

Developments in consultancy and training in the GLP arena: 1980 to 2020. A personal view

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Summary. The development of good laboratory practice (GLP) consultancy and training from the early 1980's as well as the present industrial needs in GLP consultancy and training are reviewed. At the very beginning, because the GLP principles were completely new, GLP experts often combined basic training and consultancy in one package. Training was concerned with helping trainees to understand the text of GLP regulations and make them aware of their responsibilities in the successful management and conduct of GLP studies. With the development of the OECD GLP advisory and consensus documents, training and consultancy became much more complete. Consultancy over the next ten years will also be focusing on the harmonisation of regulatory references used on the same site, such as good manufacturing practice (GMP), good clinical practice (GCP) and ISO norms, and also on the incorporation of other quality concepts into the GLP laboratory (*e.g.*, risk analysis, quality indicators, continuous improvement). A significant increase in specialised consultancy is expected as a shift towards *in-vitro* models becomes necessary through the quest for a new Research and Development (R&D) paradigm. There will be two other important developments in training, namely, the thrust for training programmes which can serve as certification and the need to provide individualised training at distance, *e.g.*, through Internet-based training programmes. Internet training, followed by assessment modules, and covered by certification from an academic institution, is expected to be run-of-the-mill in the year 2020.

Key words: good laboratory practice, good manufacturing practice, good clinical practice, ISO norms, consultancy, training.

Riassunto (*Sviluppi nella consulenza e nell'addestramento nel campo della BPL: dal 1980 al 2020, un punto di vista personale*). Vengono esposti lo sviluppo della consulenza e dell'addestramento nel settore della buona pratica di laboratorio (BPL) sin dai primi anni '80 così come le attuali necessità del mondo dell'industria in questo campo. Poiché i principi di BPL erano in quegli anni del tutto nuovi, sin dal principio gli esperti di BPL combinavano spesso nello stesso programma l'addestramento di base e la consulenza. L'addestramento era mirato ad assistere gli interessati nella comprensione del testo delle norme di BPL ed a renderli edotti delle loro responsabilità nell'appropriata gestione e conduzione di studi in BPL. Con la pubblicazione dei documenti di guida e di consenso dell'OCSE sui principi di BPL, l'addestramento e la consulenza sono divenuti molto più articolati. Nel prossimo decennio la consulenza si dovrà anche occupare di altre disposizioni regolatorie attuate nello stesso sito, quali la buona pratica di fabbricazione (BPF), la buona pratica clinica (BPC) e le norme ISO, nonché dell'inclusione di altri concetti di qualità nel laboratorio BPL (ad esempio, l'analisi del rischio, gli indicatori di qualità ed il miglioramento continuo). Avrà luogo, inoltre, una significativa crescita della consulenza specialistica man mano che diverrà necessario spostarsi sempre più verso modelli *in vitro* nella ricerca costante di un nuovo paradigma di Ricerca e Sviluppo (R&S). Vi saranno, peraltro, altri due importanti sviluppi nell'addestramento, vale a dire la richiesta di programmi di addestramento che servano anche da certificazione e la necessità di fornire addestramento individuale a distanza, ad esempio per mezzo di programmi forniti via Internet. L'addestramento tramite Internet, corredato di modulistica per la valutazione e riconosciuto da certificazioni rilasciate da un'istituzione accademica, si presume possa divenire la regola nell'anno 2020.

Parole chiave: buona pratica di laboratorio, buona pratica di fabbricazione, buona pratica clinica, norme ISO, consulenza, addestramento.

INTRODUCTION

Over the thirty years that the pharmaceutical industry has employed the principles of good laboratory practice (GLP) we have seen a number of developments in the field. Though the basic regulations

and their solid fundamentals have not changed, we have seen the publication, and subsequent implementation, of numerous guidance documents – particularly from the Organisation for Economic Co-operation and Development (OECD) – and we

have, of course, witnessed a change in industry's attitude to GLP as it first came to terms with the regulation and then started to adopt GLP concepts rather more enthusiastically. Two indicators of the way GLP activities have developed are: how training courses have changed and how consultancy activities have shifted over the years. The current situation is not, of course, frozen. More developments are on the way as the paradigm of pharmaceutical Research and Development (R&D) evolves over the next ten to twenty years.

