

Submission by The National Physical Laboratory to The review of UK Health research chaired by Sir David Cooksey

Summary

This submission is made on behalf of the UK's National Physical Laboratory. As the UK's national standards laboratory, NPL underpins the National Measurement System, ensuring consistency and traceability of measurements throughout the UK, through its world-leading capability in measurement science, its practical application and knowledge transfer.

Our experience is that for R&D to deliver the greatest impact there is a need to ensure that both measurement and documentary standards are considered at an early stage and developed in a coherent way in parallel with new technologies, medicines, techniques etc. Ensuring the proposed health research programme takes account of these issues and is plugged into the UK and international infrastructure for measurement and standards would facilitate:

- *pooling of data and results from multi-centre and multi-national research*
- *timely identification and removal of technical and regulatory barriers to implementation*
- *consistent and optimal introduction of new technology, medicines, techniques or practices*
- *transfer of best practice between centres as they seek to introduce new technology, medicines, techniques or practices*
- *minimising the risk of a failure of patient care and subsequent litigation.*

Our wide experience of collaboration with the public and private sector in maximising the impact of our work also suggests that in all but the most basic curiosity-driven research it is important that Knowledge Transfer (specifically how to shape and exploit the output of R&D to maximise its positive and real impact) is integrated into project planning from the outset and that specific KT expertise is used to advise on the best mechanisms to ensure maximum take-up.

In the light of the above, we therefore recommend that:

- *Consideration of measurement and standards issues are built into programme and project planning and assessment from an early stage.*
- *A practical "exploitation" plan is required for all but the most basic and curiosity driven research projects.*
- *High level links are established between those responsible for shaping of this programme and the body within the DTI responsible for shaping of the National Measurement System Programmes, with at minimum senior representation of the health programme on the DTI's NMS steering group.*
- *Mechanisms are put in place to facilitate collaboration with the UK's measurement capability (NPL, LGC, NEL and others), including, if appropriate, co-funding that will leverage the significant DTI investment in this area.*

Introduction

This submission is made on behalf of the National Physical Laboratory. As the UK's national standards laboratory, NPL underpins the National Measurement System (NMS), ensuring consistency and traceability of measurements throughout the UK.

Our role is to deliver world-class measurement science, to provide measurement infrastructure for the UK and to maximise the impact that this science and infrastructure has on the UK economy and quality of life – including the healthcare sector from basic R&D through to clinical practice and manufacture.

This submission draws on our expertise in measurement science and our experience in Knowledge Transfer (KT) to provide input on the importance of measurement science and mechanisms for maximising impact. In particular we feel our experience is relevant particularly to questions 5 & 6 in Annex 3 of the invitation to submit comments:

- *"What lessons can usefully be learned to improve the uptake of advances in science and medicine?"*
- *How might better links be forged between 'basic', translational and applied researchers, working across the whole field of health research, from the laboratory bench to the front line of the NHS?*
- *How might better links be forged across disciplines, e.g. with engineers, physicists, and social scientists?*

The importance of measurement and documentary standards

Our experience is that for R&D to deliver the greatest impact there is a need to ensure that both measurement and documentary standards are considered at an early stage and developed in a coherent way in parallel with new technologies, medicines, techniques etc.

An increasing level of importance is being attached to measurements and standards in health related R&D and this is being reflected not only in practice but also in regulation. Two recent examples of this in EU legislation are:

- The regulation of new pharmaceuticals now includes a requirement as part of the EU Clinical Trials Directive 2001/20/EC that any instruments used in-process or pre-release manufacture of products for clinical trials and 'specials' must be calibrated using standards from recognised bodies (for physical measurements in the UK these must be traceable to NPL).
- For development of medical diagnostics the In-Vitro Diagnostics Directive (98/79/EEC) requires that any diagnostic measurement device must be traceable to an appropriate reference procedure. This is an on-going issue in Diagnostic R&D, where regulators are tightening up on traceability and reference standards (and defining clinically relevant standards)

Overall the situation with regard to measurement standards needed as part of the R&D programme is complex, but the clear trend is towards strengthening traceability and reference standards, towards the stricter standards set by the FDA.

