Advice and Training

KT2/4a

December 2006
LGC/MfB/2006/022

Setting standards
in analytical science

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_____17th January 2007_____

The work described in this report was supported under contract with the Department of Trade and Industry as part of the National Measurements System for the Measurements for Biotechnology Programme
Milestone Reference: KT2/4a

Measurements for Biotechnology

Contents

1. Summary

The Measurements for Biotechnology (MfB) Programme aims to develop tools and awareness of best measurement practice in the biopharmaceutical and biotechnology sectors, where better measurement will mean more efficient discovery and development of products and services, more certain control of biopharmaceutical product production and better communication with regulators. This document reports on the outcome of a study on the impact of poor measurement practice on the success of exploitation of research in start-up companies in the UK.

36 experts with deep knowledge of start-up companies and their creation, funding and development were interviewed to identify case studies of company success or failure arising from technical issues. This was supplemented by literature and database information on companies and their progression and funding.

We found that failure of biotechnology start-ups at or soon after foundation for scientific or technical reasons is rare. Only a small percentage fail for technical reasons before they start product development stage, which is often some years after company creation and initial funding. Of those that do fail before product development, some were founded, and investment made, on results which subsequently could not be repeated or developed.

By contrast, failure in the early stages of product development is common. This rarely leads to complete company failure, although it can do so, but it does lead to the need for substantial rework and consequent added cost. Up to 20% of the company's total investment can be spent on such rework. This happens mainly because early research did not conform to best practice, and particularly because samples of key materials were not retained for later reference. Consequently, the rework and its cost is entirely avoidable. Respondents to this study suggested that at least 50% of biotechnology companies would be delayed or incur extra cost due to problems of this sort.

Despite this risk of unexpected and unnecessary costs due to rework at development stage, investors in early stage companies rarely do the due diligence which would identify the potential for such costs. Due diligence studies are confined to reputational aspects of the founding science and to reviews of summaries of results.

Companies that avoid technical failure and setbacks do so by early investment in best practice. The adoption of best practice early in the company's history, and in the research that precedes commercialisation, is almost always the result of the founder scientist's early exposure to best practice in a commercial or clinical trials environment.

A significant factor in the high incidence of failure at development stage is that scientists at all levels, both in research and development organisations and in technology transfer and investment, have a very limited understanding of the nature and the value of best practice in measurement and laboratory conduct.

This report recommends that material for training students and academic researchers in best practice and why it is important be created. This should be focused on the practical implications of measurement practice in academic and commercial research and product development, and should include understanding of the relationship between best practice and regulation, and the cost of poor practice.

The same material should be actively promulgated to the technology transfer and investment community to raise their awareness of these issues.

This report also recommends development of a simple, non-onerous 'quality measure' of best measurement practice which could be obtained by research laboratories in academia and industry. We recommend that grant agencies, technology transfer offices and investors encourage the creation of such as mark as a simple and transparent way of identifying research groups that are pursuing best practice.

2. Introduction

2.1 The MfB Programme

Measurement is a central part of any science-based research, development and product regulation programme. Accurate, reliable and transferable measurement has been a major asset to the development and dissemination of new technology in the physical, chemical and engineering sciences. The Measurements for Biotechnology (MfB) Programme aims to extend this success to the biopharmaceutical and biotechnology sectors.

The measurement solutions developed will apply throughout the bioindustry, healthcare, the food chain and the environment – thereby improving the use of bioanalytical measurement for wider social benefit.

The programme breaks new ground for DTI's National Measurement System, which works towards a consistent and internationally recognised basis for all measurement in the UK. The programme aims to:

- improve the accuracy and reliability of biomeasurements important for industry;
- strengthen the measurement science underpinning the regulatory regime for biotechnology;
- ensure that the UK biomeasurement system is co-ordinated and developed in harmony with those of other countries;
- undertake research and development to support the provision of reference standards and generic guidance for technologies and processes carried out in the UK.

An important component of this MfB programme is the effective transfer of technology and knowledge about good measurement practice and systems and their importance to those carrying out biological measurement in UK industry.

2.2 Knowledge Transfer

The aims and objectives of this knowledge transfer project within the programme are to:

- increase attention to, and understanding of, how measurement quality can enhance innovation and competitiveness;
- develop and provide materials to disseminate the message of measurement quality in research training;
- pilot a training course in valid analysis, following a feasibility study of which this report forms the basis.

3. Background

3.1 Good Measurement Practice

3.1.1 What is meant by measurement?

All measurements whether qualitative or quantitative have to be fit for purpose and be sufficiently robust so that they can be reproduced with confidence by any person in any place. This entails matching the level of confidence to the criticality of the measurement. Quantitative measurements are normally made whereby an unknown product is compared to a known standard. Where no such standard is available then the measurement process itself has to be controlled.

3.1.2 VAM principles

Some years ago an interdisciplinary group of measurement scientists suggested the six principles of valid analytical measurement. These principles have much in common with the international standard ISO/IEC 17025 [1] which is used to assess the competence of laboratories and ISO 15189 [2] which is used to assess the competence of medicinal laboratories. These have subsequently been widely adopted, and are given below.

1. Analytical measurements should be made to satisfy an agreed requirement.

   What does the customer want to know?

2. Analytical measurements should be made using methods and equipment which have been tested to ensure they are fit for purpose.

   Make sure everything works as it should and that the method used is capable of providing a useable result.

3. Staff making analytical measurements should be both qualified and competent to undertake the task.

   Staff should be trained to use relevant equipment competently.

4. There should be a regular and independent assessment of the technical performance of a laboratory.

   Take part in External Quality Assessment, formally through Proficiency Testing schemes and informally by taking part in intercomparison studies.

5. Analytical measurements made in one location should be consistent with those made elsewhere.

   Use Reference Materials so that your scale of measurement is acceptable at a national and international level.

6. Organisations making analytical measurements should have well defined Quality Control and Quality Assurance procedures.

   Implement a quality management system or at least the elements of such a system.

The MfB programme is concerned with furthering these principles into all areas of biological measurement, and particularly in the areas of:

- gene measurement;
- protein measurement;
- cell-based technology;
- product characterisation;

as applied to biopharmaceutical manufacture, drug discovery, diagnosis and health technologies (medical devices).

3.2 Quality Assurance

The MfB programme focuses on a research-oriented measurement community, targeting mainly the science base and research users of biomeasurement techniques. University researchers rely on peer review as their guarantee of quality and may be less familiar with quality procedures adopted by industry, where adherence to measurement quality methods and standards is used as a more transparent approach to achieving the same goals as peer review. An initiative (revised April 2003) has been lead by the Department for Environment, Food and Rural Affairs (DEFRA) to formalise requirements for academic laboratories to demonstrate the quality of their research by improving their research processes. This is distinct from the quality of the science, although to some extent they are linked. The code is endorsed by the Biotechnology and Biological Sciences Research council (BBSRC) and the Food Standards Agency (FSA) among others. Details for the code can be found at the DEFRA web site [3]. Further guidelines concerning measurement quality are available in FDA guidance documents [4] and in ICH guidelines [5]; where industrial researchers are expected to have used robust techniques in assessing their biological methodologies.

There are a number of possible consequences in not having a quality assurance system, which all lead to reduced confidence in the data produced. Apart from the wastefulness of poor measurement, the undervaluing of measurement quality has specific damaging effects. These may include potential lack of control over processes and procedures, inconsistency of analytical approach, lack of measurement and process traceability (trackability) and, ineffective risk management, leaving a company open to legal challenge regarding the quality of their results. In the absence of nationally or internationally recognised third party confirmation of a laboratory's quality status, additional effort has to be made to provide the internal checks and balances that can demonstrate the quality of the work carried out.

There are other potentially damaging effects which merit mention. First, the excitement of the 'rush to application' of novel biomeasurement techniques often diverts attention from the requirement for validation of the new methods based on these techniques: application is therefore based on poor practice, and could have a high failure rate as a consequence. Second, research students are sometimes poorly prepared for the world of employment in which measurement quality will be of increasing importance. This is to the detriment of the students and of the institution that trained them and the industry that employs them. Thirdly, the opportunity is missed to engender more confidence among companies in the technology that academic researchers seek to transfer to them. Countering those tendencies is clearly consistent with the MfB mission. It may also shed light on the reasons for some start-up enterprises failing and others are taking longer than anticipated to fully develop.

In addition, earlier research [6, 7] indicates concern about the skills gaps that exist and the training needs of biopharmaceutical sciences. We have found that the skills gaps are nebulous but there is much commonality across the sectors. Basic laboratory skills feature prominently along with the soft skills, e.g. management skills.

3.3 Importance of Links between Academic and Industrial Sectors

Biotechnology is not a 'theoretical' science. It is concerned with uncovering the nature of living things and seeking ways by which that knowledge can be put to use, often through developing products or processes based on research [8].

Discoveries about fundamental aspects of life processes are often made in an academic setting. However, application of discoveries in biotechnology is usually carried out in an industrial setting. This close link between academic research and industry facilitates transfer of intellectual property, skills, staff and materials.

Additionally, funding for basic and applied research often comes from industry supporting pre-competitive research in academia. Understanding by both parties of the processes and requirements of both sides facilitates successful outcomes of such arrangements. It ensures that the expectations of both parties are aligned in terms of the method and the outcome. An increasingly common mechanism to achieve this is to create a new company that aims to realise the commercial potential of a specific piece of research.

3.4 The Nature of the 'Start-up Company'

A new company created to develop and commercialise a new product or service is often called a 'new start-up company', or 'start-up' for short. A 'start-up' is a new venture, creating new business where none existed before and usually, in the biotechnology industry, creating that business around a new product or service that they intend to create through research and development.

Where does a start-up get its staff, intellectual property (IP) and other assets from? It may acquire them from a variety of external sources, or it may create them for itself. In the case where key IP assets come from just one institution, the start-up company is often called a 'spin-out' of that institution. Typically, a spin-out is created to exploit a specific piece of IP or business and so, at its creation is endowed with that piece of IP together with other knowledge, materials or equipment related to that knowledge, and often some of the staff that created it. Academic research has been used as the intellectual basis of many new start-up companies in this way over the past decade, and as a result 'spin-out' and 'start-up' are often used as synonyms, and all new companies developing innovative products based on research are called 'spin-outs' [9]. However, as illustrated in Figure 1, not all start-ups are spin-outs. Figure 1 shows the origins of 113 UK-based SMEs identified as 'biotechnology' companies in the Cambridge (UK) area, by Cambridge University's Cambridge Enterprise office [10]. These have been categorised into three classes according to their origins. University spin-outs are companies that were initially created substantially around academic research and staff. Industrial spin-outs are created around IP, staff, infrastructure or other assets from a single company. Stand-alone start-ups are created from assets from several sources, with no one source dominating. In this report we will use the more accurate term 'start-up' for a new company created to build new business from innovative science and technology.

