

NMS Science & Technology Programme: Biotechnology

Introduction

Final Programme Document

Measurements for Biotechnology Programme & Quality of Life

Introduction

Recent reports have shown that to maintain its lead over European competitors, the UK biotechnology industry and public authorities must have access to a better metrology infrastructure.

Comparable measurement is central to enable balanced and harmonised regulation, which will also help to improve public confidence, particularly in the agro-food applications of biotechnology. In medical and healthcare applications, the ability to make better measurements will reduce the regulatory burden on industry and will facilitate the phasing-out of animal testing, with further benefit in public opinion. Also, with the trend in pharmaceuticals towards outsourcing, issues of mutual acceptance of measurements (between customer and contractor, licensor and licensee) are becoming more important. As better measurements are essential to the exploitation of biotechnology, even a very small impact by the NMS on enabling 'fast development' could potentially increase the value of biotechnology by several £ billion.

We are responding by launching a new NMS Science & Technology Programme on Biotechnology in Autumn 2001. The Programme will build upon established facilities and expertise as well as support new measurement infrastructure; it will fund research needed to fulfil the measurement, standards and regulatory requirements of the biotechnology industry. The work funded will depend upon the outcome of the current extensive consultation being carried out with industry, academia and public organisations. Priority themes likely to be addressed include direct quantification of biomolecules, high-throughput biomeasurements, well-characterised cell lines, well-characterised biologicals and on-line process measurement & control.

Much of the work will be competitively tendered. To maximise exploitation of the outputs of this Programme, industry, research institutions and other appropriate organisations will be invited to submit proposals to deliver the requirements identified by the on-going consultation process. Delivery of projects by well-balanced consortia of industry, research organisations, academia and SMEs will be encouraged. Co-funding will be sought.

**NATIONAL MEASUREMENT SYSTEM
SCIENCE AND TECHNOLOGY PROGRAMME FOR
MEASUREMENTS FOR BIOTECHNOLOGY**

APRIL 2001 to MARCH 2004

FINAL PROGRAMME DOCUMENT

Formulated on behalf of
National Measurement System Directorate
Department of Trade & Industry
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The National Measurement System

The National Measurement System (NMS) is the UK's national infrastructure of laboratories, which delivers world-class measurement science & technology, providing traceable and increasingly accurate standards of measurement for use in trade, industry, academia and government.

The NMS supports innovation in industry generally, by enabling the benefits of new products and processes to be measured, and specifically, by stimulating new product development in the instrument sector. It also raises productivity through improved process and quality control. Measurement also underpins a wide range of public goods, including consumer protection ("legal metrology"), forensic science, environmental controls, safe medical treatment and food safety regulation, as well as the technical standards that ensure barrier-free trade.

The DTI is responsible for government programmes for the NMS and for policy on measurement standards. It is also responsible for:

- the management of the contract with NPL Management Ltd (NPLML) for the effective operation of the National Physical Laboratory (NPL);
- the management of the Teddington estate including the development of new Laboratory premises under a PFI scheme.

EXECUTIVE SUMMARY

This document describes the work programme of the National Measurement System [NMS] Measurements for Biotechnology programme, for the period April 2001 to March 2004. The document includes the background information used to formulate the programme as well as the people who contributed to the process.

In December 2000, the DTI awarded the programme formulation contract to a consortium of LGC, NPL and the BioIndustry Association. The remit was to conduct a thorough analysis of usage and awareness of biotechnology metrology and the infrastructure that currently exists. The results of their analysis are included in this document.

The team consulted widely with industry, academia, the science base, and regulatory bodies, to assess the most common metrology issues that the programme should address. It was also important to consider future issues so that the programme could support developing areas. As a result, the formulators have produced this technical programme containing five themes that will be commissioned by competitive tender.

DTI NMSD

November 2001

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1 INTRODUCTION: METROLOGY AND THE BIOSCIENCES

The National Measurement System [NMS] is the technical and organisational infrastructure that ensures a consistent and internationally recognised basis for measurement in the UK. It enables organisations to make measurements competently and accurately, and to demonstrate their validity. It ensures that the UK's measurement system is co-ordinated and developed in harmony with those of other countries. The NMS has concentrated mainly upon physical measurement, establishing traceability to the fundamental SI units. Chemical measurement has been supported and strengthened through the NMS Valid Analytical Measurement [VAM] programme, which in recent years has included projects on nucleic acid measurement. Late in the year 2000, DTI took the policy decision to address bioscience measurement issues in the NMS more comprehensively, through a programme in biotechnology.

The importance of biotechnology for wealth creation and the quality of life is widely acknowledged, and measurement plays an indispensable role in research, development and regulation for its safe and sustainable innovation and exploitation. The centre of gravity of biotechnology is still close to the science base, and SMEs have a crucial role in taking developments forward. Ultimately, many of those developments will reach the market through exploitation by large companies, particularly in sectors where regulatory hurdles are significant and deep pockets are needed to demonstrate safety, quality and efficacy. Estimates of the value of biotechnology to industry vary considerably, but few doubt that the rate and extent of its growth are critically dependent upon public acceptance and the framework for regulatory control, the development and enforcement of which relies upon measurement. Mutual acceptance of measurement is important, therefore, at the interfaces between:

- the science base and companies, in the credibility of inventions and discoveries,
- SMEs and large companies, in the efficiency of exploitation
- companies and regulators, in the credibility of evidence of safety, quality and efficacy
- the science base and regulators, since independent science is the basis of regulation

Moreover, since markets, inter-company dealings and regulations are international the need for international harmonisation of measurement is clear.

The international metrology community is led by National Measurement Institutes, which are expert mainly in the physical sciences. They are the custodians of a system that seeks to ensure comparable measurements through traceability to the fundamental SI units, via a hierarchical system of successive calibrations of instruments and implementation of best practice.

Measurement in the biosciences presents an even greater challenge for the identification and application of appropriate metrology. There is a steep gradient of difficulty, from measurements at the level of the gene, through the protein to the cell.

The scope and complexity of biomeasurement summarised overleaf is only part of the story. There are additional challenges of measurement in dynamic systems, where metabolic pathways are interdependent, where subtle processes of molecular recognition and interaction are occurring and where protein denaturation and post-translational modification are possible.

TARGET OF MEASUREMENT	WHAT IS MEASURED
NUCLEIC ACID	• Sequence of bases • Length of base sequence • Amount [quantification]
PROTEIN	• Identity, through aminoacid / peptide fragment sequence • Amount [quantification] • Size – peptide fragment size, mass • Function – receptor, signal transduction, binding • Activity – enzyme catalysis, antibody affinity • Structure – primary through quaternary
CELL / TISSUE	• Identity – cell typing, profiling, growth characteristics • Quantity – cell counting • Size – cell sorting • Viability – growth / response • Cellular functionality – gene expression, metabolism • Interactions – adhesion, recognition, toxicity

Positioning the New Programme: A Mission and Strategy

Through the new programme, DTI aims to extend the coverage of the NMS and its infrastructure to the biosciences. That extension implies a programme mission of **providing a sound internationally recognised basis for accurate and reliable measurements, which underpin the development and exploitation of biotechnology by UK industry, increase user confidence and support the formulation of policy and regulation**. In order to deliver that mission, it was concluded that the programme should:

- Concentrate at the frontiers of biotechnology to facilitate commercial exploitation of biotechnology emerging from the science base;
- Undertake R&D to support the provision of reference methodology and measurement standards for technologies and processes that are of generic benefit to UK industry;
- Enable the UK to play a leading role internationally in the development of a framework in metrology for biosciences through active participation in international fora;
- Provide leadership in improving the climate for innovation by strengthening the relation between measurement science and regulation, developing standards and reference materials;
- Attract strong industrial collaboration and partnership;

- Ensure effective knowledge transfer of results from the NMS to industry, particularly SMEs

The NMS programme will not operate in isolation; several sectoral organisations and initiatives (both from government and industry) will contribute towards fulfilling its mission, and the NMS needs to find means of benefiting from their activities. To maximise collaboration with other areas, the NMS will establish a biometrology network, co-ordinated by an independent hub, serving all sectors and interests.

2 MEASUREMENT AND THE EXPLOITATION OF BIOTECHNOLOGY

Biotechnology is notable for its cross-sectoral impact in industry, and for the importance of SMEs in the innovation chain. The role and significance of measurements are strongly sector-dependent and reflect the size and maturity of the companies.