Ensuring the proposed health research programme takes account of measurement and documentary standards and is plugged into the UK and international infrastructure for measurement and standards at all stages of the journey from basic research to implementation is not only a regulatory issue but would also facilitate:

- *pooling of data and results from multi-centre and multi-national research*
- *timely identification and removal of technical and regulatory barriers to implementation*
- *consistent and optimal introduction of new technology, medicines, techniques or practices*
- *transfer of best practice between centres as they seek to introduce new technology, medicines, techniques or practices*
- *minimising the risk of a failure of patient care and subsequent litigation.*

At the end of this document two examples illustrate our experience in the case of the mature, but still rapidly developing field of Radiotherapy and the field of Biotechnology, where measurement infrastructure is still in its infancy.

The importance of planned and best practice KT

Our wide experience of collaboration with the public and private sector in maximising the impact of our work also suggests that in all but the most basic curiosity-driven research it is important that Knowledge Transfer (specifically how to shape and exploit the output of R&D to maximise its positive and real impact) is integrated into project planning from the outset and that specific KT expertise is used to advise on the best mechanisms to ensure maximum take-up.

KT initiatives that are deployed without reference to, and without being integrated with, the core science delivery, have in our experience a lower impact. At its most basic level, technology is taken up when scientists work closely with exploiters of their knowledge. The scientists in turn learn through that close contact. Individual technical staff need to retain responsibility for transferring knowledge from their project. If researchers are removed from being directly involved in KT, awareness of the needs of the end users is reduced, and the quality and relevance of programmes suffer because formulation and delivery is less well informed.

At **project level**, the delivery route for the output of the project needs to be built in during formulation of the associated R&D or infrastructure activities. At NPL we characterize our approach to KT as *Foresight – Product - Take-up*.

- Using *Foresight* to identify future needs and/or road maps to future science and technology.
- Ensuring the output of each project is a usable "*Product*", i.e. is in a form that facilitates its take-up by users, whether they be the next step in the R&D chain or ultimate end-users/beneficiaries.
- Putting in place KT activities to maximize that *Take-up*.

NPL has now built this principle into the formulation process and it is working hard to bring about a culture change that embeds this in the thinking of NPL's scientists.

Our experience is that KT at the **project level** is the fundamental building block of KT; it is where individual scientists discuss individual technical issues with collaborators and potential exploiters of their expertise. Ideally as much emphasis should be placed in the project proposal on exploitation of the research as is placed on description of the technical work. Depending on the exploitation route, the project may need to involve stakeholders directly in the delivery process.

At **programme level** (where similar projects are brigaded together for a common aim or audience), KT can be carried out that is not only related to current projects but also promotes best practice and outputs from previous programmes. It also allows synergies with other intermediaries to be exploited. In our case these are RDAs, trade associations, Knowledge Transfer Networks etc. In the case of health R&D the best candidates would need to be identified in each case.

Also of value, in our experience, is **managing impact** through a set of Key Performance Indicators which can be regularly reviewed together with a formal impact assessment at regular intervals looking at both quantitative and qualitative measures for benefits.

Recommendations

In the light of the above, we therefore recommend that:

- **Consideration of measurement and standards issues are built into programme and project planning and assessment from an early stage.**

This might be done by a formal requirement in grant applications to specify how traceability and best measurement practice will be ensured. In particular in collaborative and/or multi-national projects (e.g. clinical trials) there should be an assessment to ensure that steps have been taken to ensure measurements in different centres are carried out on a consistent basis and, where appropriate, are demonstrably traceable to a "National Standard". As indicated above the latter is a regulatory requirement in an increasing range of health related R&D.

- **A practical exploitation or KT plan is required for all but the most basic and curiosity-driven research projects.**

Once again this might be done by a formal requirement in grant applications to provide an "exploitation plan" funded as part of the project (this is now a requirement of projects NPL undertake as part of a DTI funded NMS programme). However, it would need to be backed up by professional KT assessment and support. Our experience is that practising scientists are often not familiar with best practice in KT and, without support, will consider that publication in a learned journal and/or presentation to academic peers is sufficient, when in fact a host of other KT tools are available which may speed application, development and take-up as appropriate. Consideration might also be given to a specific KT programme funded from the Health Research Fund to research the most effective means of KT for outputs from Health Research, provide advice to scientists programme and project managers, carry out generic KT and investigate the actual uptake of outputs.