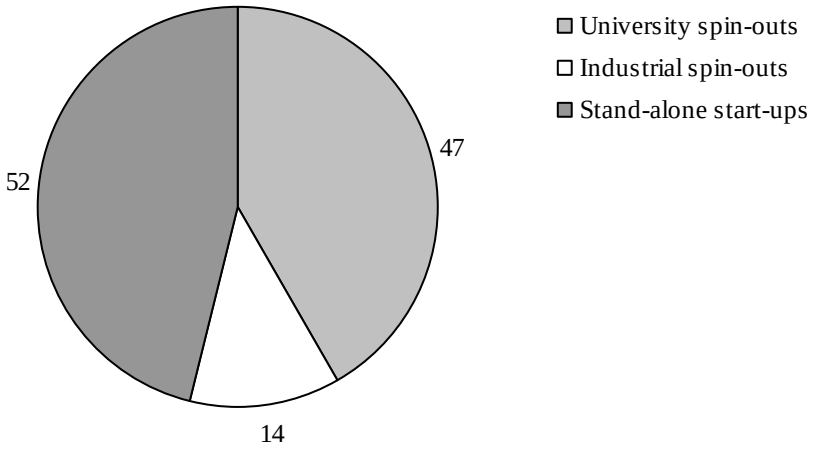

Figure 1: Origins of start-ups and spin-outs in Cambridge, UK.

Over the past decade, academic institutions have been encouraged to form spin-out companies and some researchers have seen this as a desirable activity. Start-up companies typically go through several phases of activity as they grow and mature, and their concerns for measurement, and for scientific activity in general, alter with these phases. There is a continuum of activity in the evolution and growth of any company, but broadly they may be categorised as follows:

- *Company creation*. This is when the corporate vehicle is created and initial finance raised for its operations;
- *Research.* This is when the company transfers the research on which it was founded into the company, and extends it on more directly applied lines;
- *Development.* This is when the research programmes are converted to product development programmes, aimed at a specific product opportunity, with the associated testing. For many biotechnology start-ups this involves medical therapeutic products and therefore the testing is clinical testing of those products;
- *Commercialisation*. This is the final phase when the company starts to sell its product and generate profit.

Different types of organisations and of funding resources are called on for each stage. These are summarised briefly in Table 1. Proof of Concept (PoC) funds and University Challenge Funds (UCFs) are both seed-stage investment funds. The PoC funds were created by RDAs to assist early demonstration of a concept in an applied research and development programme. The UCFs from central government intervention were introduced to achieve the same aim.

A more detailed review of the company formation process outlined in Table 1 is provided by Deakins [11] and of the process of Venture Capital (VC) investing by Mason et al [12]. The sources of funding vary substantially as fashion dictates which types of investors are willing to invest in which types of companies.

The MfB programme covers all aspects of life science research and its application. However, public perception of biotechnology often focuses on start-up companies that are researching and developing new therapeutics for human healthcare. This bias is reflected in, and to a large extent caused by, investment patterns in the industry. Venture Capital (VC) investors in Europe invest almost entirely in companies pursuing new medicines. Other types of company, such as those developing new diagnostics [13] or fine chemicals [9] are very unattractive to such investors, despite their apparently greater chances of commercial and technical success. Drug discovery is attractive to investors because the investment is large and the exit routes are well defined and timely. The practical outcome is that any sample of biotechnology start-ups

is likely to have a substantial fraction of drug discovery companies in it, and that these companies will be better known than companies pursuing other business models.

Table 1. Typical development stages for a start-up company.

Development stages	*Activity*	*Typical background of scientists*	*Type of funds*	*Level of commercial funds*	*Source of funds **
Company creation (legal entity)	Technology transfer / licensing	Academic	Seed	£10k - £100k	RDA PoC funds, UCFs etc.
Research	Research	Mixed academic and industrial research	'Risk capital'	£500k - £5M	Business Angels, Early stage Venture Capital (VC)
Development	Product development	Industrial R&D	'Development capital'	£1M - £50M	Development VC, public stock markets
Commercialisation	Market development	Industrial R&D	'Working capital'	£0 - £100M	Public stock markets

* RDA – Regional Development Agencies. PoC –Proof of Concept Funds, UCF – University Challenge Funds

Companies require new investment at several stages of their development. Investment in such companies carries substantial risk and a substantial fraction of companies fail to achieve the growth that investors seek. There are several components to the risks associated with a start-up, namely:

i. the science might fail to achieve its promise, either because the hypothesis on which it is based is flawed or because the experiments to take it forward are poorly designed or executed;

ii. the science and technology will be successful, but the market will not buy what it has produced;

iii. the business proposition on which the company was created was flawed;

iv. the company does not receive enough capital to conduct its product and market development effectively.

The business research literature suggests that lack of sufficient capital is the most common reason for the failure of start-up companies [14]. This may be because the investors did not provide sufficient funds to take the company to its next stage of development [15], or because the development takes longer or costs more than expected. Failure to provide sufficient funds is an issue easily addressed by investors. The other reasons are less easy to control, and so investors make substantial efforts to minimise the chance that risks (i) to (iii) might occur, by carrying out extensive studies of the company and its operations before they invest, the process is called a 'Due Diligence study', or Due Diligence for short.

In a Due Diligence study, an investor will investigate all aspects of a company's structure and operations. Some typical subjects of Due Diligence are:

- the scientific results and knowledge that are the foundation on which the company plans to build its products. This is usually studied through analysis of scientific papers, books and proceedings, and an independent review of the specific science of the company, often performed by an external expert who is employed by the investor;
- the reputation of the scientists that created the science or technology, as evaluated by interviews with their colleagues and contemporaries, their publications, grants, and formal professional recognition such as learned society membership and journal editorial boards;
- the intellectual property position, usually an analysis of the company's patents in light of other published information and patent databases;
- the market for the product, estimated from market reports, analysis of the company's own data, and the technical analysis of the product's likely performance;
- the costs and time needed to get to a commercial product, which is usually a critique of the company's own plans by an expert in product development;
- the background and experience of the management team, as judged by their CVs, references and part record of successfully returning profits to investors.

Thus at each stage of the company's development, investors will be evaluating the company's science and technology. Because investors rarely have the expertise themselves to evaluate the specifics of a company's operations and science, they will employ external advisors with that expertise as part of the due diligence process. This could include experts in laboratory practice, measurement methodology, and the methodological and statistical reliability of results: however, as we shall see, it usually does not.

In addition, regulators will be evaluating the quality of the research and development behind any product that is being put into public testing (such as clinical trials or field trials), and that is being launched. These evaluations are substantial milestones on the company's path to maturity and acceptance. Failure to satisfy regulators or investors of the value of their R&D is a major immediate cause of failure of many companies. Unlike investors, regulators do examine the details of methodology and the statistical reliability of primary research results as well as the broader scientific validity of a product before allowing it to be tested in humans or used in medical practice.

3.5 The Funding Environment for Start-up Companies

In the mid 1990s it was common for institutional investment companies (called 'Venture Capital' (VC)) to fund the early stages of company development as described in section 3.4. Funds raised on the public stock markets were used to fund later, more expensive stages. Since 2001 this has changed substantially and many VCs are now unwilling to invest in companies that have not progressed to the product development stage of their evolution. For companies developing new drugs, this means they cannot attract investment until they are testing a product in clinical trials. In the case of diagnostics or companies producing reagents they cannot attract investment until they have at least partly developed products and some early sales [16-19]. There remain a few early stage VC investors who will put small amounts of money into start-up companies before this stage, and Business Angels (personal investors who put their own money into companies) continue to support strongly this part of the company development process [20].

This has implications for the type of due diligence that investors might be doing, which we will discuss in section 6.1.3.

3.6 Collaboration between Companies and Academia

If a start-up company has few resources, a way to obtain high value research is to collaborate with another company or with an academic institution in a joint research programme [21]. Such programmes usually involve transfer of academic intellectual property from the academic institution to the company, joint research to develop the IP and the science or technology that it protects, and remuneration to the collaborator(s) if the programme is successful in terms of fees, success payments and royalties on eventual sales of product.

The legal structure of such collaboration is a contract for research and IP sale, and so it is quite different from a start-up company. However, the objective is very similar: to transfer knowledge from a junior partner, often an academic institution, into a company, and to exploit it there. The potential problems are also very similar: the project may fail to be a success because the science fails to achieve its promise, the market will not buy what is produced, the business proposition for the product of the collaboration is flawed, or the collaborative research is insufficiently resourced. In parallel with investment in a start-up company noted in section 3.4, investment of resources is under the control of the collaborating company. However other reasons for failure are not under the control of the investors, and so are carefully studied by companies that are considering any collaborative arrangement in a 'due diligence' study to identify and minimise future problems.

4. Rationale for the Study

Biotechnology start-ups are a significant component of the mechanism for transferring technology from academic research to commercial exploitation. At several stages along this process the value of the science and technology being transferred is tested through external examination.

Measurement quality is a central component of this. Previously published reports do not identify the specific skills gaps and do not deal specifically with measurements for biotechnology that affect the creation and subsequent success of start-up companies. Consequently, it was agreed that more research is required to:

- investigate the failures in biotechnology start-ups;
- examine if the issue of measurement is a significant factor in the success of start-up companies, and hence of successful translation of the products of the UK's research base into practical benefit for the UK;
- examine which improvements in measurement are most likely to provide most reward, including improvements in awareness and training of the scientists involved.

5. Design of the Study and Selection of Interviewees

The study contacted a sample of experts in the field of research commercialisation given the impracticality for a comprehensive analysis of all successful biotech companies (about 450 companies in the UK [22]). This study therefore chose to analyse a representative sample of cases through interview with experienced practitioners in the field. The target was 5% of successful biotech companies, but 36 interviewees (~ 8%) eventually were selected for their direct, personal experience of biotechnology start-up companies as founders, senior executives or Board members. Selection was made on the basis of interviewees' extensive knowledge of the area and their willingness to communicate openly about problems as well as successes. The biotechnology industry in the UK is highly clustered, with the majority of more mature companies based in London, Cambridge or Oxford: however a deliberate attempt was made to involve companies from outside these clusters to minimise potential for similar experiences based on location or background.