This article attempts to trace some of the changes we have seen and then to look at what we may be faced with in the relatively near future. It is, therefore, divided into three parts: the first part looks at GLP consultancy and training from the early 1980s to the mid 1990s; the second examines the current situation; while the third requires a crystal ball as we look into the likely developments over the next 15 years or so.

It goes without saying, I hope, that the views expressed here are entirely my own and not necessarily shared by other QA colleagues.

GLP CONSULTANCY AND TRAINING REQUIREMENTS IN THE BEGINNING

"The past is a foreign country: they do things differently there" [1]. This famous incipit is superbly descriptive of the vast changes that occur even in the very short space of a lifetime. Just look back at your own and you will understand what Hartley meant. Its magnificent metaphorical force also applies to the way in which the research scientists' and management's views of GLP have evolved over the last 30 years. Their attitudes towards GLP have changed so much that it is as if the two cultures, then and now, belonged to entirely different countries.

When the US Food and Drug Administration (FDA) revealed cases of misconduct and negligence in the late 1970s, researchers were not altogether surprised, but they were appalled at the idea of imposing GLP regulations in an attempt to sort out the mess. Although the Oxford English Dictionary records the acronym NIMBY (Not In My Back Yard) as first occurring in 1980, I can assure you that the concept was well applied to nascent GLP by many senior researchers and management in the pharmaceutical industry. However, GLP became unavoidable, albeit difficult to swallow. When I was asked to implement GLP and quality assurance (QA) in my first "quality job" over thirty years ago, I was instructed to do so without holding meetings or upsetting anyone. A tall order!

Scientists persistently came up with the same three grievances to express their resistance to, abhorrence of and disdain for GLP.

The first was: GLP will prevent me from being innovative and creative. To which I would reply (with the greatest of respect): on the contrary, you will still be able to innovate. GLP simply asks you to show

where you have been creative. GLP says plan and record your innovations' so that they can be duly, and fully, recognised, appreciated and repeated. In summary, GLP will highlight your creative and innovative abilities.

The second was: GLP will remove all my responsibilities. To which I would reply (with the greatest of respect): on the contrary, GLP makes sure that responsibilities are defined. Management has to clarify who does what. Because responsibilities are clear, the right people get the accolades. In summary, GLP highlights what you do well.

The third was: GLP will force me to write all those hateful standard operating procedures (SOP). To which I would reply (with the greatest of respect): well, yes, there will be SOP to write. But you can simplify them by using flow-charts, diagrams and photos. And, a good SOP system has lots of positive points; standardisation reduces experimental bias, SOP facilitate training, and troubleshooting and study reconstruction is made easier. In summary, SOP will release your grey matter to tackle more interesting things.

With this last point, I would trot out the well known quote from W. Edwards Deming: use standards (*i.e.*, SOP in our case) as the liberator that relegates the problems that you have solved to the field of routine and leaves the creative faculties free for the problems that are still unsolved. [2].

However, all to no avail. GLP, like taxes, was considered a "necessary evil" and, again like taxes, the minimum payment only should be made. The paramount need, as seen by industry, was to do the minimum required to avoid regulatory hassle.

In summary, in the beginning, when GLP was new to the world, the following applied almost universally:

- no scientists had any real understanding of the positive potential of GLP;
- consequently, there was no attempt to embrace the Quality Management aspects of GLP;
- senior scientists resisted GLP implementation where they could and were particularly allergic to QA functions (and often QA personnel);
- GLP was strictly limited to its minimal scope, *i.e.* to classical safety studies (toxicology) in the pharmaceutical and agrochemical sectors;
- the important roles and responsibilities of management in GLP were underestimated when not positively rejected;
- study directors (SD) were not well versed in the implications of their GLP responsibilities;
- QA functions were confined as far as possible to quality control (QC) activities.