Pharmaceuticals

Large multinational companies, with the resources to conduct huge R&D programmes, to secure regulatory approval of products and to market them worldwide, dominate the sector. The size of the healthcare market, and the promise of biotechnology, mean that investment in new ventures is greater for pharmaceuticals than for other sectors. Most biotechnology SMEs hope to develop by liaison - through selling partially developed products, technology or indeed their companies - to the pharmaceutical majors

- For the discovery phase, measurement is central to the identification and screening of candidate products, with a strong current impetus towards high-throughput and miniaturised measurement systems. Most candidates fail, and it is becoming increasingly important for screening systems to fail poor candidates quickly, through consistent relative measurements. Pharmacogenomics adds a new dimension to the development, testing and prescription of drugs, through the identification of sub-populations with special sensitivities.
- For the approval phase, measurement is central to gaining regulatory approval for a new product, through tests that demonstrate its quality, safety and efficacy. The FDA is dominant in the development and enforcement of regulation, and measurement validation has been systematised internationally to harmonise the process. Here the current issues are the extent to which bioproducts can be characterised effectively by physico-chemical methods and the pressure to minimise animal testing.
- For aspirant pharmaceutical SMEs there are risks that their early R&D fails to provide appropriate data for validation and regulatory requirements, and thus discourages the liaison with major companies upon which their future depends

Diagnostics

Biotechnology is a fruitful source of innovation for the diagnostics sector, and quite modest investment can yield promising new tests for human disease, for physiological markers [pregnancy, cholesterol etc], for animal disease, for food contamination or for environmental contamination. Over 95% of bioanalytical products are aimed at the human health market. Opportunities are increasing in food testing, as analysis becomes better appreciated as a management tool. Foreign companies, which offer a 'one-stop shop' for a wide range of diagnostic tests, linked to high-throughput instruments, dominate the clinical testing market. There are many 'single product' SMEs struggling to penetrate the diagnostics market. Sensors have long been seen as the trend for diagnostics but have made a modest impact.

- Measurement is the central concern for the sector but it is also the focus of competitive intellectual property for the suppliers of equipment and systems for diagnostics (including sensors). LINK, SMART and related near-market programmes can provide support for the inventive steps in product development. The NMS is better placed to support the verification of product performance.

- In the clinical diagnosis of slow-growing and fastidious bacteria, there is a need – shared more widely in bioprocessing - for the continuous, non-invasive monitoring of culture composition.

Agri-food

Biotechnology-based product innovation in the agri-food chain faces considerable hurdles of public acceptance. It is striking that the Foresight 2000 ‘Food Chain & Crops for Industry’ panel - with a 20 year time horizon - concentrated almost exclusively upon the public perception and regulation of innovation. The investment climate for innovation in food is such that there are very few research-based SMEs focused upon production. Large companies continue to develop GM crops, and expect that acceptance will grow as evidence of harm fails to emerge. Meanwhile the seed sector faces the problem of segregating GM material.

- For the short and medium term, measurement impacts upon biotechnology in the sector mainly in supporting regulation, in assuring product quality and in regaining public confidence.
- For issues such as animal health and husbandry, food safety, control of food processing and food allergenicity, hypersensitivity and functional foods, biotechnology promises improved tests and bioscience-based understanding, and there may be useful connections with the pharmaceutical sector.
- Public concerns over agriculture and food provenance demand improved and validated measurement approaches, but a firmer connection needs to be made between the establishment of regulation and the realities of analysis.

Chemicals & the Environment

Biotransformation is gaining ground in the chemicals sector as a selective and environmentally benign synthetic route, especially for pharmaceutical intermediates. Science base research is strong, and well-connected with the pharmaceutical majors. The relevance of measurement mirrors that for the pharmaceutical sector.

Biotechnology, in the broadest sense, offers opportunity in diagnosing and alleviating a wide range of environmental problems. Environmental sensors, exploiting biological signals, are widely researched. Although the specific, competitive technical innovations in sensing are an inappropriate focus for an NMS programme, there are generic issues of sampling and reference materials for environmental measurement. The ‘Biowise’ programme aims to improve the competitiveness of UK industry through encouraging the use of biotechnology in sectors traditionally remote from the biosciences. Biowise services in awareness-raising and knowledge transfer major in environmental biotechnology and a new LINK programme in bioremediation has been launched.

- The search for effective biocatalysts will employ increasingly screening systems modelled upon those used in the pharmaceutical industry, and will face similar measurement issues
- In environmental sensing, the main measurement issues are validation of specific proprietary technology – which is not for the NMS – and effective sampling. Reference samples of key analytes in complex matrices would facilitate development.

Process Engineering & Equipment

UK companies are strongly competitive in the use of bioprocess technology, and liaise well with the science base in generic approaches to monitoring and control, in theoretical analysis and in work relevant to the 'next-but-one' product. Equipment manufacture is a UK weakness since

- There are continual demands for better measurements for process control, including monitoring culture conditions, but the need to avoid adventitious contamination is a significant barrier to the use of in-line sensors.
- Difficulties remain in demonstrating conformance with regulation for the contained use of genetically modified organisms.
- The biotechnology industry faces the difficulty of convincing regulators of the validity and reliability of sophisticated IT-based process control

3 PROGRAMME THEMES

Annex 1 (The Formulation Process) describes the processes involved in deriving the technical content of the programme. The list of people who contributed to the process is given in Annex 2. Annex 3 includes the Background Documents that reinforced the formulation process.

The formulation process identified five priority themes at the frontier of biotechnology, where there are rapid developments in measurement technology that is critically important in exploiting the biotechnology emerging from the science base, namely:

- **microarray-based measurement**, which is central to product discovery and testing
- **proteomics and genomics**, the focus of much scientific interest and commercial investment
- **cell-based testing**, the way forward in assessing the effectiveness of candidate products, and central to reducing the number of animal tests.
- **physico-chemical methods in biomolecular characterisation**, increasingly important in gaining regulatory approval for marketing a bioproduct, and a necessary part of traceable measurement in proteomics and genomics.
- **trace-biological measurement**, for demonstration of control of contamination, with consideration of the uncertainty of the measurements involved.

For all five themes, mutual acceptance of measurement is a critical determinant of time-to-market at the interfaces between the science base and companies, between SMEs and large companies, between companies and regulators and between the science base and regulators. Improved comparability in all five topics will benefit the development of biotechnology across all sectors.

With it being likely that different suppliers will deliver these themes, there is a requirement for cross-programme initiatives in **knowledge transfer**, in addition to the attention that this topic should attract in every technical project. This is discussed more fully within Section 4, the Unified NMS infrastructure for Biometrology, and part 4.5 of Annex 4, the Knowledge Transfer Infrastructure.

The programme will also address the need to capitalise upon the UK lead in the developing **international infrastructure** for metrology for the biosciences. There are universal difficulties of the widely dispersed, sectoral nature of bioscience expertise and the gap between it and metrology. The UK has the opportunity to establish a network for biometrology, to solve both problems and thereby to consolidate upon the lead.

The proposed technical themes are presented under the sub-headings: aims, background, benefits, project activities and outputs.. It is important to note that these are **not** project descriptions. The NMS will issue invitations to tender with specifications based upon the sub-headings given in this formulation document, to encourage the technical community to submit innovative proposals.

Activity of the following types is envisaged.

1. Research studies

The user community, and particularly SMEs, will need to feature prominently in research studies to eliminate or reduce an identified barrier to characterisation, quantitation and comparability. The outputs of such work should have demonstrable value to the user community in improving measurement comparability, and could comprise method validation tools, guidelines, internal controls and reference standards. The subsequent uptake and usage of such outputs will be used to evaluate the success of projects. Knowledge transfer activities should be integral to each study.

Research studies are expected to be completed within 1- 3 years and to cost between £100k and £400k.

2. Desk studies of technical barriers

The programme aims to improve the quality of biomeasurement through addressing specific technical barriers to measurement comparability. Desk studies, drawing upon the experience and advice of users in industry and the science base, will be necessary to identify the most significant barriers for selected measurements. Successful studies will identify specific barriers of significant and demonstrated importance to the exploitation of biotechnology.

Desk studies are expected to be completed within 3 – 6 months and to cost up to £50k.

3. Feasibility studies

The purpose of feasibility studies is to examine, in close consultation with experts and prospective users, the technical feasibility and economic case for establishing a community-based initiative to benefit biometrology, such as an advisory network or a database.

Feasibility studies will be short, focused and urgent. Each would last up to three months and cost up to £50k.

* Activities marked by an asterisk will be delivered by the programme ‘hub’ (see Section 4).

3.1 Theme 1: Microarray measurement

Aim: To improve the comparability of data from microarray-based measurements, cross-connecting with IT-based initiatives in harmonisation.

Background:

Multiplexed and high-throughput microarrays, exploiting sensitive and specific biological recognition, represent the future of measurement in many aspects of biotechnology – in genomics and proteomics, in protein/drug and lipid/drug interactions. The existing NMS VAM programme (2000-2003) addresses some of the technical challenges faced by the development of DNA based microarrays for SNP analysis. Protein microarrays present even greater technical difficulties, but many expect them to provide an invaluable tool in the analysis of protein activity and interactions. There is a multitude of platforms and approaches for both DNA and proteins, and a widely acknowledged difficulty of relating results between them. There is much current activity

in database construction and informatics-based ‘normalisation’ of data, but reducing variability at the detailed experimental level is a more fundamental and important target. For example, there are significant doubts over how representative and uniform are the immobilisation of biomolecular probes to surfaces, and the labelling and binding of targets. The sensitivity and stability of the signal, usually fluorescent, is a concern shared with nucleic acid microarrays. Novel approaches, using quantum dots, for example, will raise further issues for comparability.