The experts were selected to cover:

- academics involved in research application;
- start-up company executives and Board members (some of whom were or still are academics);
- technology transfer executives in universities;
- investors active in investing in start-up companies, i.e. with direct experience of start-up companies.

The investors contacted are not typical of 'the biotech investment community', which covers all investor types from those willing to back very early stage companies to those that invest in established companies. Only those involved with investing in the earliest stages of a company's life history were contacted for this survey. The way that investors identify and evaluate investments depends on the nature of the investments they are seeking. Investors seeking to invest in early-stage companies are familiar with evaluating early stage projects and companies soon after formation, rather than established companies, and consequently have quite different evaluation mechanisms and criteria from the majority of VCs. These investors (and their investment criteria) are the ones relevant to the early stage companies examined in this report

The principal role of the interviewees is summarised in Figure 2, for those involved in founding companies, this includes their current employment (if any) as well as their role as a founder. Four classes of executive were contacted: academic founders of start-up companies, academics who were not company founders (as the focus of the study was on start-up companies there was only one person in this category), company founders who were not academics, and executives or directors who spoke about companies they had joined after foundation. In addition, we interviewed investors and technology transfer professionals involved in start-up company creation, and two others with insights into the field: one patent agent with extensive experience of working with start-ups and one research council executive. Between them the 36 interviewees had personal executive-level or board-level knowledge of 59 companies. They were for the most part experienced entrepreneurs and investors, and so had indirect knowledge of many more companies.

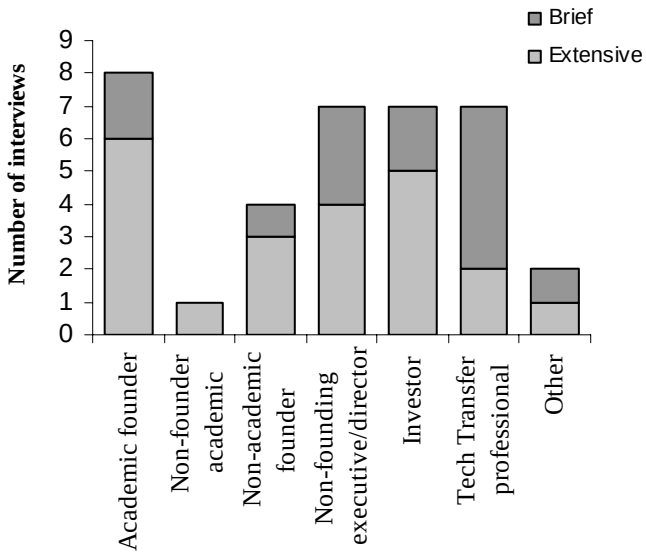

Figure 2: Role of interviewees.

The project was aimed specifically at evaluating the issues of company failure. To that end we asked all the early responders for suggestions of case studies of technical failure in companies. Several interviewees essentially provided lists of potential cases of early, start-up failure (which was the initial focus of this study). Three examples were identified by more than one respondent, and one (Case Study III) was identified by three. This suggests that this study has identified a significant fraction of the high-profile cases of early technical failure in UK biotechnology. The project followed up all these suggestions, and identified 29 start-up companies which were exemplars of success or failure resulting from measurement practice. As noted in section 3.6, collaborative research between companies and academia is a substantial route for IP transfer. 6 collaborative research programmes between academic institutions and start-ups were also analysed in detail. This makes a total of 35 cases of transfer of knowledge, expertise and ideas, usually accompanied by IP and skilled staff, from academic research into start-up companies.

Figure 3 shows the MfB topics addressed by the cases analysed in this report. The 'product characterisation' cases are shown split into cell, gene and protein products, and 'other' products being characterised by biotechnological means. Note that some companies conduct measurement in more than one area of interest to MfB. Over one third of the companies were involved in protein product development, and so embraced both the 'protein measurement' and 'product characterisation' categories of MfB activity.

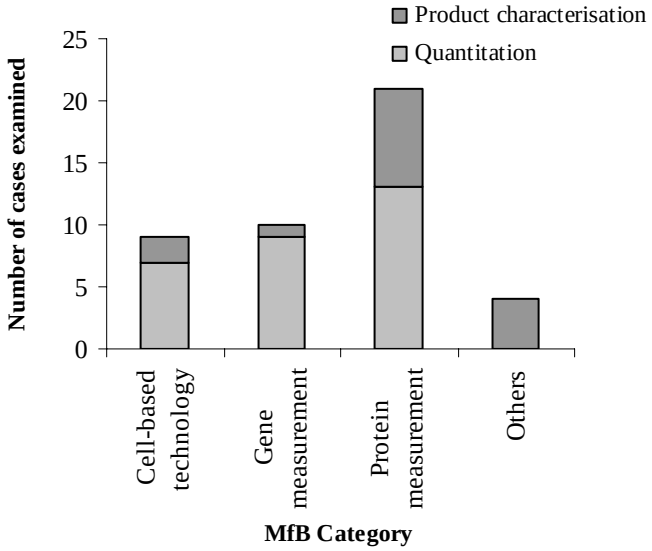

Figure 3: Topic coverage of cases analysed.

Interviews were conducted in a structured format to cover a range of issues around the success of start-up companies and their science, the quality of measurement systems, and the need for training in measurement. The questionnaire used is provided in Appendix I.

6. Outcomes of the Study

This study provides a semi-quantitative view of the relevance of measurement standards and measurement training methods to the creation and development of start-up companies. The project identifies measurement and training issues and examples of good measurement practice and their link with scientific and commercial success. This section analyses the outcome on this in terms of those issues.

6.1 Method Validation and Reliability of Results

ISO/IEC 17025 defines validation of a method as 'the confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use are fulfilled' [1]. In other words the tests that are carried out to show the method is fit for purpose. This includes showing that it operates in an appropriate way under all the conditions under which it will be called upon to operate.

The extent of the effort required to validate a method will depend on the purpose of the measurement and the criticality of the result. However, some effort is always required. If a published method is going to be used for the first time in a laboratory then the process of validation is usually slightly different and is called verification. In this case, the laboratory needs to demonstrate it can achieve the published performance criteria. This is adequate so long as sufficient information is provided with the method to describe accurately what the performance criteria are, and how they were achieved, in the published description.

Validation of a new method to replace an existing validated method is normally achieved by carrying out a paired comparison. This involves splitting the sample so that one portion is analysed using the validated method and the other portion is analysed using the new method. If the results are not statistically significantly different then the new method can be considered to be validated. If the tests demonstrate that the new method's performance is superior, e.g. it may be more selective, then it will probably replace the original method. This will depend on whether the improvement is significant and the cost/time implications are acceptable. It could be that it is actually measuring a different measurand.

This study has found that the concept of 'method validation' was poorly understood and rarely implemented in the academic research that is the seed-corn of many start-up companies. This has practical implications for those companies in terms of subsequent technical failure, see section 6.2.

6.1.1 The rate and nature of technical failure in start-ups

'Failure' in a start-up company can mean that the company is not an obvious 'success', that it has to abandon a line of work and initiate another (either on the same product concept or a different one), wasting time and money, or that it is formally failed in the sense of becoming dormant or being closed down completely. In this study, we have taken 'failure' to mean that the majority of the effort and investment in the company did not result in any useful outcome, either in terms of securing further investment (from an equity investor or a corporate collaborator) or in terms of generating a product or service. This could be because of outright technical failure, or because research or development took so much longer to demonstrate success that the company ran out of money before this could happen.

Failure can occur for a number of reasons, which can be grouped in to 'commercial', 'financial' and 'technical'. Commercial reasons may be that a partner company on which they were relying themselves cease trading, the market conditions alter so as to render the company's product or service unwanted, competition renders their product 'redundant', or change in regulatory requirements renders their product unusable by its intended users without substantial further development. Financial reasons may be that the investment market ceases to be interested in investing in the industry sector (no matter how successful the company), that previous investor's policies make the company difficult to back for technical reasons, that the investors who had supported the company stop investing in that type of company for internal reasons, or that changes in financial regulation make investment less attractive.

Technical failure is usually the most visible cause of company failure. Companies such as British Biotechnology [23] and Scotia Holdings [24], and more recently Tegenero [25] have suffered collapse of their value and consequent disbanding of the majority of their operations

following high profile failure of products in clinical trials. However, it is important to distinguish between failure of this sort, where the original science was believed to be sound but did not achieve the outcome predicted of it in practice, and failure that was due to poor procedures and practices.

As mentioned in section 3.4, technical failure, may be because the hypothesis on which the science is based is flawed (failure of concept), the implementation of the science is not suitable for the commercial market for which it is intended (failure of prototype to achieve commercially valuable performance), or because the experiments to take it forward are poorly designed or executed (failure of process). The third of these reasons is the subject of this study.

Of the 29 companies and 6 collaborations analysed in detail in this study, the nature and cause of failure or success may be enumerated into these categories as shown in Figure 4.

Figure 4: Causes of failure among sampled companies.

Note that the data in Figure 4 do not imply a 68% failure rate among UK biotechnology companies overall. This survey contacted 36 people to ask specifically about examples of technical failure. Naturally, therefore, this lead us to interviewees who could provide in-depth discussions of failures, and these are over-represented in our sample compared to the industry as a whole.

6.1.2 Role of 'black box' science in failure

Several of the respondents commented that failure to follow good practice in research was due to what was commonly referred to as the 'black box' effect. Scientific instrumentation has become increasingly complex, sophisticated and costly. Procedures which once would have taken weeks of manual labour, such as DNA sequencing, can now be done entirely automatically in hours. Analytical tools such as HPLC and MS are packaged into systems with internal software that allows the user to simply programme their requirements in order to achieve a result. In parallel, reagents are pre-packaged into 'kits' which provide all the tools needed to perform complex molecular manipulations, which can work simply by following the 'recipe' provided.