The leitmotif of management and researchers alike was: "what is the minimum necessary for us to obtain GLP compliance so that we can get on with our real work?" or put another way; "What is the least we can do to avoid failing the GLP inspection?"

Because GLP was completely new, GLP experts often combined basic training and consultancy in one package. Consultants used GLP awareness training

as a lever to implement compliant systems. Particular attention was devoted to the development of compliant prescriptive documents (*e.g.* study plans, SOP) and descriptive documents (*e.g.* raw data, reports), concentrating, as you can see, on the “study”.

The important concept that GLP is a quality management system that could be used to strengthen processes which lead to right product, in this case reliable data and reports ready for registration, was missed entirely by most managers. Consequently, management wanted QA to check and check again to make sure that what left the office was in good, compliant, shape. This was an old fashioned approach based on outdated industrial methods (roughly 1930-1950) where the emphasis was on release of good product, rejection of bad, rather than on promoting the right processes to deliver good product [3].

Overall the aim of management was to ensure that the inspector would go home having given the company the green compliance light and “leave us in peace for the next couple of years”.

The impact on GLP consultancy

Clearly, management’s minimalist approach had an impact on what consultants were asked to do. Gap analysis, based on the two questions, “Where are we?” and “Where do we need to be?” was in vogue, with the implicit addition of “What is the least we can do to bridge the gap?” Not in vogue, in fact positively “out” (before even it had even been “in”) was any attempt to import ideas from other quality management systems. ISO, for example, was anathema.

Because of the researchers’ aversion to writing SOP, consultants were often commandeered to write them instead. It was difficult to persuade scientists that there are palpable benefits from involving the real actors, the technicians and operators in writing SOP. The SOP written by consultants were, of course, designed to fill the non-compliance gaps found during their gap analysis.

All efforts were focussed on the minimum scope of GLP, clearly targeting animal toxicology. But even more minimal than this, efforts were concentrated on study activities almost exclusively, excluding the important processes surrounding the studies. This

truncated view of GLP was aided and abetted by the FDA 1987 edict which stated that “The agency advises, however, that each study, *no matter how short*, needs to be inspected in-process at least once” (my emphasis) [4]. This ruling was far from helpful, because it emphasised the notion of studies as isolated events subject to ever increasing QC, thus slowing down progress towards the idea of using GLP to strengthen processes and reinforce quality management. Even today, it holds back some of the more timorous pharmaceutical companies in the USA.

The impact on GLP training

Like consultancy, training activities also serve as an indicator of the culture of the “foreign country”. Since GLP was new, training was essentially about getting to know the regulations. As course participants came with little or no GLP knowledge, classroom style presentations predominated. Some were excruciatingly boring, but even the lively ones consisted of the GLP expert telling participants what GLP is and, if they were lucky, how to cope. There was little room for discussion, little room for debate and even less room for exchange of GLP experience. Trainers stuck very closely to the letter of the GLP principles, with only the most imaginative stepping outside of the GLP regulatory mould to embrace relevant notions and the fundamentals of quality as explored in other standards. Training around the mainstream GLP activity of toxicology animal studies naturally took pride of place.

Management also held the reins tight on QA, promoting training in QC measures rather than in quality management systems. It was as if management wanted to make QA responsible for quality and tried to train the personnel to this effect, forgetting that, “The most dangerous belief that can permeate a pharmaceutical company is that quality is the responsibility of the quality assurance department. Every worker should be accountable for the quality of his own task.”[5]

GLP CONSULTANCY AND TRAINING REQUIREMENTS AT THE PRESENT TIME

One present day view is that GLP can be compared to a “muffin” (*Figure 1*). That is, GLP involves much