- **High level links should be established between those responsible for shaping this programme and the body within the DTI responsible for shaping of the National Measurement System, with at minimum senior representation of the health programme on the DTI's NMS steering group.**

The DTI have recently carried out a review of the NMS. The recommendations of this review have been accepted by Lord Sainsbury and will be implemented in 2007. One key recommendation was the organisation of the NMS into two main suites of programmes: The first of these are termed "Knowledge Base" programmes and are predominantly geared towards the essential economic and quality of life requirements for definitive measurement standards and techniques. The second are termed "Metrology R&D" programmes, predominantly aimed at developing new measurement capabilities in areas of strategic national priority, and particularly in areas of prioritised new and emerging technologies. The latter will include a programme which includes work on "Metrology for healthcare and security". Whilst the outputs from both programme groups will significantly impact Health R&D in the UK there is a clear alignment between the purpose of the single fund for Health research and the work on "Metrology for healthcare and security" and it will be important for there to be close links between the two.

Another key recommendation of the NMS review concerns the advisory structures to oversee and direct the programmes. The review recommends that a *"new Measurement Advisory Group be set up with named members from business, wider Government, Research Councils, representative organisations such as the CBI and regional representation from the RDAs, together with an explicit link with the DTI's Technology Strategy Board through a shared member."* This body would have a role in defining the strategic direction of the NMS. The review also

recommends that “*independent expert DTI Advisory Working Groups, attached to individual programmes, continue at the heart of the formulation and review of the new portfolio of NMS programmes.*”

It seems clear to us that there should be appropriate and influential representation of the single fund for health research both on the main “Measurement Advisory Group” and on appropriate Advisory Working Groups (and at minimum on the group overseeing work on Metrology for healthcare and security).

We also recommend that consideration be given to how the NMS (either its sponsoring department or the National Measurement Institutes themselves) might best be represented on the advisory structures for the single fund for health research.

- **Mechanisms are put in place to facilitate collaboration with the UK’s measurement capability (NPL, LGC, NEL and others), including, if appropriate, co-funding that will leverage the significant DTI investment in this area.**

The UK’s National Measurement Institutes (and in particular NPL - the dominant and Government owned NMI) represent a significant historic and continuing investment by the DTI in world-class (and in many cases world-leading) measurement science capability. Consideration should be given as to how to extract the maximum benefit from this for health R&D in the UK. At present at NPL there are strong links with academia, hospitals and the healthcare industry and we anticipate that this will continue. The links between the programmes proposed above will have a positive impact on future collaboration and we would hope that a requirement to explicitly consider measurement issues in R&D projects would also encourage increased collaboration. However, to maximise the leverage from the DTI investment in the NMS it would be valuable to consider mechanisms for co-funding measurement work such as allowing NMI’s to bid directly for funding and working with the NMS to directly co-fund work in the NMS.

At present NPL may not bid (except as a subcontractor) for RC funding. This is a surprise to many of our academic collaborators, who often would like to use us as partners rather than sub-contractors. Removing this restriction from the single fund for health research would facilitate collaboration and be a mechanism of co-funding NMS work in a related field, bringing greater benefit to both health R&D and the UK’s wider measurement science capability.

Consideration should also be given with the DTI to mechanisms for more directly co-funding work in NMS programmes. The Metrology R&D programmes will be explicitly multi-disciplinary and seek co-funding from non-NMS sources. A mechanism whereby the health research fund could co-fund appropriate work would leverage the existing capability. Metrology R&D projects could use NMS money alongside Health research money to achieve the aims of the health Research Programme and/or enable generic work funded under the NMS to be applied to specific health R&D issues.

EXAMPLES

Radiotherapy

Of the 250,000 people in the UK who develop cancer each year between 150,000 and 200,000 will be treated with radiotherapy. The success of radiotherapy treatment depends, inter alia, on the accuracy and reproducibility with which doses can be delivered to the tumour. NPL has worked closely with the medical community, and in particular with medical physicists, to ensure that as radiotherapy has developed, there has been measurement science and infrastructure to support its continued improvement.

In the UK, the calibration of high energy X-ray radiotherapy provision is governed by the IPEM Code of Practice. This is explicitly based on an NPL calibration service which, when introduced, enabled for the first time in the world, calibration of radiotherapy systems in terms of the clinically significant quantity absorbed dose. The equivalent Code of Practice for high-energy electron radiotherapy introduced in 2003 is again based on the world's first service for calibration of therapy level electron beam ionisation chambers in terms of absorbed dose to water. The uncertainty in calibration provided by these services is the lowest in the world for the whole range of beam qualities used in UK radiotherapy provision.