There is no doubt that such tools allow scientific research to advance far faster than it would have done otherwise. Embedding the technical knowledge necessary to perform sophisticated procedures into apparently simple reagents and instruments themselves is part of the progress that allows many scientists to use the techniques developed by the few. However, there is a risk, felt strongly by some respondents, that users of such tools have no understanding of how these tools work, and hence of what their limitations might be. This was particularly true of reagent 'kits', which only operate reliably under very defined sets of conditions. Users are therefore not capable of identifying under what circumstances the results provided by their 'black box' might be wrong, and hence when those results are not reliable. Even such apparently simple devices as pH meters are only reliable under appropriate conditions (and, of course, if properly calibrated). Used outside those conditions the results are meaningless. These respondents felt that use of sophisticated tools was essential to scientific progress, and their development was worthwhile, but that their users should have a better understanding of what the basic principles behind them are, and hence when the tools are no longer applicable and the results cannot be relied upon.

6.1.3 The due diligence process

Suitable analysis of companies should enable potential investors to identify which companies or potential start-ups have failures of basic technical concept or technical execution, or failures of their commercial understanding, before start-up or before investment. This is the role of the due diligence process, discussed in section 3.4. However, surprisingly, the respondents to this study reported that very few investors carry out extensive due diligence on the quality of the execution of the science before investing.

It is expected that, out of a syndicate of investors in a company, only one or two 'lead investors' would do due diligence on the company, the others following their lead (reviews of the process by which VCs invest are provided in references [26, 27]). A very consistent view emerging from the interviews carried out in this study was that these lead investors satisfied themselves on the validity of the science by checking the reputation and standing of the founding scientists, reviewing top-level summaries of the science, and asking experts with experience, usually commercial experience, to review more detailed summaries and to interview the scientists rather than examining any of the data or the processes that generated them.

Although some interviewees claimed that this attitude was changing, and that investors today carried out reviews of the way that the science had been conducted, we found little evidence for this: interviewees who had recently gone through a due diligence investigation said that the same applied today. Only one investor interviewed claimed to examine the scientific data and the methods used to generate them when planning an investment in a start-up company. One investor was reported to finance essentially on the basis of a personal conviction that the entrepreneurial scientist had a good idea and was personally committed to it, although in this case the business opportunity had already generated revenue so this is not typical of a start-up.

We have characterised the level of scientific or technical due diligence carried out on start-up companies prior to their receipt of commercial investment at three levels:

- *Minimal* – due diligence is confined to taking references on the scientists involved, reading their papers and a summary report from the company;
- *Modest* – in addition to the 'Minimal' level, external experts are brought in to receive summary presentations on aspects of the science, and to interview key scientists;
- *Extensive* – in addition to 'Modest' level, investors or their agents view methods, SOPs, laboratory processes, and primary data reports.

Some of the interviewees offered opinions on their experience of the level of due diligence carried out in start-up companies and this is shown in Figure 5.

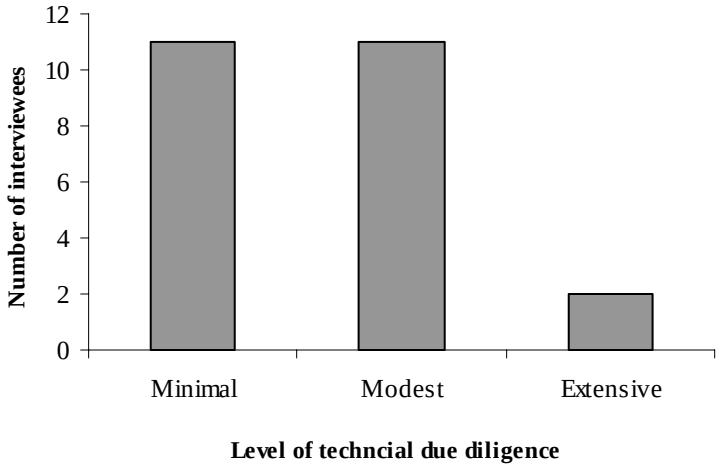

Figure 5: Level of technical due diligence.

As summarised in Figure 5, institutional investors in early stage companies – VCs – tend to use the 'Minimal' or 'Modest' level of due diligence. They very rarely carry out the 'Extensive' due diligence that is required to determine whether the processes used to create the science in which they are investing are robust. The generality of this attitude is confirmed by the history of a company specifically set up by a leading group of biotechnology academics to provide detailed scientific due diligence. Despite good contacts with the investment community, a world-class scientific reputation and substantial marketing effort over more than a year, the company did not attract a single paying customer for its service.

The situation is quite different when a company does due diligence on a technology it wishes to licence. Here much more extensive studies of the science, including the underlying raw data, is the norm, whether the technology is a well developed product or an early stage project. Even programmes which are still in the planning stage, for which no laboratory work has been started, are examined by potential industrial collaborators for the methods to be used, their robustness and their fitness for purpose.

6.1.4 Company failure

Part of the reason for the investment community's attitude to due diligence is that it is widely believed, by investors and others, that scientific failure is rare in biotech start-ups. This study confirmed this. We could identify only 4 companies where measurement aspects of the founding science were recognised to have caused subsequent company failure and two others where such problems became apparent before formal development work. Of 13 respondents who offered an opinion based on personal experience (out of the total of 36 interviewed), only 2 said that failure of the founding science was other than a rare occurrence.

Despite this, problems with the science, and specifically with the quality and nature of measurement systems underlying the science, were a relatively common stumbling block later in company's history. Of the 29 companies discussed in depth, 22 had experienced problems with the measurement quality and standards resulting in significant commercial set-backs and, as a result, 19 of these were categorised by the interviewees as 'failures' (Figure 4): the other three were not counted as 'failure' because, although delays and setbacks cost money and

wasted time, the companies survived to become commercial successes (see for example Case Study IV).

The reason for the apparent contradiction is that technical failure is rare (or rarely recognised) in start-up companies in their early stages, but common in later stages of the companies' growth and development. Figure 6, illustrates the stage of development of start-up companies at which technical failure, identified in the study, caused the company substantial delay or commercial failure.

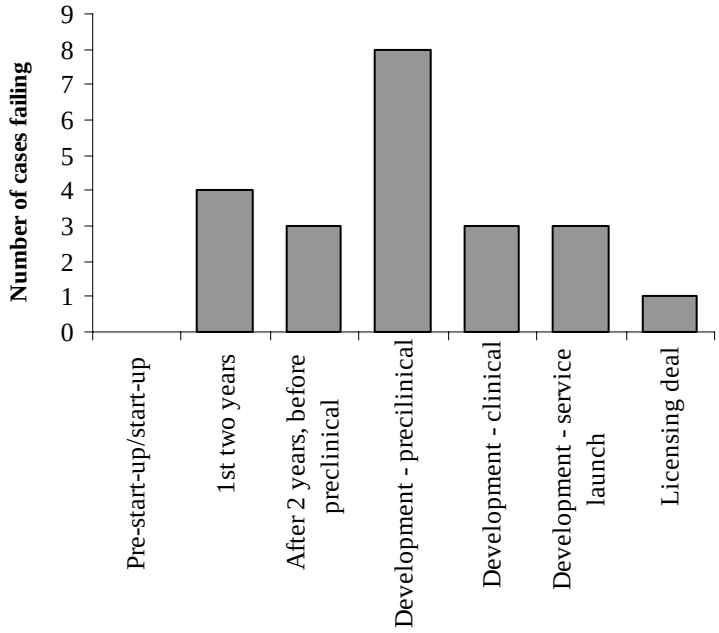

Figure 6. Stages when technical failure was recognised.

An important conclusion of this report is therefore that, while immediate and catastrophic failure of the founding science is rare, problems with the science often lead to problems for the companies at a later stage of their development.

6.1.5 Failure at product development and the cost of rework

The issues identified that give rise to delay, additional cost or company failure at product development stage were primarily concerned with the process and quality of measurement in the original research, both in academic laboratories and in company ones. The specific issues identified are discussed further below.

The factors identified are recognised to result in substantial cost, but the explicit financial burden is rarely calculated. In one case the company had to bring in an external Contract Research Organisation (CRO) to put its processes on a credible footing before development could begin. A modest amount was budgeted for this, but poor practice in early research meant that the task was substantially harder than expected, and cost £50,000 out of the total of £350,000 that the company had raised in investment. Clearly, committing nearly 20% of the company's total financial assets to rework is a poor use of funds.

This additional cost, and sometimes programme delay, can mean the difference between survival and failure. Start-up companies are financially fragile. Typically, start-up companies

in the UK receive between £1.5M and £4M in their first round of VC investment [15, 28]. With this they employ approximately 20 staff, which cost between £1.5M and £2M per annum (a typical breakdown of this cost is shown in Table 2). If these staff are to work in the company's own laboratories, then those laboratories have to be equipped at a cost of between £0.5M-£1.5M (depending on the type of equipment and infrastructure needed).

Table 2: Typical approximate costs for research based start-up company.

Item	*Cost average*	*Cost basis*	*Total/year*	*Comment*
CEO, CSO, FD, Board of directors	~£120k	per person per year (£50k for all Non-executive directors)	£0.5M	Including National Insurance, pension
Other staff (20 people)	£50k	per person, per year	£1M	
Laboratory / office space	£25 - £30k?	per square foot/year - ~150 square feet per person	£0.1M	
Scientific running costs	£15k	per person per year, 50% of staff are research scientists	£0.15M	Mostly technical scientific supplies
Legal, patent and other central office costs	£100k	per year	£0.1M	This increases substantially later in the company's life
Total			£1.85M	

(Based on a company with a staff of 20 people. Data from 4D Biomedical)

Costs are rough estimates only and assume a company that employs its own staff in its own laboratories. Kenny [29] came to a similar sum in the 1980s, so this is probably an under-estimate for a high quality laboratory. A 'virtual' organisation costs less to run, but has other drawbacks as indicated by Cavalla [30].

At best, therefore, a typical start-up company has enough money to run its operations for two years before it needs further investment. As raising new investment for a start-up takes an average of 11 months in the UK [15], this means that any delay in reaching scientific goals will put the company at risk of running out of money before it has achieved enough to convince investors to put further cash into the company. If this happens, the company will fail to raise investment and will have to drastically reduce operations – it will be considered a failure.

Why do technical problems arise so frequently at the transition from research into development? Respondents with knowledge of this problem all said that it was a lack of awareness of the importance of good measurement and laboratory practice at the start of the commercial project. Specific issues mentioned included defining SOPs for methods, or if the methods were new recording accurately what was done, tracking materials used, retaining samples of experimental material for future comparisons, and calibrating measurement instrumentation properly. In some cases this lack of awareness was confined to the academic laboratory, and the company started to set things right fairly soon after it was formed. In others the issue of proper processes continued to be unaddressed through several years of the company's growth.