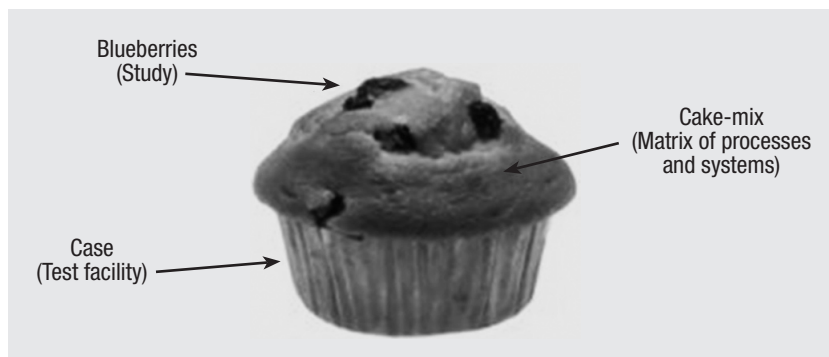


Fig. 1 | Good laboratory practice as a “muffin”.

more than just the studies. You cannot have a GLP-compliant study if the surrounding environment – facilities, systems and processes – is not well managed and supportive. But this realisation of the obvious came gradually. It was helped greatly by the various consensus meetings which were the initiative of the OECD. The OECD guidance documents, particularly the early ones on QA and short-term studies, talked openly about systems and processes and about how different approaches to dealing with problems were possible, while still remaining GLP-compliant. This woke up industry to the notion that GLP is a quality system analogous to other quality systems, and potentially a tool one could use for improving efficiency; something that QA professionals had been trying to tell management for some time.

Of course it was not only the consensus documents that influenced management's view of GLP. These documents represent a significant part of the general erosion of management's GLP aversion. Other factors included the influence of QA professionals who had grouped themselves together to form societies on a national and supra-national level. But mostly it was due to the hard work in-house of the QA unit, helped by some converts from the ranks of the researchers, notably some SD, who became aware of the advantages of well organised studies and support services. To these scientists a special word of thanks because they acted like disciples who, having glimpsed the promised land, promoted GLP with the sort of messianic zeal that only new converts have. What they rightly realised was that GLP helped them produce reliable, traceable data which reinforced the credibility of their studies. They also saw the advantages of streamlined organisation from the planning phases of studies, through the conduct of studies and on to archiving of material. Furthermore, they recognised that well controlled studies gave them greater ability to reduce experimental bias. The overall effect was that GLP helped scientists obtain demonstrably reliable results more rapidly, facilitated regulatory filings and helped reduce time to market.

Constant GLP evangelism, mostly by the QA unit, coupled with the proof, day upon day, of the advantages of this quality management system, gradually brought management to consider the GLP principles with something other than contempt. It took years of patient persuasion.

So, today, the GLP situation is a new country compared with where we started, in particular as regards the following aspects:

- mainstream safety study research scientists are now well versed in the GLP principles and often appreciate the benefits that they bring. New recruits have never known anything else and find the GLP principles natural and obvious;
- systematic refusal of the GLP principles is so rare that it is now considered idiosyncratic, outlandish, antediluvian and unsustainable;
- the regulatory scope of the GLP principles has

been widened. The increase has not always been intentional on behalf of the regulatory authorities (RA), sometimes industry has simply adopted the GLP principles because there is nothing else suitable on the agenda; this is the case for clinical laboratories, where the regulators have failed industry by not regulating!

- there is a realisation that multi-site studies present a real challenge and that the GLP principles can help sort things out;
- the importance of the “muffin” approach has focused GLP, and incidentally OECD guidance documents, on the GLP matrix, targeting, for example, computer use and validation, multi-site organisation, where the core is about communication, and archives;
- monitoring authorities (MA), now highly experienced and competent, are harder on QA personnel and SD and also concentrate efforts on the responsibilities of management;
- the QA profession has matured, with the formation of national QA societies, which are often given consideration by the national MA, the creation of supra-national federations and the creation of a scientific journal specifically for the QA professional (*The Quality Assurance Journal*, published by Wiley, founded in 1996 is still the only international journal specifically for QA professionals working in R&D in the Pharmaceutical, Health and Environmental sectors: www.interscience.wiley.com/journal/qa);
- considerable resources are invested in professional document management and secure storage and rapid retrieval of data and documentation.