In addition to the overall uncertainty in the absolute value of absorbed dose, radiotherapy clinical practice depends on *consistency* in dose delivery with time and place at a level significantly better than that of the absolute level of absorbed dose. This is ensured in the UK by consistency in the type of secondary standard ionisation chambers used at radiotherapy centres (an NPL design for high energy photon radiotherapy), by their regular calibration at NPL (which includes monitoring their performance history) and by the cycle of audits (both regional inter-centre audits and external reference dosimetry audits by NPL). Once again NPL has led the world in the development of the measurement science, techniques and protocols for this. In addition, along with development of the measurement science NPL has used a variety of means to ensure maximum impact of the developments in measurement science including, alongside peer-reviewed papers and presentations, "User Groups", representation on appropriate national and international bodies, secondments, and training courses.

The close and direct relationship between the UK's National Measurement Institute and radiotherapy R&D and provision in the UK continues, with collaborative work underway characterising and assessing 3D dosimetry systems and development measurement standards for proton radiotherapy.

The value of this relationship was demonstrated earlier this year when the first unit offering a new sophisticated form of radiotherapy was installed in a major private hospital in London later this year. Helical Tomotherapy is a novel system that enables complex dose distributions to be delivered in patients. One potential problem with the new system is that it cannot deliver the reference conditions required by the UK code of practice for ensuring traceable calibration of the radiation dose being delivered. The significance of this was recognised by the NPL Radiation Dosimetry group, who drew it to the attention of the hospital and manufacturer. The radiation dosimetry team also rapidly developed and offered a practical solution, which the manufacturer and their UK agent have decided to use every time one of these machines is commissioned in the UK (and potentially worldwide). The technique also offers a solution to providing traceable dosimetry for the small fields used in other modern radiotherapy systems, such as IMRT (intensity modulated radiotherapy), where currently the traceable calibrations are performed under reference conditions that are rather different from the beams used to deliver treatments

Measurements in biotechnology

In contrast to radiotherapy, the measurement infrastructure underpinning measurements in the biotechnology sector are in a much less developed state.

The NMS Measurements for Biotechnology Programme (MfB) was launched in 2001 as part of the NMS, with the aim of providing a sound international basis for accurate and reliable measurements, which underpin the development and exploitation of biotechnology in the UK, of increasing user confidence and of supporting the formulation of policy. Its objective is to improve the comparability of measurement at interfaces key to the exploitation of biotechnology – between:

- Discoverer and developer
- Small company and large company
- Company and research organisation
- Industry and regulator.

The specific aims of the MfB programme is to:

- Improve the accuracy and reliability of biomeasurements
- Strengthen the measurement science underpinning the regulatory regime for biotechnology
- Ensure that the UK biomeasurement system is co-ordinated and developed in harmony with those of other countries
- Undertake R & D to support the provision of reference methodology and reference standards for technologies and processes that are of generic UK value
- Ensure effective knowledge transfer to industry.

Healthcare applications of biotechnology have always required a high level of regulation to ensure patient safety and measure drug efficacy but the formal application of measurement science to biotechnology is only now beginning to show real impact. This is in part due to the maturing of the biotechnology industry but also an increase in the scale of biological research. The project to sequence the human genome generated so much data that it was beyond the ability of a single organisation to analyse it and the biological research community is now taking on an even bigger challenge in the form of Systems Biology. With this need for large-scale experimental design and data analysis has emerged the need for greater comparability and standardisation.

An example of the benefits of good measurement practice is in allowing industry to make informed decisions on the best way to update current practice. Biopharmaceutical products contain trace amounts of contaminating proteins that cannot easily be removed. Instead these impurities are monitored for safety. Current industry practice for the detection of these impurities is based on old methods with known measurement issues. A consortium of industry and measurement institutes including NPL, LGC and NIBSC are performing a series of technique evaluation exercises to determine the best alternative methods. The independent forum allows industry to contribute information without risking commercial advantage, while the measurement institutes ensure that the evaluations are rigorous and that the outcomes are aligned with both regulatory and industrial need. The project has generated considerable interest from all biopharmaceutical companies and regulatory bodies. The long-term objective is to develop new reference methods and standard operating procedures to facilitate the adoption of more accurate and precise state-of-the-art impurity detection techniques.