Rework of this sort should be distinguished from repetition of work performed as part of the technology transfer process. Several respondents said that a central part of transferring new science or technology into the company was to repeat the work that others had done. This is also standard when smaller companies or academic groups licence their technology to larger companies: the in-licensing company will repeat the work on their own systems in part to confirm its validity (their own due diligence) and in part to effectively transfer the tacit knowledge behind the technology into their own company processes. However, this is not a sign of failure and is factored into the time and cost of acquiring new technology.

The evidence collected here suggests that poor measurement practice and consequent rework is a major issue for start-up companies and their funders. As discussed above, funding of biotech companies must be sufficient for them to achieve validated preclinical results to obtain a pharmaceutical licensing collaboration, or clinical results to achieve a stock market listing. In short, they must transition from research to product development to achieve commercial success. To do so they must address the common shortcomings of the measurement processes in the founding science, quite apart from the conceptual validity of the science, the reputation of the scientists, and other matters usually covered by 'due diligence'.

It therefore behoves company founders and investors to confirm that the science was done to an appropriate level of quality at the start of the commercialisation project. Alternatively they need to build extra time and cost into their budgets for rework. Clearly the former is financially preferable to the latter, especially in fields where science and technology is developing very rapidly, so lost time can equate to lost market opportunity.

6.1.6 Success at product development

If over 60% of companies analysed have problems with the quality of their measurement science as they transition from research to development, there must be a significant minority that do not have such problems. This study identified several aspects of those companies that differed from the 'norm' of biotech start-ups.

Three common themes emerged from discussions with founders and executives of those companies that were successful, i.e. which had not had major technical setbacks or failures after several years of operation.

Good systems from the start. The dominant theme emerging was that these companies imposed good measurement discipline from company foundation. Not surprisingly, applying good measurement standards to a project from the start avoids problems later when validated measurements are needed to support regulatory processes. Most of the interviewers who commented on 'success stories' said that this approach of care and use of validated methods from the very start of the project, was the key.

Industrial background of founder/associate. Successful companies often attributed their technical success to having a member of the founding team who had direct experience of the appropriate industrial quality standards. This is echoed by the comments of one observer who said that companies which have been staffed entirely by scientists with no other industrial experience often do not put validated measurement systems in place. This applies to companies which have been in operation for several years and have 100 or more staff as well as small start-ups. The size, age or funding of the company is not the principal issue: the issue is the experience of the people involved. A reason for this, cited by several interviewees, was that exposure to industrial practice and to product development shows the founding scientist in a company the value of incorporating good practice into the research process from the start.

Validation of science, Writing relevant SOPs, QC standards etc. Clearly, the constituent parts of a 'good system of measurement' are a set of SOPs, validated methods and controlled reagents, and appropriately calibrated equipment. These are components of the international standards, e.g. ISO/IEC 17025 and of GLP requirements [31]. In academic research

environments, it is often believed that adopting international standards such as ISO/IEC 17025 or having a GLP study plan is too prescriptive and restrictive and is not appropriate for a research environment. (We note that this perception of GLP is not accurate: we discuss this further in section 6.2.1).

One respondent commented that a reason for this is that scientists in academia and in companies view measurement accuracy as a duty, not a benefit. This is also an inaccurate perception. It is generally true that new measurement methods enable new discoveries, and improved measurement accuracy or reliability can be as effective at new discovery as new technologies to enable new types of measurement.

Thus this project has found that companies that are successful in commercialising their science or technology in the biotechnology industry place substantial weight on good measurement practice, and emphasise that this is a practice that needs to be in place from the start of a research programme, not 'bolted on' when product development begins.

6.2 The Nature of Failure due to Measurement Inadequacies

This section discusses the issues relating to measurement that commonly arise at start-up (which are rare, as discussed) and as companies transition to development. Many of these problems are felt across the four MfB thematic areas, but are more important in one, and are therefore discussed under that theme.

6.2.1 Validation approaches and work in established start-up companies

A general theme to respondents' comments was that academics believe that 'validation' means 'doing the experiment again'. (This relates to academic misunderstanding of the implications of GLP, discussed in section 6.1.5). Respondents were asked a number of questions around how reliability and repeatability of measurements was assured, and how methods were validated as fit for the purpose for which they were being used. Table 3 summarises the responses across the four MfB thematic areas.

Table 3: Approaches to assuring reliability.

	Total commenting on this	*Defined by regulatory requirements*	*Internal QC and validation*	*Repeat if 'wrong result' seen*
Cells-based technology	5	0 (0%)	4 (80%)	1 (20%)
Gene measurement	10	2 (20%)	4 (40%)	4 (40%)
Protein measurement	16	5 (31%)	5 (31%)	6 (38%)
Product characterisation	15	5 (33%)	8 (53%)	2 (14%)

About one quarter said that their processes were defined by regulatory requirements – by their definition, if a process met regulatory requirements, then it was performing as required, as their goal was to meet regulatory requirements. Regulations being discussed here are principally those applying to pharmaceutical product development, and specifically the requirements for entry into clinical trials. In fact those regulations do not specify how

methods should be validated, only that they should be validated to specific standards and, in the case of GLP tests and GMP material, that the relevant company should be compliant to those standards. The reliance on 'regulation' as a standard for validation is, in effect, a statement that those concerned with regulation (either the regulator themselves or the appropriate executive in a company) will solve the problem later. This is particularly common in the protein measurement and product characterisation fields, which, as noted before, overlap substantially as many proteins being measured are protein products.

Slightly under half of those who could answer the question commented that internal QC/QA processes were in place to address this. But a quarter, primarily academic researchers or research stage companies, said that methods were validated by being sufficiently reliable, i.e. they 'just did not fail' more than a small fraction of the time and, when they did, the worker repeated the experiment and got a 'good' result. This approach should be contrasted with the regulatory position in pharmaceutical production, where it is unacceptable to 'test into compliance', i.e. to continue testing until the 'right' result is found. If the result from a sample does not meet the specification then repeat samples cannot be taken or repeat measurements made unless it can be demonstrated that the measurement process or the sampling has failed. This approach relies on all the processes being validated. Validation can be achieved either as an in-house activity or using a number of laboratories. This latter approach is appropriate if all the laboratories are going to be involved in the project.

Seeking to enforce formal, audited QA regimes rigorously on academics doing exploratory or 'blue sky' work may be excessive. However, the value of validated approaches to even 'blue sky' research should be appreciated. Research done using poorly calibrated instruments or using unreliable methods is unlikely to be productive. Reliance on a philosophy of 'just repeat it if it goes wrong' was a significant root cause of many of the problems that companies experience when they move from the research to the development phase.

6.2.2 Cell-based technologies

Interviewees from companies working in the area of cell-based technologies fell into two groups – those working in the stem cell field and those implementing cell-based assays using 'conventional' cells and cell lines.

Stem cell companies emphasised that this is a young field of research and so there is a lack of consensus about what constitutes a valid reference material for comparing cells. This is particularly important in the stem cell field, where the nature of 'stem cells' is still a subject of scientific debate.

This being so, companies working successfully in the field emphasise the need for standard reagents and protocols, reference cell lines and reference materials, against which any new observation can be validated. 'The standard' approaches of QC/QA, such as well defined SOPs, can then be applied. Failure in this field often follows directly from failure to validate new observations against existing ones.

Scientists using more conventional cell assays also brought up issues of cell characterisation, and the 'inherent variability' in cell culture methods and reagents, which have to be understood, controlled or compensated for. Characterisation of cells and the complex reagents that are used to grow them remains a significant technical challenge. There seems to be an awareness of the need to control those parameters that can be controlled.

6.2.3 Gene measurement

The principal failing in gene identification and quantification stems, paradoxically, from the perception that it is easy to do. The ready availability of reagent kits for PCR, real-time PCR, and a range of analytical techniques disguises the need for good procedures. Among these are

the need for rigorous standards of contamination control. One respondent commented on a group running PCR in a qualitative analytical mode:

"[The analytical process] had been set up and running in an academic laboratory, but these were not GLP [compliant] laboratories, and were not clean enough to meet appropriate standards, so they could detect [the target analyte], but the 'baseline' results were 'all over the place'. The appropriate checks and balances, cleaning and isolation procedures and other protocols were not in place……."

This lack of awareness of potential problems is not atypical. In an MfB funded project, Birch et al [32] performed an External Quality Assessment (EQA) comparison of a qualitative PCR based DNA detection among fifteen academic, clinical and commercial laboratories. The scheme was designed to cover all aspects of sample analysis from DNA extraction to reporting of results. Participants were requested to report the presence of DNA and not how much was present. The assessment was run in two rounds with a workshop between the rounds to discuss the results and possible modification of the scheme. Initially, the fifteen participating laboratories were asked to perform the PCR using prescriptive analytical conditions, which included amplification and electrophoresis conditions. This was an attempt to limit variability between the laboratories, however this proved challenging for some participants. Taking into account the feedback from the workshop sessions the second round was designed to remain prescriptive in terms of the PCR amplification conditions but laboratories could choose all the other variables within the process including the extraction kits used. Despite expectations that the majority of laboratories would improve in performance in the second round, some laboratories obtained lower scores in round 2. In fact the overall percentage of good scores decreased for all sample types. The poor consistency between rounds observed for some participants is attributable in part to the different degrees of prescriptiveness in the two rounds. The trial was intended to be a learning exercise to raise awareness of quality issues. It highlighted analytical problems and where they arose; from extraction and amplification to recording the results. Adequate staff training and subsequent monitoring, experimental planning, and good housekeeping practices can overcome most of these problems. This improvement shown by some participants highlights how careful planning and control of the analytical process can produce measurable improvement in performance.

Academic laboratories typically deal with unexpected results by 'just repeating the experiment': one respondent commented that 'quality is not an issue in molecular genetics – it just works'. Several respondents with experience of quantification of DNA in a commercial context emphasised that this was not true, and that reagent kits gave an illusion of universal reliability, in part, because of their sophisticated design, the very limited conditions under which they were used and the high skill level of their users, and in part because of the 'just repeat the experiment' approach when they failed. Changing from this approach to gene quantification to more carefully defined protocols, where the sources of contamination and variation are better understood, are central steps on the path to turning a DNA quantification concept into a product.