Given the dynamism of the technology, there is no case for the NMS to pick winners or to seek immediately to develop formal standards. Rather the need is to raise awareness of the need for comparability and to enable read-across of results between competing systems, thereby encouraging their assessment and improvement. This activity will set the stage for standardisation as the technology matures. The topic attracts a ‘highest priority’ rating from the pharmaceutical industry in considering candidate topics for the programme, and will become increasingly important in the agri-food sector.

Handling the mass of data generated by microarrays requires informatics, and there are international initiatives in train to harmonise approaches at that level. The NMS projects will address technical issues that represent barriers to comparability between microarray measurements, but it will be important for them to acknowledge and reflect informatics approaches.

Benefits:

Increased acceptance of the comparability of data by all stakeholders, enabling knowledge and technology

Faster, cheaper and more secure identification of targets for novel drugs

Project Activities and Outputs

Demonstrate a clear understanding of the technical reasons for poor comparability between microarray measurements

Identify a key generic problem or set of problems constituting a barrier to achieving comparability

Conduct, through an appropriately structured consortium, a programme of research to reduce or eliminate that barrier

Transfer the outputs, which might comprise method validation tools, technical guidelines, internal controls or reference standards, effectively to the user community, through direct contact as well as the scientific and technical literature.

3.2 Theme 2: Proteomics and Genomics

Aim: To develop and promulgate valid methodology for comparable proteome measurements while ensuring the continued relevance and timeliness of the nucleic acid measurement projects in the current NMS VAM programme.

Background:

The technologies for measurement of DNA are well established and applied widely in the field of genomics. The NMS has directed significant effort towards fostering comparability of nucleic acid measurement, currently in the five projects starting under the VAM programme 2000-2003.

Those projects, focusing upon primary methods, standards, harmonisation and validation, were the product of an extensive prior consultation. The pace of technical development is such that it will be necessary to monitor their continuing relevance carefully, to ensure responsiveness to emerging requirements. This work now needs to be extended to achieve the same objectives for protein measurement.

The genome is responsible for only a small proportion of the variation between individuals; the rest comes from differences in gene expression and the activities of the products of this expression, namely RNA and proteins. Proteomics is the comparative analysis of the variation of the population and activities of an individual's proteins. The measurement of protein populations is in its infancy. No technology is capable of separating and analysing the full range of proteins and their network of interactions in the cell. Mass spectrometry is central to protein identification and quantification, but the validity of measurements close to its limits is rarely demonstrated. There is scope to apply new methods to the measurement of the complex mixtures that constitute the active components of the cellular machinery. Both absolute and relative measurements are important and determining the post-translational modifications of proteins, such as phosphorylation and glycosylation, is a further challenge. Identifying and quantifying nucleic acid and the expressed proteins will be central to product discovery in biotechnology for many years to come. Comparable measurements will greatly facilitate that process.

Proteomics is the subject of significant academic and industrial R&D programmes and it is anticipated that there will be technological breakthroughs and refinements to existing techniques in the short term. The NMS projects will identify and address technical barriers with a view to developing comparability in the measurements from the new technologies and in the exchange of the data emerging from these measurements. The long-term aim is to standardize the new measurement technologies and accessibility of the resulting data.

Benefits:

Better technology transfer between the science base, SMEs and large companies

Faster development of understanding of the relation between proteomic and genomic data and biological behaviour, and hence more effective product discovery

Project Activities and Outputs:

Demonstrate a clear understanding of the technical reasons for poor comparability between proteome measurements

Identify a key generic problem or set of problems constituting a barrier to achieving comparability

Conduct, through an appropriately structured consortium, a programme of research to reduce or eliminate that barrier

Transfer the outputs, which might comprise method validation tools, technical guidelines, internal controls or reference standards, effectively to the user community, through direct contact as well as the scientific and technical literature

*Commission a desk study by invited experts to identify measurement issues associated with the identification and quantification of protein/protein interactions

*Monitor the current VAM projects on DNA measurement for their continued relevance and timeliness, and recommend changes if necessary

3.3 Theme 3: Cell-based Testing

Aims: To increase confidence in cell-based testing and to correlate cell-based assay data with genomic and proteomic data in collaboration with industry.

Background:

The reduction in the use of animal testing of candidate drugs and chemicals is widely acknowledged as a necessary target, both in responding to public concerns and in facilitating pharmaceutical development. Cell-based testing has long been seen as the alternative, with the potential to screen large numbers of drug candidates quickly, cheaply and reliably, saving much development resource. In addition, cell models are increasingly being applied to medium-throughput screens for lead optimisation and to the development and regulatory approval of gene therapy products, therapeutic peptides, recombinant vaccines and nutraceuticals.

National and international programmes have made significant progress, but confidence in cell-based tests needs to be increased further. The key barrier to the standardisation of cell-based assays is the inconsistent behaviour of cell-lines. Ensuring the authenticity and reproducible behaviour of a cell-line is no light task since biological material is inherently and, if living, continuously variable. Sources of variation between cell-lines, or separate isolates of the same cell-line, include the culturing conditions, the storage system and the length of time over which the cell-line has been cultured. Developments in DNA technology mean that assuring authenticity at the genotype level is now straightforward. The new challenge is the application of existing methods and/or the development and validation of novel methodologies to the identification of cell-lines and to test for cellular functionality. These methodologies might exploit the identification and characterization of markers unique to individual viable cell-lines or identify standard markers for relative measurements between different cell-lines. They might be applied to comparing the differences between primary and secondary cell-lines. This work should focus on human cell-lines but it is hoped that the techniques will be applicable to cells or tissues from other species.

Despite the wide range of molecules now being screened as candidate drugs, it is probable that there will be common elements in the results of testing these molecules on cell-lines, such as the induction of specific stress responses, or reproducible changes in cellular metabolism. There is evidently the potential for pharmaceutical companies, SMEs and academia to contribute to and share a database of such information, thus decreasing the number of parameters to be monitored during cell-based assays. It is anticipated that the data of interest will be generated from toxicity assays correlated with appropriate information derived from proteomics and genomics.

Benefits:

- More reliable characterisation of the effects of candidate drugs etc
- Faster and more certain identification of good [and poor] candidates
- Replacement of some animal tests
- Increased regulatory confidence in the reliability of cell-based tests

Project Activities and Outputs:

Develop, through collaborative research, novel tests for the functionality of cell lines [human and animal] and primary cultures to be used in cell-based tests, so as to demonstrate their suitability

Hence develop validation criteria for such measurements

Transfer these validation criteria to the user community, through direct contact as well as the scientific and technical literature

*Evaluate the market for a database of information relating toxicity markers to proteomic, metabolomic and genomic data, with the information supplied by companies and accessible by subscription [To be followed by an ITT if the project is viable]

3.4 Theme 4: Physico-chemical Methods in Biomolecular Characterisation

Aim: To increase confidence in the use of physico-chemical techniques in biomolecular characterisation, by extending the validated limits of established techniques and by evaluating the application of emerging methods.

Background:

The physico-chemical characterisation of biomolecules has assumed great importance for two main reasons.

First, the regulatory community, led by the FDA, is seeking to increase the use of physico-chemical characterisation in the control of the quality of biological products. This 'Well-Characterised Biological' initiative shifts attention from the regulation of the process to the regulation of the product itself and has opened up new challenges for physico-chemical methods. Most of the widely used methods for biological analysis, such as circular dichroism, NMR, optical spectroscopies and - centrally - mass spectrometry, are stretched in characterising and quantifying large, complex molecules or mixtures, where the limitations of these techniques are poorly understood. For instance, the identification of post-translational modifications and the determination of immunogenicity of therapeutic proteins are very demanding for existing technologies but they are essential for the product to gain regulatory approval. This, combined with the perception of these techniques and their IT data analysis as "black boxes", leads to the reliance on comparative methods for data analysis, which are viewed poorly by both industry users and regulators. In addition, there have been few attempts to compare results of physico-chemical methods, or to identify the method of choice for specific classes of biological products, to validate methods and to foster comparability of measurement. SMEs frequently rely upon contractors in the science base for such specialized measurements, most often by mass spectrometry, but harbour doubts over quality and comparability. Moreover, since SMEs seek large company partners to develop and market products, a failure to use mutually acceptable means of characterisation constitutes a barrier to innovation.

Second, there have been exciting research advances in the detection and characterisation of single biological molecules, through such methods as atomic force microscopy, which promise to become central to bioscience research. UK academic scientists are leading the way in developing these novel technologies that are anticipated to emerge as possible complementary candidates for characterising biologicals. They promise to provide fundamental information on structure that will inform the molecular design of products. Their timely validation is important, so that their

fitness for purpose can be established. If suitable, they can then be employed more rapidly and confidently in biopharmaceutical discovery and, where appropriate, in regulation.

