Quality: an old solution to new discovery dilemmas?



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'…quality fuels success at every level.'

The pharmaceutical industry of today stands close to the Sword of Damocles and faces a multitude of challenges. Rapidly spiralling costs, fierce competition, recalcitrant drug targets, data overload, intellectual property erosion, poor public perception and an ageing population are but a few of the topical issues that tax the industry [1]. Meanwhile, the opportunities that are afforded by new science, technology and understanding open the door of possible therapeutic intervention ever wider [2]. Thus, the system is finely balanced. Which of those factors that are under the control of discovery scientists might help to tip the balance favourably in the future? The development and implementation of a novel quality initiative in early, non-regulated drug discovery research is one such possibility. Hence, is quality an old solution to a new dilemma?

What factors influence the quality of research?

To a scientist, the immediate perception of quality is dependent on the environment in which they work. Within early phase, non-regulated drug discovery, and particularly in academic research, quality equates directly to publication. Timely publishing of breakthrough data in high-impact research journals stamps the global seal of quality on scientific endeavour. Although publication remains an important component of science in regulated environments, quality here more accurately reflects adherence to the predicate rules – the regulations and laws [Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and Good Clinical Practice] that ultimately afford an investigator the right to operate within the broad clinical arena. Whereas the perception of quality can fuel lively debate within the wide scientific community, low quality is well understood by all.

Endless repetitions of experiments, poor decision-making, the inability to replicate results and the waste of time, resource or talent are some of the hallmarks of poor quality in discovery science: irrespective of the environment, the list is almost generic. The cost of low quality is indeed high. Within the pharmaceutical industry, low standards in early phase research can help precipitate ethical concerns, vulnerability of patents, compromised relationships with regulatory authorities and collaborators and, ultimately, low speed to market. These inefficiencies shake the metal of the discovery engine. Would it not make good scientific sense, and thus good business sense, to implement a quality initiative within early phase research? We think so, as does academia (http://www.defra.gov.uk/science/publications/2003/QACoP_V8.pdf). The idea that high-quality processes in research will yield high-quality results is not a well-tested hypothesis in discovery.

It is patent that, for example, keeping accurate experimental notes to assure faithful data reconstruction is an important, fundamental (but easily overlooked) precept of scientific methodology. Similarly, ensuring that key equipment is functioning correctly, experiments have appropriate statistical power and reagents have been characterised such that they are of a standard suitable for their designated purpose seems entirely obvious and not worth a second thought. However, a closer examination could reveal that standards have not been adhered to, and headlines are made of such errors [3]. Given that research moves forward by making timely, and often costly, decisions on data, it is entirely reasonable to assume that the more robust the data, the better the decision-making process and thus the more efficient the business. Indeed, a breakthrough compound without the appropriate documentation offers little. It is not as exciting as 'the omics', as awe-inspiring as mapping all chemical space *in silico* or as elegant as crystallising transmembrane receptors and gathering their innermost secrets, but simply developing systems to assure the quality of the data might have as great an impact on the efficiency of discovery science than all these functions. Because the thoughtless use of such quality systems is likely to drive free scientific thought to distraction, how can an organisation achieve such a goal in a balanced manner without stifling intellectual talent?

Construction of guidelines to attain Good Research Practices

Over the past two years, Eli Lilly (http://www.lilly.com) have internally developed, and subsequently globally

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implemented, Good Research Practices (GRPs) for the early phase, non-regulated drug discovery (the process adopted is outlined in Box 1). Careful thought underpins the initiative, which begins with a detailed assessment of risk. These key data drive the construction of principles, policies and guidelines that subsequently control the risks and optimise the processes involved in their management, which could include the control of discovery data architecture, electronic (e)-data, research material characterisation, computer systems and experimental design (the ten principles of the GRP programme are presented in Box 2). With the building blocks and strategy of the initiative in place, training the scientific workforce constitutes the next significant hurdle.

During the implementation of the initiative, it was observed that focused, thought-provoking training that 'gripped' scientists was fundamental to the success of the programme. One question that inspired considerable debate was 'What causes you pain in the lab?' Building on their identification of processes that underpinned chronic problems and a clear wish to get compounds to market efficiently, scientists from all disciplines were, albeit tentatively at first, keen to pursue the concept of 'right first time'. In global efforts, sensitivity to local culture and diversity is of particular importance during the training phase.

Implementation of guidelines

After detailed gap analysis throughout the organisation to identify the key domains in which to 'close the gaps', the significant undertaking of implementation of the initiative begins; this should not be underestimated in terms of resource or time. A careful balance needs to be struck and embraced at all levels to ensure short-term business goals are met in concert with the achievement of long-term, sustainable quality. Indeed, it could well be the case that in the first instance productivity is seen to fall with the mobilisation of resource in the quality initiative. Thus, management support from the higher to lower echelons is crucial. In our experience, the effort required across the entire organisation to achieve appropriate quality levels in specific areas of the business, for example, data architecture, have been relatively modest. By contrast, the attainment of other levels of quality, including the validation of discovery computer systems, appears Herculean. Given the difference in timing for full implementation, the expectations for compliance to all components of the process will be phased. How, if at all, is the extent of compliance measured? To maintain the support of the scientists, this issue must be handled sensitively.