Quantitative PCR is a technique which has been mentioned several times as one that is hard to operate reliably. As well as contamination control problems common to all PCR techniques, real-time PCR is a relative quantification technique, and so requires well-characterised internal standards. A senior executive of a company that sells RT-PCR kits commented that in his experience this is rarely done in a valid way, and often relies on methods chosen for their convenience or their historical use in a laboratory rather than objective criteria.

Gene analysis is an area where several interviewees said that the pace of change in technology worked against the establishment of well-validated methods even by companies who wished to do so. As an example, detection of species- or strain-specific genetic variants is a well-known technique for material identification, has changed every 5-10 years over a 20 year span, as summarised in Table 4. Five ways of detecting polymorphisms in DNA and the date

at which each method was first published in the scientific literature are listed along with, the date at which more than 10 papers using a particular method were published, and the number of papers published in 2005.

Table 4: DNA detection methods.

Method	*Comment*	*First publication*	*Widespread use > 10 publications*	*Numbers of papers 2005*
RFLP	Restriction Fragment Length Polymorphism, detected by Southern Blot	1980	1983	2189
Microsatellites	Microsatellite DNA length polymorphism, detected by Southern Blot	1984	1987	880
AFLP	Amplification Fragment Length Polymorphism, generated by PCR	1989	1996	275
SNPs (PCR)	Single Nucleotide Polymorphism, detected by PCR	1997	2000	41
SNPs (Arrays)	SNP, detected by hybridisation to oligonucleotide array (“gene chip”)	2000	2001	31

Based on keyword searches of Medline performed in October 2006).

As each technology is introduced it provides new benefits over the previous technology, but users of the technology are then faced with a choice as to whether to continue to develop and validate an old technology, or move to a new one and start again. Academic researchers almost always chose the former, leaving start-up companies based on their work the task of validating a new technology every 5 years. This is not a problem that is unique to the life sciences. Researchers in all fields are faced with a conflict between the potential benefits that advances in approaches to analysis bring and the lack of validation of new procedures. It has been mentioned as being particularly acute by respondents in this study because of the pace of development of molecular biological techniques and the amount of research that uses them.

6.2.4 Protein measurement

The problem in protein quantification discussed most prominently by respondents to this study was the relativity of protein quantification measurements. There is a difference between what can be done at a routine level and in research. Unlike DNA, which is chemically uniform, and cells, which are large enough to directly visualise and count under magnification, it is very difficult to determine the absolute amount of a protein in a sample.

Common methods for protein characterisation are chromatographic or electrophoretic separation followed by a labelling step and a fluorescence measurement or isotope labelling followed by identification using mass spectrometry (MS). In principle, MS alone can both separate and identify, but the complexity of some protein mixtures usually requires a separation step prior to MS for more complex samples, such as cell lysates, although it is not required for simple protein mixtures.

Making comparable measurements is hampered by not having reference standards which can be used to calibrate the instruments. In order to be able to quantify biological changes then it is essential that the measurements are well controlled, and this is made more difficult by the variation of proteins between different samples. For techniques requiring a digestion step, the efficiency of the digestion also needs to be repeatable. Understanding the variations in

proteins in both circumstances (assay and digestion) is extremely important, and considerable effort is taking place to evaluate the extent to which the protein has been cleaved reproducibly. A study was conducted by the Proteomic Research Group (PRG) of the Association of Biomolecular Resources Facilities (ABRF) to investigate quantitative estimation of proteins [33]. This study looked at determining quantitative protein differences between two samples; examining the different techniques and the data evaluation process. Substantial variation was found. However, no respondents to this study referred to this or similar authoritative studies of methods and their strengths and weaknesses.

In therapeutics discovery programmes such validation is rarely done: for biotherapeutics, methods for doing so are developed as part of the development process, discussed in section 6.2.5. When proteins are used as part of a tool or as a product in their own right, there can be substantial difficulty in validating that an appropriate amount of protein material is there, and even greater difficulty in verifying that it is active and in an appropriate conformation.

Developing robust protocols whereby different protein measurements may be compared reliably is a substantial focus of the MfB experimental programme.

6.2.5 Product characterisation

Biological product characterisation issues are well-known for therapeutic proteins. The principal issues identified by the respondents to this study were documentation and retention samples from early work, transfer of research analytical tools into a GLP environment, and lack of validated methods for analysis of new types of material.

Documentation of early research was the principal issue brought up. Apart from the scientific papers and primary laboratory notebooks, there is often no documentation of a project's research stage. Quite often there are no retained samples from early work on which later results depend, as freezers are 'cleared out' once a PhD or a grant programme ends. By contrast, in a pharmaceutical company there would be documents summarising progress at specific stages, referencing the primary data, how they were generated, the SOPs used and where reference samples were retained. An example in therapeutics discovery is the 'Candidate Nomination' document – this would summarise all the results to date and argue why a specific molecule should go forward for preclinical development, and would be discussed by the candidate committee (or equivalent) which would then approve based on these data. This document would be a basis for future clinical trials applications or a licensing package.

Companies licensing in new technologies look for documentation of this sort, which several respondents have referred to as 'the usual package', documentation describing the basic biological concept and the evidence for it, and data on the compound that show it is safe and effective.

By contrast, academic groups and many start-up companies neither record the research process thoroughly nor retain samples for future referencing. Case Study IV, and the example cited in section 6.1.5 illustrate the financial consequences of this omission.

Related to this is the transfer of research techniques into a GLP environment. For development, analytical methods have to be validated. It is not unreasonable that the original research assay was not a validated method – as it was research, it is likely that it had never been done before. However, the lack of any attempt at validation, coupled with lack of adequate documentation, and retained samples against which more robust methods can be tested, means that in essence the development stage must include complete re-invention of the original science, rather than extension of it.

This is made worse when the material being analysed is a fundamentally new type of entity, which is often the case for a start-up company. This is particularly acute in cell-based therapeutics and gene therapeutics, where the appropriate methods of analysis have not been

established. A company developing phage therapy said that they used a plaque assay as their standard of activity. Apart from issues of validating the method, ensuring consistency of the test bacteria from an academic base, and other procedural aspects of method development and validation, there is doubt that this is a suitable assay method. Another respondent commented that for viral gene therapeutics the US FDA is requiring particle counts as well as infectivity counts. The company and its academic collaborators are not equipped to do such counts, and do not know how to store reference samples so that particle counts do not change.

6.3 Needs for Training and Education

Almost all industry respondents confirmed that the level of graduate awareness of measurement approaches and issues was poor. The few experiences they reported of hiring well-trained staff at this level were recruitment of staff who had come from a laboratory where good practices were in place, so they had learned 'on the job'. Most also said that the gaps in undergraduate and postgraduate understanding were mirrored right to the top of academia, and in many start-up companies. Therefore including measurement science in the curriculum at the university level is a clear need confirmed by this study. Specific topics should include what is meant by method validation, what an SOP should contain, what GLP compliance requires, and the practical value of doing this.

6.3.1 The value of measurement and its context

Academic researchers at all levels appears to have a lack of understanding of the components of good measurement practice. This results in a lack of appreciation of the value and impact that this has on research output. The majority of academics contacted were or had been associated with a start-up company. However, as one senior academic said, most academic researchers do not think about application, except in very vague terms. Career progression is still primarily a reward for grant awards and publications, neither of which require the validation necessary for a measurement that can be used in development.

Several academics also commented that funding for academic research does not allow the work needed for method validation and does not pay for skilled technicians who could become expert in methods, as opposed to the conceptual and exploratory aspects of science in which PhDs are trained. 'There is not enough money to repeat work' is a common comment, although it is not clear what the value of doing research that is unrepeatable might be.

6.3.2 Validation

Among academics interviewed there was confusion between validation, experimental design, and 'fitness for purpose', and there was a tendency to regard 'validation' as equivalent to 'statistically tested'. Repetition of an assay to confirm its performance under specific conditions may be a component of validation, but itself only validates the assay if those conditions are the ones for which it is being designed. This was mirrored by the state of awareness and of training in methods generally. Most respondents said that they expected to train new staff 'on the job' in good practice. This was true across the range of the MfB subject areas. Table 5 shows the comments of 30 respondents to questions relating to the current awareness of new employees, undergraduates and postgraduates of measurement issues, and the method by which new employees gained understanding of good measurement practice.

Table 5: Interviewee comments on awareness and training.

Thematic area	*Number of respondents*	*There is very little understanding on all aspects*	*Good awareness derives from previous laboratory experience*	*New staff are trained in good practice on the job*
Cell-based technologies	2	0%	0%	2 (100%)
Gene measurement	8	3 (37.5%)	1 (12.5%)	4 (50%)
Protein measurement	11	5 (45%)	2 (18%)	4 (36%)
Product characterisation	9	5 (55%)	1 (11%)	3 (33%)

6.3.3 Specific areas mentioned as training needs

Few of the respondees had any specific suggestions about methods or tools that would be of general value in the training of undergraduates or postgraduates. Only two were mentioned by more than one person:

- PCR, especially real-time or quantitative PCR. This technique is in widespread use and has a significant impact. However, it is easy to make errors that lead to false results;
- 'Basic' laboratory skills, including measurement of pH, mass and volume, which have never been explained systematically to undergraduates or postgraduates.

However, the general feeling was that training needed to be at a basic and general level. A number of themes were mentioned by the interviewees and are summarised in Figure 7.

The separation between 'experimental design', 'fitness of measurement method for purpose' and 'validation' were those brought out by respondents' comments.

- '*Experimental design'* was the most commonly mentioned topic, with sub-topics in designing an experiment for a specific purpose and designing experiments which are capable of statistical interpretation.
- '*Validation'* is seen by many respondents as being closely related to reliability and reproducibility of the assay over a range of conditions.
- '*Fitness for purpose'*, by contrast, is seen as relevance of the method and the interpretation of the results to the project in which it is being used.