Benefits:

More confidence in the analytical characterisation of bioproducts among manufacturers and regulators

Clearer guidelines on quality requirements when commissioning characterisation work

Project Activities and Outputs

Part a The well-characterised biological

Demonstrate a clear understanding of international trends in the regulatory approval of biopharmaceuticals and their dependence upon measurement techniques

Evaluate and validate a key method for current regulatory developments, chosen for the demonstrable need to increase confidence in its use

Transfer the outputs to industrial users and regulators

Part b Emerging methods for characterising biomolecules

Develop and validate, in collaboration with the originators of the methods, the application of techniques newly emerging from the science base

Transfer the outputs to industrial users and regulators

Monitor regulatory developments in biopharmaceuticals for their implications for measurement, and transfer the knowledge, including validation requirements and approaches, to SMEs

3.5 Theme 5: Trace Biological Measurement

Aim: To increase confidence in the regulatory control of biotechnology through encouraging the application of the concept of measurement uncertainty and improving the comparability of key trace biological measurements

Background

Trace biological measurements are central to the safe and sustainable exploitation of biotechnology in detecting, for example, adventitious GM events in seed and contamination of biopharmaceuticals with residual host-cell protein or DNA. In principle, amplification methods and immunoassay can deliver reliable trace measurement. In practice, difficulties including sampling, extraction, interference and antibody production introduce uncertainties that are rarely acknowledged and seldom quantified.

Identifying and tackling the main sources of uncertainty in measurements with a significant economic impact would allow the regulatory control of biotechnology to be based more securely in sound science, to the benefit of industry, regulators and the public. Companies could develop products with a clearer perception of the regulatory hurdles ahead. Regulatory limits could reflect what can be measured reliably. The level of the regulatory debate could be raised.

The requirement for this work has been heightened by the introduction of an international standard ISO 17025, which demands that testing laboratories include an uncertainty estimate in

method validation. The concept of an uncertainty budget is foreign to most biological measurement and requires study of the entire measurement process, from sampling to calculated result. Promotion of the concept, through example, among the relevant regulatory communities is central to the programme. Facilitating comparable trace biological measurement is likely to demand reference materials and debate within the community on criteria and procedures for their production.

Benefits:

A more balanced regulatory burden for the industry, through a better acknowledgement of metrological constraints

Improved user confidence through integrating trace biological measurement with the NMS

Project Activities and Outputs:

Conduct a study of approaches to the production of reference materials for trace biological measurements, chosen for their impact upon regulation significant for competitiveness

Quantify, in close collaboration with the bioprocessing industry, existing CEN standards for bioprocess containment

Promote the concept of the uncertainty budget through case studies in biological measurements significant for regulation [which might entail experimental work], and through direct contact with regulators and regulated

4 A UNIFIED NMS INFRASTRUCTURE FOR BIOMETROLOGY

Biotechnology expertise relevant to an UK infrastructure for a ‘Measurements for Biotechnology’ programme exist in various centres, but there is a need for focus and co-ordination with a clear strategy to promote the development and establishment of a reliable, comparable and traceable measurement system that is recognised internationally. This can be best achieved by establishing, in the form of a network, a **virtual Centre of Biometrology**, securing benefits for all sectors in the UK.

The Centre should co-ordinate and provide the missing elements of the infrastructure, most notably a firm connection with the SME community and with international developments. For this purpose the virtual Centre needs an independent core or hub; the principal tasks and deliverables attached to the hub are shown below.

1. To manage the development of a biometrology infrastructure

<u>ACTIVITY</u>	<u>DELIVERABLES</u>
Establishing and informing a MfB network of managers of relevant programmes, initiatives and laboratories and relevant officials in regulatory agencies and departments	• MfB website, covering the programme, digests of technical progress and complementary activities • An MfB newsletter
Engaging the SME community	• A BIA measurement committee • A regular biomeasurement feature in BIA Newsline

2. To co-ordinate the programme and its relation with complementary UK activity

<u>ACTIVITY</u>	<u>DELIVERABLES</u>
Facilitating the work of the Working Group [WG]	• Reports on progress of projects & technology developments at WG meetings
Ensuring that biometrology issues are reflected, where appropriate, in other NMS programmes	• At least one bio-related activity in each programme • Contribution to orientation of other NMS programmes • Advice on future of current VAM DNA projects • Costs saved through working with KT programme
Developing synergy with OGD programmes	• Common interests identified • Joint projects, with co-funding where possible

3. To co-ordinate the programme with international activity

<u>ACTIVITY</u>	<u>DELIVERABLES</u>
Capitalising upon the UK lead in the international biometrology debate	• Lead in development of CCQM programme • Full UK participation in CCQM intercomparisons • Reports on biometrology in overseas NMIs
Improving SME knowledge of international biometrology	• Identified opportunities for overseas missions
Influencing European R&D and standards programmes	• Contribution to consultations & technology foresight activities

4. To manage programme-wide knowledge transfer

<u>ACTIVITY</u>	<u>DELIVERABLES</u>
Raising SME and regulator awareness of the relation between regulation and measurement	• Seminars for SMEs and regulators • A web-based atlas of biopharmaceutical regulation
Keeping MfB up to speed technically	• Technical audits and updates for WG and website
Promoting the concept of the uncertainty budget	• Case studies of measurements significant for regulation • Company-specific consultancy
Promoting the sharing of toxicity data	• Evaluated market for a database relating toxicity markers to 'omic data, with the information supplied by companies and accessible by subscription* • Establishment of such a database, if viable

5. To promote the programme

<u>ACTIVITY</u>	<u>DELIVERABLES</u>
Raising and maintaining the profile of biometrology and the programme	• Literature on biometrology issues • Seminars, workshops and an annual scientific meeting • Representing the programme at significant biotechnology events

5. PROGRAMME BALANCE AND PRIORITISATION

The central aim of the Measurements for Biotechnology programme is an increased ability of UK companies to exploit the biotechnology emerging from the science base. The technical themes of the programme were prioritised in accordance with their likely impact upon that ability. The formulation study identified three broad ways in which that aim will be achieved.

1. Better measurement comparability will facilitate product discovery, product development and technology development [data interpretation within companies; stronger partnerships between the science base and companies], especially in ‘frontier biomeasurement’ [microarrays, proteomics & genomics and cell-based testing].
2. Appropriate application of metrological principles to physico-chemical methods of characterising bioproducts, to trace measurement and to bioprocessing will contribute towards a more secure relation between regulation and sound science.
3. The climate for investment in biotechnology is volatile and sensitive to public perception. Confidence in measures to ensure the safe, ethical and sustainable development of biotechnology is an important component of public perception, and will be heightened by projects encouraging the replacement of animal testing and risk assessment founded in sound measurement science.

So, facilitating technology development, lightening the regulatory burden and improving the climate for investment are dimensions along which the impact of projects in a biomeasurement programme can be appraised.

Then there is the question of the importance of the technology developed, the burden lightened and the climate improved. Current investment and activity in biotechnology is directed overwhelmingly towards human healthcare, suggesting that the programme should be focused there. Some 80% of the UK’s biotechnology SMEs are directed towards pharmaceutical targets. There is, moreover, good reason to believe that measurement techniques pioneered in the pharmaceutical applications of biotechnology will find wider application later. On grounds of the importance of technology developed, therefore, projects relevant to pharmaceuticals scored highly.

On grounds of impact upon the regulatory burden and the climate for investment, however, there can be little doubt that the agri-food sector has most to gain.

There is no sound way of quantifying these arguments and criteria across the set of themes proposed for the programme. Market forecasts for biotechnology suffer invariably from hype. Most of the proposed themes are relevant to several sectors. Improved measurement will be only a minor player in improving public perception. It was suggested rather that the programme should aim at a balanced portfolio of projects, demonstrably covering the significant sectors of biotechnology and introducing the concepts of metrology so as to facilitate technology development and transfer, and to contribute towards lightening the regulatory burden and improving public perception. The following table scores the proposed themes crudely in terms of their sectoral importance and their potential impact upon perception and regulation.

sectors & issues themes	Human Healthcare	Agriculture	Food & Drink	Chemicals	Perception	Regulation
microarrays	**	**	*			
proteo & genomics	**	**	*			
cell-based testing	**		**		*	*
physicochem methods	**	*	*			*
trace measurement	*	*	*		*	*

ANNEX 1: THE FORMULATION PROCESS

The Bioindustry Association, LGC and NPL, with technical advice from Prof Tony Atkinson (NSE), were commissioned to formulate a new NMS ‘Measurements for Biotechnology’ programme, which has the declared aim of **increasing the ability of UK companies to exploit the biotechnology emerging from the science base** through:

- extending the coverage of the NMS and its infrastructure to the biosciences
- improving the accuracy and reliability of biomeasurements important to industry
- strengthening the measurement science underpinning the regulatory regime for biotechnology, and thus improving the climate for innovation

The formulation was to be based upon a thorough consultation with the industrial community and stakeholders in the science base and Government, addressing five central issues.