Within the non-regulated research environment, few scientists have ever had their research formally audited or assessed. Although, for publication, the data is invariably scrutinised by peer review, the preliminary rudimentary traces, laboratory books and print outs are seldom examined by independent eyes. Thus, there is a sensitivity that needs to be approached in a measured and pragmatic manner.

Box 1. Stages in the development of Good Research Practices

1 Define balanced strategy.
2 Construct policies, principles and standard operating procedures.
3 Deliver training.
4 Implement training.
5 Identify gaps.
6 Monitor and set expectations.
7 Develop quality systems.
8 Assess and/or audit strategy to improve quality.

Box 2. The ten principles of Good Research Practice

1 Scientists, supervision, management and support personnel are all owners of, and accountable for, Good Research Practices.
2 Individuals must have documented training, education and/or experience to perform the tasks required by their current roles.
3 Test materials (e.g. compounds, test substances and controls) and reagents must be identified, characterised and stored to ensure that they are suitable for the intended research purpose.
4 Laboratory equipment that is used to generate research data must be maintained and calibrated.
5 Computer systems that are used to generate, manage, analyse or maintain data must be validated.
6 The optimisation, validation and data analysis of *in vitro* assays must be performed in a manner that follows scientific and statistical principles.
7 A study design and data analysis plan for *in vivo* assays must be based on established scientific and statistical principles.
8 All experimental procedures, observations, data and results must be recorded or referenced in laboratory notebooks and data books to ensure data integrity.
9 All notebooks and related research materials are the property of the company and must be securely maintained and archived.
10 Research reports that are intended for the portfolio management decision committees, or for submission to external agencies, must be prepared according to appropriate quality standards and reviewed to ensure integrity. Furthermore, if a graph or chart is used in a report, it must contain a reference.

Within the first year of implementation of the initiative at Eli Lilly, it was decided to adopt an assessment approach to monitoring compliance to the GRPs. Those involved in conducting the assessments are experienced in both the scientific and audit arenas, and the interests of the scientists, and thus the business, are their principal concern. Because the assessors also learn a great deal during this process, the tone set at assessment is one of partnership and bilateral education and not one of policing rules. This approach ensures that important information 'from the bench' can be gathered objectively and used to drive changes and iterations to help modify aspects of the policies that do not add value. 'We have never had our data looked at like this before' is a common statement when scientists realise that this assessment is an aid to improving the quality of research rather than an opportunity to critique their work.

Given that full implementation of the GRPs has been progressive and is not yet complete, Eli Lilly have assessed elements of compliance in a phase appropriate manner. Thus, the validation of discovery computer systems, for example, has been conducted initially to raise the awareness of all parties concerned to assure the integrity, format and security of e-data. The observation of conventional data architecture, including laboratory books, raw data, archives and reports, has been more stringent. Irrespective of the area under analysis, open, regular and frank communication with the scientists and their management has been central to success. The assessment cycle highlights a spectrum of achievement, giving a finger on the pulse of discovery quality. Be prepared for the unexpected.

Progress and outcomes

One of the biggest surprises arising from the initiative was the observation of the blatant positive attitude and ownership of the GRP initiative by scientists at all levels. Irrespective of the extra 'out-of-hours' work and the added pressure of looming business deadlines, the scientists were keen to deliver high-quality research in the fullest sense. Many areas of best practice were observed throughout the organisation and, perhaps predictably, some areas that are in need of development were noted. Areas that historically had previous exposure to GLP and GMP viewed GRP as a potential lowering of the quality standard. Those scientists that had previously been unexposed to these concepts (i.e. the vast majority of discovery scientists) initially struggled to gain a working feeling for quality and, most importantly, where the implementation of quality systems could assist their science; however, these feelings were short lived. Although the focus of Eli Lilly has been on early phase research in drug discovery, similar initiatives are being implemented in academic research in the UK. What is the payback of this cultural change that is taking place 'on the bench'?

The positive outcomes of a quality initiative in non-regulated research are huge and multilayered. On a personal level, people feel good about producing a truly high-quality product; it is not only the quality of the compound and hypothesis, it is also the quality of the data package (i.e. documentation) around the product. Teams take a greater pride in their work, safe in the knowledge that the data is dependable and, accordingly, many of the chronic niggles in their everyday science begin to evaporate. There is an increase in the confidence and pride in the quality of data packages used internally within the organisation and externally with regulatory agencies and business partners. Indeed, quality fuels success at every level. To the drug discovery scientist, success means not only getting a compound to market, but also helping it to remain there for as long as possible in the face of ever-stronger patent erosion by the generics. We believe that this grass roots culture change at the bench will ultimately further raise the quality bar within the industry and help provide patients with the therapies they need in a more-timely and cost-effective manner.

The journey from 'the cost of low quality is high' to 'the cost of high quality is low' is a long one, and could perhaps be never ending. However, to tackle the huge new challenges our industry faces head on and to harness the promise of breakthrough scientific innovation, we need to do something differently, and perhaps quickly. Quality could hold the answers that matter.

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