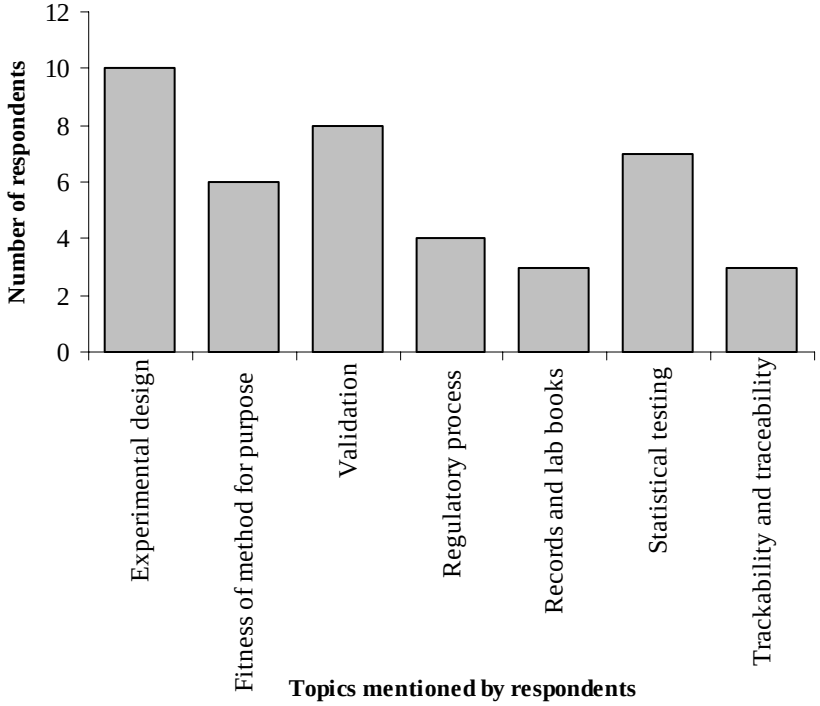

Figure 7. Areas of measurement stated as requiring additional training.

One respondent used an example of fitness for purpose from contract toxicology testing. Tests may be conducted and audited to GLP standard, but if they do not collect data that are relevant to the development programme, then they are not fit for the purpose for which they have been designed. Thus the 'fitness for purpose' issue fits between the over-arching area of 'experimental design' and the specific procedural issues of 'validation'.

As seen for the definition of validation in section 6.1 all three of these themes are in reality part of method validation, making this the most pressing concern of the respondents to this survey, but also identifying a common lack of understanding of what method validation entails. There is also some confusion about the requirements of GLP which is a statutory requirement for some studies.

The regulatory process, and what is required to develop a biotechnology product, especially a drug product, was another topic mentioned by several respondents. Undergraduates in all disciplines had very limited understanding of regulatory requirements unless they happen to have been taught by someone who has been involved in drug development. Such involvement might be as a member of a company's Scientific Advisory Board, or as an expert advisor or company member (shareholder). While they may understand the procedural elements (such as the nature of the clinical trial phases) they rarely had any understanding of how good measurement practice linked with these requirements.

By contrast, project management skills were generally thought to be adequate, largely because they are required both for applying for, and executing, grant-funded research.

6.3.4 Method of training

There was some scepticism expressed that developing seminar and workshop materials for training in best practice would be a fruitful delivery vehicle. The principal reason is that measurement methods and validation is seen as being very uninteresting. Such seminars

would have to be cast in terms of why it was in their interest to identify and implement best practice and show how this can be implemented elsewhere.

Another delivery method suggested was materials for undergraduate teaching, such as a set of slides of examples of where measurement went wrong, and how best practice could have prevented this.

It was originally envisaged that examples of start-up company failure could interest the investment community in demanding higher measurement standards. However, as discussed above, VCs now rarely invest in such companies, preferring to invest in companies with products at the 'prototype' stage, where measurement quality, trackability and method validation are of central importance. Early stage investors, Business Angels and technology transfer professionals now realise that in order to attract VC investment they must have companies that are capable of getting to the prototype stage. This, coupled with examples of how failure to do so results in cost, time lost and sometimes complete company collapse at the transition from research to development, should be a key message in material aimed at this community, so that they are also motivated to identify best practice and implement it in their potential start-up companies

6.4 Identified Gaps and Needs

This project clearly identifies a lack of understanding about the value of validated measurement and associated good research practice. This project focused on start-up failure, and has identified that start-up failure per se is relatively rarely due to failure of measurement, or of any aspect of the start-up science. However it is common for time and money to be lost as projects move from research to development because original measurements were not carried out to an appropriate standard, reference samples were not retained, SOPs of the process were not documented and the experiments were not designed with statistical evaluation in mind.

If the technology transfer and early stage investment industries in the UK were aware of these issues, they could identify such potential problems and create and invest in those start-ups that are less likely to suffer later set-backs because of weaknesses in the measurement practice.

The same conclusions also point to a gap in understanding about the need for good measurement practices in academia. The needs of the academic research environment are different from those of an industrial one. However, both need to do research of high quality and produce results that can stand up to scrutiny. The search for new knowledge rather than new products still requires careful work; exploratory research need not mean sloppy research. There is no doubt that quality assurance of measurement methods, proper record keeping, keeping retention samples and other basics of good measurement would result in better research.

In concert with this, several respondents to this study were of the strong opinion that academic scientists should consider whether their research could be turned operationally into a development programme, regardless as to whether it seems likely that it will. By definition a scientist pursuing exploratory research does not know where it is going to end up, and hence it cannot be stated, of even the most 'pure' research, that it will not generate practical implications. We recommend that academic researchers be encouraged to understand that their research could have practical implications, so their research should be conducted in a way that makes such an outcome possible.

Two further ideas arose from this study that merit mention. One respondent suggested the concept of a 'quality measure', for academic and early company research, which showed that the research had been done to a quality standard that was capable of being converted to an applied programme. This would be equivalent to the 'Kite mark' for quality of process. This would enable the due diligence process to rapidly assure investors and others that research was of an appropriate quality, without having to employ experts to do this. A quality standard

of this sort could lie between 'good practice' implemented without external auditing and a full accreditation to ISO/IEC 17025 as provided by the United Kingdoms Accreditation Service (UKAS) which was also mentioned.

The second arose from the observation that technologies move faster than validation of the application of those technologies. A 'Foresight' programme to look into the measurement needs for emerging technologies is therefore valuable. The authors of this report are aware that this is a goal of the MET programme.

6.5 Materials for the Case Studies

Several studies of the effects of good (and bad) practice on the success (and failure) of research and development have been identified in this project. These have been documented for further use in training and awareness programmes. They illustrate many of the general findings above. The case studies are documented in Appendix II.

7. Conclusions, Future Activities and Recommendations

Failure of biotechnology start-ups at or soon after foundation for scientific or technical reasons is rare. The experience of the 36 people interviewed for this project, with personal knowledge of 59 companies and second-hand knowledge of many more shows that only a small percentage appear to fail for technical reasons before they enter the product development stage of their company growth. Of those that do fail, some fail because initial work was not done to best practice standards, and so companies were founded, and investment made, on results which subsequently could not be repeated or developed.

Failure in the early stages of product development in start-up biotechnology companies is common. This rarely leads to complete company failure, although it can do so, but it does lead to the need for substantial rework and consequent added cost. Up to 20% of the company's total investment can be spent on rework. This is mainly because early research did not conform to best practice, and particularly because samples of key materials were not retained for later reference and SOPs are not used or recorded to allow replication of experimental work. Respondents to this study suggested that at least 50% of biotechnology companies would be delayed or incur extra cost due to problems of this kind.

Despite the risk of future unexpected costs due to rework, investors in early stage companies rarely carry out the due diligence which would identify the potential for such failures. Due diligence studies are confined to reputational aspects of the founding scientist and the review of high level summaries of data.

Companies that avoid technical failure and setbacks in their initial stages and when they enter development do so by early investment in best practice. The adoption of best practice early in the company's history, and in the research that precedes commercialisation, is almost always the result of the founder scientist's exposure to best practice in a commercial or clinical trials environment.

A significant factor in the high incidence of failure at development stage is that scientists at all levels, both in research and development organisations and in technology transfer and investment, have a very limited understanding of the nature and the value of best laboratory practice and measurement science. In particular, there is a substantial deficit in undergraduate and postgraduate training in best practice and why it is important. There is also a substantial misunderstanding about the meaning of 'method validation', and an erroneous belief in academic research that it is synonymous with the onerous documentation necessary for formal GLP compliance.

This report did not identify any specific techniques or methods as ones for which there was a demand for improved training. The principal requirement for technical training was in basic laboratory techniques such as measurement of volume, mass and pH. The only advanced technique mentioned as one in which greater training in good measurement quality was generally required was quantitative ('real time') PCR methods.

There are many reasons for the current situation which are only in part due to limited funding. There is a culture of 'repeat the measurement until the results satisfies the current situation', instead of validating methods and controlling those aspects of the processes which can be controlled. It is clear that poor measurement practice does not cause problems at the early stage of research, but that poor measurement practice at the research stage can cause problems when that research is used as the basis for product development. It is not easy to identify the real issues that have given rise to the current situation. There was an implication that there was lack of generic laboratory capabilities, related in part to the increasing culture of technology as a 'black box', where the implication is that is not necessary to know about what goes on between the sample input and the result. This is a dangerous situation because without a thorough understanding of the processes that are going on 'behind the scene' it is impossible to identify critical points or set up a system to check that the system is functioning correctly. This applies to software and hardware.

On the basis of these findings and our interpretation, we recommend that the following future activities be undertaken, although a number of them may be beyond the scope of this MfB programme.

1. Preparation of training material suitable for undergraduate and postgraduate use, based on material developed here and other material developed by the MfB programme, to illustrate:
    - what best measurement practice entails, and how this can be implemented in exploratory research without onerous documentation procedures;
    - how best measurement practice leads to better research in academic (pre-competitive) and commercial (competitive) research, and particularly how it can enhance the goals on which academic researchers are assessed as well as the chances of successful exploitation and commercialisation of research results;
    - the regulatory processes in therapeutics development and elsewhere in biotechnology, and how these require good practice in discovery research as well as in the development and approval processes;
    - the meaning and value of method validation;
    - case studies in which pursuing or failing to pursue good practice can result in financial, product and career losses to all concerned.
2. Integrating into this training material some basic laboratory skills training, e.g. work organisation, measurement of mass, volume and pH, including practical examples of good and bad practice.
3. Developing the same material into awareness material for academic researchers in UK universities and research institutions, exploring effective methods of getting these messages across. Such methods may include:
    - seminars and workshops dedicated to measurement issues;
    - sessions or streams in scientific conferences;
    - visual training materials, such as DVDs or CD ROMs;

- papers describing case studies.