1. An NMS programme in biotechnology needs to acknowledge established programmes and centres of expertise and to continue to reflect their rapid scientific progress. Moreover, formulation requires alertness to requirements that can be satisfied most effectively by LINK or Faraday initiatives.
2. In order to reflect DTI biotechnology policy, as presented in the ‘Genome Valley’ report, the NMS Measurements for Biotechnology programme needs to focus upon ‘high biotechnology’ and the science base / SME nexus, and to acknowledge regulation as a key influence upon competitiveness.
3. The international regulatory debate, and the growing international interest in measurement and standardisation in biotechnology should inform formulation.
4. In order to identify the generic, cross-sectoral measurement requirements most appropriate for an NMS programme, formulation should be addressed at the level of the targets for measurement - namely the cell, the gene and the protein - complemented by a consideration of advanced physical measurement and bioprocessing.
5. Criteria for prioritisation of candidate projects in a biomeasurement programme are likely to differ from those established for the relatively mature NMS programmes in the physical sciences.

Other sources of information and areas for review included [Annex 1]

- the documents circulated with the ITT for the formulation activity
- the relevance and potential of the current NMS programmes
- current issues and challenges for the UK bioindustry,
- international technical and regulatory developments [NIST, CCQM, FDA]
- relevant Foresight sectoral documents [Health Care, Food Chain, Crime Prevention]

This developed the following preliminary draft of a set of programme themes and rationales for the biotechnology NMS.

CANDIDATE THEME [Focus]	CORE RATIONALE
<u>The effects of genetic modification</u> [Fuller measurement of the effect on protein & metabolite profiles]	• more predictable genetic modification • more balanced regulation and public perception
<u>Direct quantification of biomolecules</u> [Direct, non-amplification approaches: single molecules, mass spectrometry]	• amplification-based methods are near-universal, but lack traceability and standards
<u>High-throughput biomeasurements</u> [Validation of arrays, miniaturisation]	• arrays popular for throughput, but lack traceability and standards
<u>Well-characterised cell lines</u> [Traceability, genetic drift]	• comparability enhanced in biotech R&D • help to phase-out <i>in vivo</i> tests
<u>Well-characterised biologicals</u> [Employing physico-chemical techniques; exploiting UK lead with proteins]	• reduce the need for case-by-case regulatory review of biopharmaceuticals, mirroring US developments
<u>Process control</u> [Real-time measurements and quantitative containment standards]	• reduce costs and minimise health & safety risks • public perception benefit

This list of topics was used to initiate discussions and elicit responses from a wide community. Care was taken to emphasise that this was a preliminary and non-exclusive list, and to invite the identification of additional topics in the consultations summarised below. Discussions and approaches were co-ordinated through the use of an agreed ‘script’, which presented some key questions:

1. What are the measurement difficulties and challenges that really impact upon **innovation** and **competitiveness**, now and in the future?
2. Where, specifically, do you need measurements to be faster, more accurate, more comparable and more reliable in order to increase **user confidence** and/or to reduce **time-to-market**?
3. Might a highly visible programme to improve biomeasurement contribute towards increased **public confidence** in biotechnology?
4. Are there any standards related issues in the area of interest?
5. What should be the priorities for a new biomeasurement programme?
6. What key benefits would you wish to flow from such a programme? And why are they important to you?
7. Do you know of any current programmes, national or international, that address these issues?

It is noteworthy that the process of consultation and iterative development of the set of programme themes yielded no inputs inconsistent with the preliminary list of topics, and no advice that any one of them was misconceived. The process was rather one of refinement and focusing, through consultations with the industrial community, the science base and the regulators.

It was important to acknowledge some limitations of the formulation. First, it was evident that knowledge of the likely size of the proposed programme was a disincentive for many industrialists to offer serious, considered comment. The common perception was that a much larger programme would be necessary to impact significantly. Second, time allowed us only to identify programme themes and to define broad technical subjects that the programme should address. Specific project descriptions were not a requirement of the formulation, but will be addressed by bidders in response to invitations to tender.

A1.1 The Industrial Community

The formulators

- alerted the 331 members of the BIA to the formulation of the programme through the BIA web-based 'NewsCast'
- briefed the members of the relevant BIA committees [Regulatory, Manufacturing, Environmental], on the programme and secured their advice on a document to be circulated to the full membership.
- circulated the full BIA membership - now expanded to include the Scottish bioindustry association - with a document eliciting responses, supplemented by telephone chasing
- circulated the industrial membership of the Diagnostics Club [42 companies], and followed up by e-mail
- approached representative industry organisations [ABPI, BIVDA, SCIMAC, BSPB, SCI] and were referred to individual company members for detailed comment
- convened a BIA-hosted workshop on 6 March 2001 for the whole industrial community , securing the following advice:

ADVICE FROM THE BIA WORKSHOP: 6 MARCH

Toxicity testing

- Fostering in vitro and in silico testing is a sound target, but planning development work needs to reflect the reasons for the modest impact of past efforts, and to be clear over validation issues
- There might be potential for collaboration in developing methodology for geno- and proteo-toxicity, and to establish a database of genomic and proteomic toxicity markers
- Such collaboration would be beneficial in both the pharmaceutical and food sectors [hypersensitivity and functional food].

Product contamination

- Detecting host DNA, protein and endotoxin in recombinant biopharmaceuticals is difficult for SMEs especially
- Demonstrating conformance with regulation of adventitious GM levels in seeds is a major problem; cheap tests are needed but current programmes [MAFF, DETR] are not getting there; accreditation is required of methods and laboratories
- Validated bioassays are needed for food contaminants, including mycotoxins

Bioprocess control

- On-line methods for sterility testing when vials are sealed, for filter integrity and for fermentation substrates and products have long been identified as requirements, but are still elusive
- The exemption of specific GMOs from contained use regulation requires environmental survivability data
- The requirement remains for active monitoring of low-level process leakage, acknowledging the difficulties of ambient sampling; DERA work is relevant
- Validating the results of data mining for GMP regulators is demanding
- Chemical sterilisation procedures require validation

Characterising biologicals

- SMEs have to outsource characterisation, often from universities, but worry about their quality
- ‘Single molecule detection’ has merit for the programme in the simultaneous study of physical and biological properties, but not as an end in itself
- The UK needs to respond to the FDA push towards comprehensive physical testing, but generic testing is limited by product specificity and by case-by-case review. A planned approach is needed.
- In the pharmaceutical sector, standards and measurement repeatability become more critical for out-of-patent products

Nucleic acid measurement

- SNP detection needs validation
- There is a tacit conspiracy to ignore transcription errors inherent in PCR
- There are many competing array technologies. Validation is required.

Miscellanea

- Knowledge transfer from the pharmaceutical sector [where validation is systematised] to the food sector is a sound objective for the programme. There is a wide gap, however, since food matrices are more complex, since sampling is more demanding and since there is no tradition of close technical contact between food regulators and companies.
- Consumer and regulatory demands for knowledge of food provenance require validated assays [eg for fish]
- Novel technologies require timely validation; they are often oversold and turn out to have limited niches

- This summary of advice was circulated to the entire BIA membership and to the 951 industrial, research and regulatory organisations listed in the UK Biotechnology Handbook 2001 for further comment.

A1.2 The Science Base

- Discussions were held with officials of BBSRC and EPSRC, focusing upon the ‘Metrology for the Lifesciences’ programme, which takes the term metrology to mean novel measurement.
- The formulators held face-to-face meetings staff of key technical centres [NIBSC, CSL, CAMR, DERA Porton, Babraham Institute, Institute of Food Research, John Innes Institute, FRAME, UCL Biochemical Engineering, AEA Bioprocessing], and made contact with key regulatory agencies [MCA, MDA, EMEA, HSE]. In collaboration with NIBSC, the formulators held a workshop [29 March 2001], for industry and metrology laboratories [including the USA and Germany], on the ‘well-characterised biological’ and standards for fluorescence, including a discussion session on the proposed programme. This yielded the following advice:

ADVICE FROM THE NIBSC WORKSHOP 29 MARCH 2001

Instrument calibration and qualification

- Confidence in instruments would be increased if manufacturers used common calibrations and qualifications, for example after lamp changes. ‘Self-validating’ instruments, increasingly popular in clinical chemistry, prompt the question ‘who checks the checker?’
- Seeking to focus an instrument standard upon one manufacturer’s product threatens damage to competition. Better routes include [1] a neutral, state-of-the-art facility [eg synchrotron-based CD at Daresbury] and [2] carefully probing the scientific basis common to a family of instruments [eg NPL’s work in Auger spectroscopy]
- There is a place for the ‘cheap & cheerful’ instrument giving a yes/no answer, especially in the food sector

Reference materials [RMs]

- It’s whole operational measurement systems that need qualification. Pure RMs serve to validate instruments. Matrix RMs [eg GM material in seeds] present an important challenge to the whole operational system, and their production often demands an combined understanding of the relevant physics, chemistry and biology.
- Measurements in the biosciences should always include internal controls

Measurement support for SMEs

- Many SMEs – frugally supported by venture capital or requiring a specific measurement only occasionally – need access to expert measurements. Bioincubator schemes encourage shared access, often to science base instruments.

