearly 4000 organ transplants taking place annually in the UK, increased confidence and greater accuracy could offer significant savings associated with medication costs. Lower doses of ISDs than currently administered have been reported to significantly prolong short term allograft survival, reducing the cost association with re-transplantation. In the financial year to March 2012, 508 people in the UK on the active transplant waiting list died due to a lack of viable organs. Therefore any measures which can be taken to improve allograft survival rates (and need for re-transplantation) will go some way to

reducing waiting list numbers.			
Support for Programme Challenge, Roadmaps, Government Strategies Aligns with CBM Strategy Theme 'Chemical Measurement and Calibration', sub-theme 'Drug development, Diagnostics/Therapeutics'' as well as the UK Technology Strategy Board priority for Healthcare.			
Synergies with other projects / programmes The project builds on the knowledge gained from the previous CBM project OA2 and benefits from advances made in a related NMS project (IRD project 'Ultratrace analysis') to automate sample preparation for IDMS.			
Knowledge Transfer and Exploitation Through presentations and publications aimed at the clinical community, either specifically on the technical aspects of developing RMP and/or more generally, as has been requested externally, to provide guidance and education on general aspects of standardisation, including topics such as metrological traceability and measurement uncertainty.			
Deliverables			
1	**Start: 01/06/13**	**End: 31/03/14**	
Production of a Pure Tacrolimus CRM: Production and characterisation of ≥ 250 units of a pure tacrolimus CRM, approved by ERM and released for sale.			
2	**Start: 01/06/13**	**End: 31/03/16**	
Production of a Tacrolimus matrix CRM using Pooled Patient Blood: Investigate most beneficial and cost effective approach to provision of tacrolimus in pooled patient blood CRMs. Production and characterisation of a tacrolimus matrix CRM, approved by ERM and released for sale.			
3	**Start: 01/06/13**	**End: 01/06/15**	
Development of new RMPs for TDM applications: Includes literature review and sourcing of materials for chosen ISD (either ciclosporin or everolimus), purity analysis of calibrant (small quantity for in-house use only), development/validation of IDMS methodology. Final output will be provision of reference value(s) for an EQA scheme.			
4	**Start: 01/06/13**	**End: 31/03/16**	
Knowledge transfer: Publications and presentations aimed at clinical community. Dialogue with clinical community through the UK Clinical RM user group and British Mass Spectrometry Society clinical & forensic SIG meetings to identify and understand end users measurement challenges and RMP/CRM needs.			
5	**Start: 01/06/13**	**End: 31/12/13**	
Complete production of a sirolimus matrix CRM: Completion of work started under previous CBM project OA2. Final certification, ERM approval and release for sale of sirolimus in blood matrix CRM.			
6	**Start: 01/06/13**	**End: 31/03/16**	
Project Management: Project delivered in a cost effective manner. Customer reporting requirements fulfilled.			