4. Encouraging grant agencies or universities to provide funding to support the staffing and infrastructure necessary to achieve best practice and to give preference to laboratories that can demonstrate best practice in pre-competitive research.

5. Encourage editors of Journals to follow the example set within the Microarray technology field where authors are required to provide evidence that they have followed the MIAME (the minimum information about the microarray experiment) guidelines [34].

6. Dissemination of the conclusions of this report and case studies of commercial failure resulting from poor measurement practice to the investment community to enforce the value of audit of, and investment in, best practice in research. Suitable vehicles for such dissemination are conference presentations and trade journal articles.

7. Increase awareness of DTI programmes relevant to the biotechnology industry, both MfB and MET. Involvement of academics and organisations working in emerging technologies where product development is starting to be considered, such as phage therapy and viral vectors for gene therapy, could provide valuable future input.

8. Explore the possibility of a 'quality measure' of best practice in research conduct. This should be less onerous than full external accreditation such as UKAS accreditation, but should provide grant agencies, technology transfer professionals and investors with a standard against which they can judge a research programme.

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9. Appendix I

9.1 Questionnaire

Questionnaire to address skills gaps in the measurement requirements of biotechnology

Initiation problems

1. Do measurement issues ever cause problems when instigating start-up companies and subsequently with their future progression?

Training and understanding

2. What training is given to postgraduates on;

   Project management,

   Experimental design,

   Objective statistical testing,

   Traceability of measurements/Comparisons with 'gold' standards, reference materials

   Method validation,

   Measurement uncertainty/Errors,

   Quality control

   Other?

3. Do postgraduates have any concept of the regulations that apply in the pharmaceutical and related industries?

4. Do you think that there should be a component of undergraduate/postgraduate studies that covers the key aspects addressed in the MfB programme?

Due diligence and assessment

5. What issues are raised after 'due diligence' has been carried out?

6. How confident are you that, after all the safeguards and quality checks have been carried out on your product/service, the end product/service performs in the way you lead your investors to believe they do?

7. What percentage of the work that is carried out prior to spinning-out has to be repeated when you start formulating the commercialisation aspects?

8. What do you think are the products/processes that enable you to assess reliability and fitness for purpose of equipment used to make measurements? (e.g. Reference Materials; Equipment qualification; System suitability testing).

9. Do you think your processes are sufficiently transparent so that they can be audited?

10. If your experimental work is challenged how do you defend the reliability of the data?

First stage improvement strategy - Seminars/Workshops/Case studies

11. How can we enhance the skills of students entering laboratory-based employment after undergraduate or postgraduate studies?

12. What subjects should be covered in workshops for lecturers/postgraduates, to help the teaching and reduce the skills gaps?

13. Do you have some material that LGC could use to formulate a short case study (half A4 page) to illustrate the need for better measurements?

10. Appendix II – Case studies

10.1 Case Study I:

Company A is a spin-out company from a world-class UK University formed in 2002 to be a contract bioanalytical service for protein therapeutics. The company's science base developed from a GMP manufacturing facility set up within the University to support clinical trials with the first humanised monoclonal antibody drug, a protein therapeutic derived from cultured mammalian cells. Analysis of the protein during and after manufacture is a critical part of quality control due to a tendency for batch inconsistency, and is technically demanding. The academic group developed the methods to do this. The company has grown steadily to profitability this year. They have successfully developed a range of cutting-edge analytical methods for analysis of antibodies, vaccines and recombinant proteins, and used them to solve their clients' unique analytical challenges. To meet the demand for their services, the company is constantly seeking scientists and project managers with suitable training and experience.

The CEO commented that their close work with commercial licensors showed them what industrially robust measurement meant. They developed and validated methods to support late stage clinical trials of various therapeutic antibodies. When approval was gained for treatment of leukaemia, the licensing company came back and asked them to continue the analytical work. This contract provided the commercial basis to spin out. Good practice has subsequently allowed them to rapidly expand and now the company has a wide range of clients from the pharmaceutical and biotechnology industry across the globe.

The CEO believes that, "binding science with quality" - should benefit any research endeavour, whether applied or fundamental. Leaving an academic environment to run a bioanalytical company did not mean abandoning science to become a 'box-ticker'. "Academics should realise that good practice, records, SOPs etc. actually make life easier. It may be hard work to set up, but a robust quality system ultimately saves time and resources."

Conclusions. Creating a company with good measurement practice embedded in the science from the start allows steady growth and expansion, without the need for rework, and attracts industry collaborators.

10.2 Case Study II

Company B is one of the pioneering stem cell start-up companies in Europe, founded as a spin-out from a leading UK research centre. Early experience and technical challenges lead Company B to develop a set of standards and references that allows them to validate any new stem cell technology against their own successes.

Their QA approach is based on attention to the specifics and detail of the system, understanding of the providers of materials and reagents, a standard set of reference cells, and "good grounded common sense". This has allowed them to take their products towards clinical trials planned for 2007 in a field where no 'standards' exist, as there are no existing products in trials or on the market to determine what needs to be tested to ensure product safety or reliability.

They were approached by a leading US university with a world-class research reputation with a proposal to collaborate. Company B's initial evaluation of the technology, including detailed analysis of the methods and comparison of the proposed technology with their references, suggested strongly that the planned programme would not work. However, it also suggested a different research line which resulted in a successful programme. Company B funded a postdoctoral researcher for a year; validation of methods was part of this work. At

the start Company B sent over their SOPs, protocol sheets and other records of their standards. “They thought this is wonderful” the CSO of Company B commented – the academics had never seen a briefing packages like this, which allowed them to start productive research much faster, and the academic collaborators were so enthusiastic that they brought their collaborators in to the programme, because they see it is worthwhile.

Conclusion. High quality method validation, SOP development and back-checking to reference samples enables industrial research funding, but also accelerates basic and academic research.

10.3 Case Study III

Company C was a spin-out of a UK University with a world-class reputation for biomedical research, to create new therapies for neurodegenerative diseases. It was funded by ‘Business Angels’ and raised over £5M from these and VC investors.

Measurement validation issues were not raised at the company’s inception, but with Company C moving towards further financing, it became clear that the first £3M had been spent on science that was unreliable. “It was ‘sometimes it works, sometimes it does not’ data, no use for developing into a screen”. So the company licensed an assay from a major pharmaceutical company, but again did not carry out tests to see if it was fit for purpose, which it turned out not to be. The need to repeat much of the early science to identify causes of variability, and to generate a screen that could be validated, spent most of the rest of the cash in the company. The investment climate was turning against high-risk ventures, so the company was reduced to two postdoctoral researchers.

In the following 4 years the same research has identified further, more robust IP to take forward. A substantial part of this research has been developing a new screening method which, among other things, can be used to correct for screening errors in other types of screen.

Conclusion. Even world-class research can fail to deliver if the basic work on assay validation is not done. In this case 4 years’ research and over £5M investment cash was spent before the basic weakness in measurement was found, and with it the weakness in both the scientific proposition and the company’s ability to exploit it.

10.4 Case Study IV

Company D was founded by a group of experts from a leading UK institution to develop gene therapy applications of the founder’s research. The Company thrived, attracting substantial investment for a portfolio of programmes, including one which went rapidly to human clinical trial.

Much of the early work to show that the therapeutic was transfected effectively into cells, that it functioned there, and that the gene function had the intended effect on the cell was done in the founder’s academic research laboratory. The work was to a high standard and published in leading scientific journals. However, the assay processes were not suitable for regulatory requirements and the ‘academic’ therapeutic proved hard to manufacture, so both therapeutic and methods for monitoring were changed during the preclinical development phase. The need to do this was built into the start-up’s business plan.

As they approached clinical trial, the Company had developed a gene therapeutic that met all the safety, trackability and patent requirements needed for them to take it to a final product. However, this gene therapeutic was a different construct from the one used in the original research, so the company needed to demonstrate that the efficacy of their production therapeutic was equivalent to that of the research material used by the company’s founding academic group in the 1990s. Assay methods used at the time were well established in the literature, but no SOPs had been written and no samples had been retained. So it was

impossible to show that the original research results could be replicated with the new, production therapeutic. “We ended up looking under [the Principal Investigator’s] bed for old laboratory books” to track down primary methods descriptions, commented one senior executive, and had to remake the ‘research’ vector to run tests using the new assay systems with the research and production vector in parallel. The extra cost of this was around £2M, just repeating work of the past cost nearly 10% of all the funds invested in in the entire business up to that date. This could have been avoided simply by recording the original research methods and retaining samples of key materials at the time.

Conclusion. Even high quality and successful science can be held up as it is transferred into development and application if basic measurement and trackability issues are not addressed in the early science. This delay could have been avoided at negligible cost if records and samples had been kept during the research that lead to the company’s foundation.

10.5 Case Study V

Company E was founded to exploit an exciting observation in the hormonal control of aspects of physiology relevant to cardiomyopathy. An initial observation in a complex, expensive animal system was rapidly translated to a smaller animal model, and an active agent tentatively identified. On the basis of this, £100,000 investment was raised from Business Angels with a view to developing a therapeutic. Using this money they partially characterised the active agent, using the original small animal assay to identify the agent through a complex purification process, and on the basis of this raised a further £800,000 to test the agent in models of disease.

However, Company E then discovered that the material they had thought was producing the effect in their small animal assay was a well-known contaminant material. Four other substances with similar chemical properties were identified from the original source material as being candidates for the active agent. Two of these failed to reproduce the original result, one could not be re-identified by better analytical techniques, and one was weakly active in the assay. Based on this success, the investors provided another £350,000. However, subsequent research suggested that this agent might also be a bacterial contaminant.

About one year later the putative active agent was still producing erratic results, and the investors asked an expert in the relevant biology to review the primary data. The expert advised that the small animal assay was unreliable, invalidated as a measure of the original large animal effect, and did not control several other competing effects which could have generated spurious ‘positive’ results. They considered that it was not proven that the activity claimed of the putative active agent was not an artefact, even though the original observation was real. The investors pulled out in 2001.

Conclusion. Thus two failures – failure to develop an appropriate, validated assay for the original effect and failure to control adequately for contamination in the purification process – resulted in 6 years and over £1.2M wasted. Both could have been solved at the start of the project, and the reality of this active agent confirmed or eliminated quickly and cheaply.

11. Appendix III – Confidential.

Confidential Annex with list of interviewees.