- When confidence in the repeatability of measurement is low, technology transfer is inefficient. Much effort is devoted to checking extramural measurements [even between departments in large companies].

The regulatory climate

- ‘Post-genome’ biotechnology presents the regulatory system with many new challenges [gene therapy, cell therapy, genetic testing, personalised medicine]
- Key current trends are towards regulatory interest in: the operational quality of instruments; the validation of *in silico* contributions to measurements and reporting; the use of physico-chemical characterisation for batch release
- The ‘well-characterised biological’ demands study by a battery of techniques [MS, NMR, FTIR, CD] and threatens to become an additional regulatory burden. Vaccines present the most difficulty in demonstrating consistency of production

Microarray techniques

- Notwithstanding the persistence of measurement difficulties in classical bioassay, the new programme should be forward-looking. Arrays raise many measurement issues [eg effects of surface attachment on signalling systems, validity of inferences from pattern recognition] and should be a focus.

Fluorescence standards

- Quantitation of fluorescent intensity is complicated by the heterogeneous nature of biomeasurement systems using fluorescent tags [conjugation to spheres and cells, attachment to array surfaces].

A1.3 The Regulatory Community

The programme was discussed at:

- The Biotechnology Industry/Government Regulatory Advisory Group [BIGRAG]
- The Microbiological Analysis Group for the Provision of Information Exchange [MAGPIE]
- The Medicines Control Agency committee on Good Manufacturing Practice and Good Development Practice

Additionally, regulatory agencies were represented at the formulation workshops and at other technical meetings attended during formulation.

Annex 2 presents lists of the individuals whose advice and comment influenced the formulation.

ANNEX 2: THE COMMUNITY CONSULTED

The following individuals offered comment [directly, in writing, by phone or e-mail] on the proposed programme content, or influenced planning through contributions to meetings during formulation. Their contribution does not imply endorsement of the final programme content.

Dr Jeff Adamson	Adaptive Biosystems	James Jackson	SmartSensor Telemed
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Dr Vernon Barber	NFU	Dr Lloyd King	Celltech
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Dr Jane Cockram	Food Standards Agency	Dr Fred Mellon	Institute of Food Research
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Views of the following individuals contributed to formulation through contact with NSE

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Dr Andrew Lane	Serotec Ltd	Dr Peter White	C N Biosciences UK
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Dr Bill Lindsay	Hybaid Ltd		

ANNEX 3: THE BACKGROUND DOCUMENTS

The formulators reviewed and debated the three documents circulated with the ITT, the current NMS programmes and the sector reports of the relevant Foresight panels, with the following conclusions:

Report of a Workshop organised by the DTI on 21 July 2000

This event was dominated by consideration of incremental solutions to current problems in the development and enforcement of regulations, with frequent reference to their impact upon public perception. Little attention was given to the leading edge of measurement research, and how developments there would impact upon future competitiveness. Of the Report's suggestions for further work, there are strong arguments for attention to:

- Improvements in the standardisation of cell lines
- The notion of 'well-characterised biologicals', where the UK has a technical lead with proteins
- The fuller characterisation of GM organisms and the effects of modification
- Methodology to make CEN standards quantitative
- Improved SNP diagnostics, especially the validation of array technology
- The cross-sectoral problem of sampling complex matrices

Summary of a 'Deep Study' of Requirements for a National Measurement System for Biotechnology

This Study addresses some 'technology push' and resource requirement aspects, and has the merit of developing a metrological perspective, but it is based upon limited experience and contact with the bioscience sector. The requirements identified for the NMS in biotechnology are acknowledged to be preliminary, but the survey highlights usefully some current NPL expertise that could be deployed in a new biotechnology programme. There is clearly the potential for NPL to contribute, at the interface between the physical and biological sciences, to the development of a biomeasurement infrastructure, in collaboration with UK centres of expertise in bioscience.

Principle (sic) Characteristics of the UK Market for Nucleic Acid Measurements

The main conclusions of this 1999 Report have been reflected in the development of projects recently introduced into the NMS programme. It was proposed by the formulators that the Report has been overtaken by developments in array technology and in rapid DNA sequencing, and by the international collaboration in DNA metrology, all of which need consideration in formulation.

Relevance and potential of the current NMS

A review was undertaken of the potential of current and proposed projects in the **physical NMS**, in length, thermal measurement, acoustics, ionising radiation, flow, photonics, mass, software support for metrology, optical radiation and physical VAM.

Many of these programmes have relevance – more or less direct – for the medical sector, which is of course the target of much investment in biotechnology, and for food processing. There is likely to be more central relevance for the future of the biotechnology industry in current and proposed physical NMS work that impinges upon:

- miniaturisation
- software support in relation with bioinformatics and data fitting
- liquid-based fluorescence
- single particle detection and spectroscopy

The NMS **Valid Analytical Measurement [VAM] programme** shares some significant features with the prospective NMS biotechnology programme:

- Both the chemical and biological measurement systems are immature, with poor inter-laboratory comparability
- Both demand the identification [chemical or biological nature] of the measurand, as well as quantification
- Both face the problem of measurement in complex, interfering matrices
- Reference materials play a critical role in ensuring traceability in both

The experience and position established with chemical VAM provides a strong basis for the development of a biomeasurement system. The resource established in high-accuracy chemical measurement should find significant application in biomeasurement.

Successive VAM programmes have included an increasing commitment to DNA technology, focusing mainly upon PCR analysis. The evolution from identifying critical points in PCR analysis, through the promotion of best practice via a laboratory manual to the production of a novel reference material has been successful and has kept pace with wider technology development. The current programme [VAM 2000 – 2003] includes five nucleic acid projects that take this evolution further.

BM1 Development of primary methods and standards for quantitative DNA measurement

- developing an international infrastructure based upon intercomparisons
- seeking primary [non-amplification] methods and standards

BM2 Validation of enhanced sensitivity techniques

- identifying and investigating critical factors in precision and detection limits
- limits of detection

BS1 Harmonisation of nucleic acid measurement techniques and processes

- provision of proficiency tests, reference materials, good practice guidance, benchmarking
- assessing and demonstrating fitness for purpose

BQ1 Validation of high specificity techniques

- identifying and investigating critical factors in multiplexed nucleic acid measurements

BQ2 Validation of measurement performance of novel integrated bioanalytical systems

- tackling validation issues during development of out-of-laboratory systems

It will be necessary to monitor carefully the progress of these projects for their continued responsiveness to technical changes in a very active area of science.

Relevant Foresight priorities

Chemicals Panel: ‘A Chemicals Renaissance’ [which included the pharmaceutical sector]

- support research at the chemistry/biology interface, including structural biology, molecular recognition, bioprocesses and biosensors
- post-genome opportunities for identifying disease targets and pharmacogenetics
- surface microscopies for biomacromolecules
- better protein analysis
- high-throughput robotic systems for synthesis, purification and analysis
- targeted drug delivery
- miniaturised systems for synthesis and analysis
- a regulatory system based upon science and risk/benefit

Crime Prevention Panel: ‘Turning the Corner’ [for which LGC led the Biology and Gene Technology Task Force]

- genetics, biometrics, sensors for identity and authenticity
- genetics, miniaturisation and sensors for crime detection, especially at scene of crime

Health Care Panel: ‘Health Care 2020’

- individuals may have encrypted health biographies, including genetic information
- need a flourishing UK biotech sector, but wary of unbalanced regulation [animal testing]
- need facilities to produce DNA at regulatory standard for human medicine, especially nucleic acid vaccines
- better biology/chemistry collaboration in eg protein/protein interaction [prion detection]
- genetic tests to inform choices of diet and life style
- genome merely the start of a process; pharmacogenetics; gene therapy; genetic testing
- stem cells for tissue/organ production
- detection/avoidance of viruses in xenotransplantation
- ‘platform technologies’ of cell control biology, tissue imaging, cytomexics, biochemical engineering for tissue engineering for bioactive implantable materials
- miniaturisation for near- and in-patient surveillance

Food Chain & Crops for Industry

- perception and regulation of innovation in food and industrial crops

Energy & Natural Environment: 'Stepping Stones to Sustainability'

- carbon-based chemistry eschewing fossil fuel [industrial crops, biotransformations]
- better resource use through biotech & genomics

ANNEX 4: THE INFRASTRUCTURE

The defining usage of the term ‘infrastructure’ is ‘a system of communication and services as backing for a military operation’. There is a significant range of communication and services relevant to measurement aspects of the exploitation of biotechnology emerging from the science base, but it falls short of the requirements for an infrastructure for a biometrology programme. There is a need for additional arrangements for co-ordination, for deriving cross-sectoral benefits, for connection with the developing international debate on biometrology and for effective knowledge transfer to the SME community.

A4.1 Biological Resources

The provision of biological resource [cell-line cultures, tissue samples, clones] plays an important role in biotechnology. The inherent variability of living organisms and the ‘grey market’ in cultures between researchers mean that ostensibly identical cell lines rarely are, so that there is much room for disagreement between research results. Questions of the authenticity and reliability are resolved by measurement, through DNA and MS analysis, but reproducing the behaviour of a given cell line demands precise control of culture conditions. Not much is known about the sensitivity of biological activity of cell lines to culture conditions. In the ‘post-genome’ world, there is wide interest in establishing banks of human and animal cells, tissues and clones, the authenticity – and use by the community – of which need careful attention. The European Collection of Animal Cell Cultures [ECACC: funded initially by DTI], and the MRC Human Genome Mapping Resource Centre are very relevant. The wider community of UK culture collections, funded by a variety of public sources, is a significant resource; they are co-ordinated by BBSRC, with linked access to information on holdings. The American Type Culture Collection [ATCC] dominates the world market. More needs to be done to encourage the use of cultures stored expertly in recognised collections, and of clear [and short] traceability chains to such authentic sources.

A4.2 Reference Materials

The establishment of a measurement system for biotechnology follows upon that for chemistry, under the Valid Analytical Measurement programme of the NMS. Reference materials [RMs] have a crucial role in the chemical measurement system, in transferring to a wider community the agreement established between national expert laboratories. They are necessary because chemical measurement entails identification as well as quantification, and because of the measurement challenge presented by complex matrices containing the target analyte. Both requirements feature, even more strongly, in measurement for biotechnology. And there is the additional and fundamental requirement to quantify biological activity. The National Institute for Biological Standards and Control [NIBSC] supports the regulators [MCA; EMEA] in assuring the quality of biological medicines, through the production and distribution [for a handling fee] of a wide range of biological RMs. These cover retrovirology, allergenicity, antibiotics, bacteriology, bacterial vaccines, blood products, virology and viral vaccines. Specific requirements for biotechnology RMs have begun to be met by NIBSC [cytokines and HIV PCR], NIST [forensic DNA profiling], IRMM [GM material in flour] and LGC [PCR control and DNA quantification].

The use of biotechnology in measurement, especially in the food and environmental sectors, would be facilitated by the availability of reference samples of key analytes in representative matrices

A4.3 International Harmonisation and Standardisation

There are significant biotechnology-related harmonisation and standards initiatives. The **OECD** works towards the harmonisation of regulatory oversight in biotechnology (BioTrack Online), and has a recent policy report considering the benefits of international harmonisation in regulation of the validation of genetic tests, standards for the recording of genetic data and evaluation of the efficacy of new genetic tests and technologies. The **United States Pharmacopoeia** has recognised the growing importance of biotechnology and has formed a standards development subcommittee charged with developing chapters which include tests and assays for biotechnology-derived products and validation of biotechnological processes. They aim to pursue harmonisation of standard requirements and reference standards for these products, and are considering the philosophical challenge of using standards as facilitators, not impediments, in the rapidly developing areas of biologics and biotechnology. **NIST** has an active Biotechnology section focusing on development of measurement methods and QC standards in a number of areas including biocatalysis, tissue engineering, DNA technologies and bioinformatics (NIST manages the international protein data bank).

The **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)** is a unique project bringing together the regulatory authorities of Europe, Japan and the US and experts from the pharmaceutical industry to promote harmonisation in the interpretation and application of technical guidelines for product registration so as to realise a more economical use of human, animal and material resources. The **International Association for Biologicals (IABS)** also acts as a major international forum for bringing together relevant stakeholders to develop a consensus on issues concerning the standardisation, quality control and efficacy of biological medicinal products for human and veterinary use such as vaccines and blood products.

The **Codex Alimentarius Commission** has an ad hoc intergovernmental task force on foods derived from biotechnology, and has proposed draft recommendations for GM food labelling as part of the FAO/WHO Food Standards Programme. Current **International Organisation for Standardisation (ISO)** technical committees (TC) are also developing biotechnology related standards on GM foods (TC34) in addition to standards on the biological evaluation of medical devices (TC194) and clinical laboratory testing and in vitro diagnostic test systems (TC212).

In Europe, the JRC **Institute for Reference Materials and Measurement [IRRM]** attaches high priority to the development of biotechnology related reference materials, particularly in the areas of biomedical CRMs for clinical diagnostics, microbiological CRMs and RMs and validated methods for GMO and TSE detection. Several EU FPV research projects aim to harmonise biotechnology method development and application. These include Harmony (harmonisation of antibiotic resistance measurements), Food-PCR (standardisation of PCR for detection of food-borne pathogens) and PlantNet. There is an active international effort to develop and validate alternative methods of testing which minimise the use of animals, through the ‘three Rs’ of reduction, refinement and replacement. The UK effort is led by the **Fund for the Replacement of Animals in Medical Experiments [FRAME]** at the University of Nottingham, which is well-connected to the ECVAM programme at ISPRA.

CEN, acting on a mandate from the Commission, has developed some 50 standards related to biosafety issues in biotechnology [listed below]. After extensive review by Member States, publication has been approved and their issue by BSI as national standards is almost complete. Their full implementation, in important respects, depends upon supplementary measurement research to allow quantitative data to be obtained. This will ensure that safety requirements imposed by regulators are achieved and that the public is reassured that safe practices are used within the biotechnology industry.

There is also relevant CEN activity in standards for the analysis of GM food [TC275 WG11] and in the uncertainty of measurement [BT/WG 122]

CEN Standards in Biotechnology
Containment levels of microbiology laboratories, areas of risk, localities and physical safety requirements
Guidance for handling, inactivating and testing of waste
Guidance for good practice for biotechnology laboratory operations
Guidance for the containment of animals in experiments
Guidance for the containment of plants in experiments
Guidance on the selection of the equipment needed for microbiological laboratories according to the degree of hazard
Microorganisms - Further examination of organisms in support of the classification work carried out under Directive 90/679/EEC
Microorganisms - Examination of the various existing lists of plant pathogens and production of a report
Microorganisms - Examination of the various existing lists of animal pathogens and production of a report
Microorganisms - Report on the criteria used to classify group 1 genetically modified microorganisms
Plant Building according to the degree of hazard
Equipment implementation according to the degree of hazard.
General requirement for management and organisation for strain conservation procedures
Control procedures for raw materials
Personnel: guidance for good practice, procedures and control
Procedures for fermentation and downstream processes
Guidance for the handling, inactivation and testing of waste
Guidance for the characterisation of GMO by analysis of the genomic modification
Guidance for the characterisation of GMO by analysis of functional expression of the genomic modification
Guidance for the characterisation of GMO by analysis of molecular stability of the genomic modification
Guidance for sampling strategies for deliberate releases of genetically modified plants
Guidance for sampling strategies for deliberate releases of genetically modified microorganisms, including viruses
Guidance for monitoring strategies for deliberate releases of genetically modified plants
Guidance for monitoring strategies for deliberate releases of genetically modified microorganisms, including viruses
Guidance on assessment of purity, biological activity and stability of microorganism-based products
Guidance on quality control of diagnostic kits used in agriculture, plant and animal pest and disease controls and environmental contaminations
Guidance on sampling and inoculation procedures
Guidance on testing procedures for cleanability
Guidance on testing procedures for sterilisability
Guidance on testing procedures for leaktightness
Performance criteria for autoclaves
Performance criteria for pumps
Performance criteria for shaft seals
Performance criteria for microbiological safety cabinets
Performance criteria for centrifuges
Performance criteria for cell disruptors

Performance criteria for piping and instrumentation
Part 1- general performance criteria
Part 2 - Couplings
Part 3 - Sampling and inoculation devices
Part 4 - Tubes and pipes
Part 5 - Valves
Part 6 - Equipment probes
Performance criteria for filter element and filtration equipment
Performance criteria for off-gas systems
Performance criteria for vessels
Part 1 - General performance criteria
Part 2 - Pressure protection devices
Part 3 - Glass pressure vessels
Part 4 - Bioreactors
Part 5 - Kill tanks
Part 6 - Chromatography columns

A4.4 International Biometrology Infrastructure

The international community in metrology acknowledges the importance of addressing biotechnology, but few of the National Measurement Institutes central in the community are expert in the biosciences. LGC took the lead in 2000 in initiating debate at the CCQM on an international infrastructure for biomeasurement. A Task Group was set up, led jointly by LGC and NIST, and a Biotechnology Working Group will be formed, following further discussion of the nature of biomeasurement and the appropriate activity in an international programme. Identification and quantitation of nucleic acid and protein are *prima facie* candidates for priority action. Fluorescence - used widely to signal biological recognition in complex systems - has emerged as one candidate topic where improved traceability in terms of physical metrology would bring benefit. The international debate will have to address how a concept of achieving measurement comparability through traceability to SI units can find useful application in a field where:

- measurement entails identification as well as quantification,
- complex, high-throughput, multiparameter measurements are common,
- biological activity must be quantified
- there are competing technology platforms.

The UK's leading role in these debates has value for our scientific reputation and for influencing international developments, which will, in the longer term, impact upon regulation and competitiveness. It needs to be sustained through appropriate activities in the Measurements for Biotechnology programme.

A4.5 Knowledge Transfer Infrastructure

Knowledge transfer in biotechnology is facilitated by several initiatives. **Biowise** seeks to encourage companies in traditional sectors of process industry to adopt biotechnological approaches, through providing information and supporting demonstrator projects. The main focus has been environmental applications and biocatalysis. Measurement matters for Biowise in strengthening the supplier base for the wider take-up of biotechnology, in increasing the confidence of potential adopters of biotechnology and in underpinning the regulation that helps to drive take-up. The treatment of contaminated land is expected to feature strongly in the programme, but user confidence is weak in the measurement of ecotoxicity through cell-based systems. Reference samples of candidate materials for biological clean-up [soil, metal surfaces] would help Biowise. The **Biotechnology Mentoring Initiative** fosters early-stage SMEs in incubators associated with science-base centres. The incubators could provide a focus and opportunity to encourage these early commercial developments to adopt measurement approaches likely to command the confidence of large companies and regulators. **Biotechnology Exploitation Platforms** seek to establish portfolios of exploitable intellectual property from the work of science base centres; again, their foundation in widely acceptable measurement approaches would enhance their prospects. The **Diagnostics Club** pulls together a wide range of interests in bioscience-based measurement, and could provide a valuable support for knowledge transfer from the Measurements for Biotechnology programme. The **Bioindustry Association** has a wide membership – extended recently when the independent Scottish association agreed to merge with the BIA – and effective web-based means of disseminating information to them. The **Regional Biotechnology Clusters**, too, offer a conduit for knowledge transfer to SMEs. Knowledge transfer from the DNA projects in the **VAM programme** is facilitated through SME networks and by a ‘biomeasurement’ webpage, with links to the BIA and ABPI.

A4.6 Scientific Institutes

A dispersed clutch of scientific institutes is engaged in Government programmes relevant to Measurement for Biotechnology, mostly concerned with Government’s responsibility for sectoral regulation. The National Biological Standards Board, a Non-Departmental Public Body of DoH, manages the **National Institute for Biological Standards and Control [NIBSC]**. Its purpose is to safeguard and enhance public health through the standardisation and control of biologicals used in medicine. NIBSC produces most of the WHO standards. NIBSC is separate from the regulator [MCA], whose work it underpins. NIBSC has a strongly ‘public service’ ethos, and has concentrated mainly upon vaccines [50%] and blood products [15%].

DoH funding for NIBSC has been frozen for five years, with damaging consequences for meeting needs for updated instrumentation, more space, additional animal facilities, improved security and more staff. DoH has paid half the cost of a new £15m production facility for RMs [aseptic processing, handling infectious materials]. NIBSC has ambitions for an enhanced and central role in regulation of genetic testing, standardisation of genetic marker testing; safety of vectors in gene therapy; adventitious viruses in cell therapy; bioinformatics for DNA and proteomic arrays; reduced animal testing, especially in vaccine evaluation. NIBSC’s most relevant current expertise is in the physico-chemical characterisation of vaccines

The **Centre for Applied Microbiology and Research [CAMR]** is part of the Microbiological Research Authority, reporting to DoH. The Authority was established in 1994 to conduct research in microbiological hazards associated with healthcare and to develop and manufacture diagnostic, prophylactic and therapeutic products. There is a close relation with **DERA Porton**.

About half of CAMR's turnover [£19m] comes from Government customers [36% DoH, 5% MoD] and half from commercial customers, including technology licensing and contract manufacturing by fermentation. CAMR's experience in fermentation technology to GMP could be relevant to the process control theme of the Measurement for Biotechnology programme. DERA Porton has innovative technology in the identification of viruses by mass spectrometry.

The MAFF and FSA programmes relevant to biotechnology are concentrated at the **Central Science Laboratory [CSL]**, with interests broadly in agriculture and horticulture [pest management and disease], the environment [alien species, dioxins, pesticides] and food [authenticity, safety]. CSL manages far-reaching proficiency testing schemes for MAFF [a Food Analysis Performance Assessment Scheme (FAPAS), in which 200 UK laboratories participate, and a microbiological Food Examination Performance Assessment Scheme (FEPAS)]. DETR is the customer for CSL programmes in the risk assessment of GMOs and for the inspection of GM crop trials [pollen flow]. CSL has developed a systematic approach to testing for adventitious GM material in seeds etc. Some 11% of CSL's turnover [£33m] comes from the private sector; MAFF supplies some 76%, divided equally between R&D and non-R&D.

The **Forensic Science Service [FSS]** acts as custodian of the National DNA Database, and remains the principal supplier of the Short Tandem Repeat [STR] profiles to it. The Home Office funds a substantial FSS programme of R&D to improve DNA measurement technology for collecting the profiles, through quantitation, automation and miniaturisation.

The **Laboratory of the Government Chemist [LGC]** has led in the development of the chemical measurement system, and has built upon experience gained in managing DTI's biotechnology programme to establish a strong presence in nucleic acid measurement and, more recently in the mass spectrometry of biomolecules. LGC supplies analytical services across the range of sectors impacted by biotechnology, and is a leading supplier of reference materials for those sectors. LGC leads in the VAM programme, many of the aspects of which are centrally relevant to the development of a biotechnology measurement infrastructure.

The **National Physical Laboratory [NPL]** has limited direct experience of biotechnology, but represents a valuable technology resource [nanotechnology, single molecule detection, software validation, optical measurement and mass spectrometry] capable of underpinning significant parts of a Measurements for Biotechnology programme.

AEA Technology majors in bioprocess development and fermentation, including contract manufacture of biological products. There are also services in antisense technology, automated systems for drug delivery, inhalation toxicology and orthopaedic testing.

The BBSRC and MRC institutes, and some 200 university departments comprise the **academic science base** for biotechnology. BBSRC funds 8 strategic research centres (including Babraham Institute; Roslin Institute; Institute of Food Research; John Innes Centre and Silsoe Research Institute), and 6 structural biology centres of excellence. The structural biology centres were set up to remove the need for every research institution in the UK to install the costly equipment necessary for cutting edge structural biology, by providing a national resource that gives access to state-of-the-art equipment and the highest quality expertise. Thus the Centre for Protein and Membrane Structure and Dynamics focuses on using synchrotron radiation for circular dichroism; and the North of England Structural Biology Centre focuses on x-ray and electron diffraction, and NMR. MRC funds over 50 units, most of which are based on or near university campuses or hospitals. Many of these units provide a national focus of expertise in a particular area of science. In addition to these units, the MRC funds 3 institutes: the National Institute for Medical Research in London; the Laboratory of Molecular Biology in Cambridge; and the

Clinical Science Centre in London. The EPSRC leads in a 'bioscience interface' initiative with BBSRC, including a 'Metrology for the Lifesciences' programme, which interprets the term metrology to mean innovation in measurement.

The broad policy interest in biotechnology as a source of wealth creation through innovation has led to relatively generous funding for this community. Many, encouraged by innovation policy and programme support [LINK, Foresight challenge, Faraday] have close contact with industry, and much of the research has a strong measurement relevance. Indeed some programmes [Analytical Biotechnology, Lab-on-a-Chip] focus explicitly on measurement. The 'Measurements for Biotechnology' programme needs to keep close contact with that work. Moreover, there is the question of the quality of the measurement work that underpins science base research across the biosciences. The Research Councils should be encouraged to foster attention to questions of metrology throughout their portfolios.

ANNEX 5: Measurement Advisory Committee Working Group

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Measurements for Biotechnology Programme & Quality of Life

Biotechnology plays an important role in the improvement of quality of life. We demand better health, better living conditions, confidence in our food and trust in the effect of medicines –developments in biotechnology are core to helping industry and public services meet these demands.

Scientists and biotechnology companies need to verify and demonstrate the quality of their products and services. To do this the UK is developing an independent, internationally recognised measurement infrastructure that provides for facilities, standards and sector-specific expertise.

The Measurement for Biotechnology programme which will be procured later this year is likely to include a range of development projects including:

- a) standardisation and verification of cell-based testing to help minimise animal testing;
- b) improving methods for trace detection and quantification of biological contaminants, such as GMOs in food;
- c) verification of the performance of environmental monitoring devices;
- d) development of a database to help anticipate the toxicity and performance of new drug combinations.

DTI/NMSD

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