Management has always looked for efficacy and, if possible, efficiency in the running of their business. They now look at the GLP principles as an ally to finding this efficiency.

The impact on GLP consultancy

In common with other industrial activities, GLP consultancy is subject to the normal constraints of the client-supplier relationship. So the consultant is now asked, “How can we ensure the integrity of the muffin”? Identifying the non-compliance issues in the matrix of support areas and interfaces has, therefore, become a major issue.

However, parts of the “muffin” may be outside of the sponsor company, so consultancy has developed two main functions; the first to audit on behalf of the client company (both in-house and externally), the second to prepare companies for regulatory inspections (e.g., mock inspections, inspection readiness).

Specialist consultants have grown up in new fields such as equipment qualification, computer validation, 21 CFR Part 11, analytical processes and risk analysis. Specialists are also required in areas outside main stream GLP, notably in biotechnology and in the analytical areas. There is also a slow awakening of interest in business processes.

The impact on GLP training

GLP training has been dusted down and redesigned to cover all aspects of the GLP principles. Of course, training still exists for basic GLP, but added to these we see special training programmes concerning the roles and responsibilities of major actors in GLP, namely, SD, QA personnel and, occasionally, management. There are also programmes designed to deal specifically with multi-site studies, use and validation of computerised systems and GLP applied to specific areas such as the clinical laboratory and archiving. You will notice that often these follow closely the ideas already developed by the OECD consensus and advisory documents. The whole ethos of the GLP principles grew positively with the formulation of consensus, the partnership between the OECD, the MA and industry. The free and extensive exchange of views at such meetings has had a truly positive effect on the development of the GLP principles. I would like to see consensus continue to be at the heart of OECD GLP initiatives.

In addition, nowadays, participants come to training sessions with some knowledge of GLP, often from organisations that are already compliant. As a result there is more debate and discussion. Thus it is far easier to organise stimulating training around workshops and case studies. Participants are not passive; they have their own experiences and points of view about how best to do things. Real understanding about the underlying issues is possible through the confrontation of ideas and opinion. Training under such circumstances has become a real pleasure for both trainer and trainee.

GLP CONSULTANCY AND TRAINING REQUIREMENTS INTO THE FUTURE

Few major companies are now worried about their GLP compliance status, although regulatory inspec-

tors still find occasional major problems. I said the same thing in 1990, but was perhaps too bullish; now it really is true [6]! However, particularly in the biotechnology sector there is a burgeoning of small, highly specialised companies that need the type of consultancy services previously provided to larger companies. Also there are GLP facilities being created in the countries of the emerging economies; these will need help in all aspects of GLP. In addition to these, there are other areas which require servicing: analytical laboratories facing the problems of the Registration, Evaluation and Approval of Chemicals (REACH) program, small scale chemical synthesis to provide test item for GLP studies, clinical analytical laboratories caught in the good clinical practice (GCP) regulatory hiatus, etc.

However, I believe that there will be one, single, overriding pressure that will influence the way GLP consultancy and training develops over the next ten to twenty years: this is the need to find a new paradigm for R&D as the R&D costs rise and the success rate falls.

Consider *Figure 2* [7]. This shows how between the year 2000 and 2005 R&D spending for big pharmaceutical groups has relentlessly risen so that today it costs around 820 million US \$ to bring one new chemical entity to the market. This trend has been fairly constant for the last 15 years. Is there any hope that without changing the R&D paradigm the trend will discontinue?

You will note also from *Figure 2* that the number of New Molecular Entities (NME) reaching the market is in constant decline. In sum, we are getting considerably less for considerably more. Can this go on for many more years? Moreover, the biotechnology sector has fared somewhat better than big pharmaceutical area, and this is one reason why some companies have pinned, and will continue to pin, their hopes, and their money, on this sector.

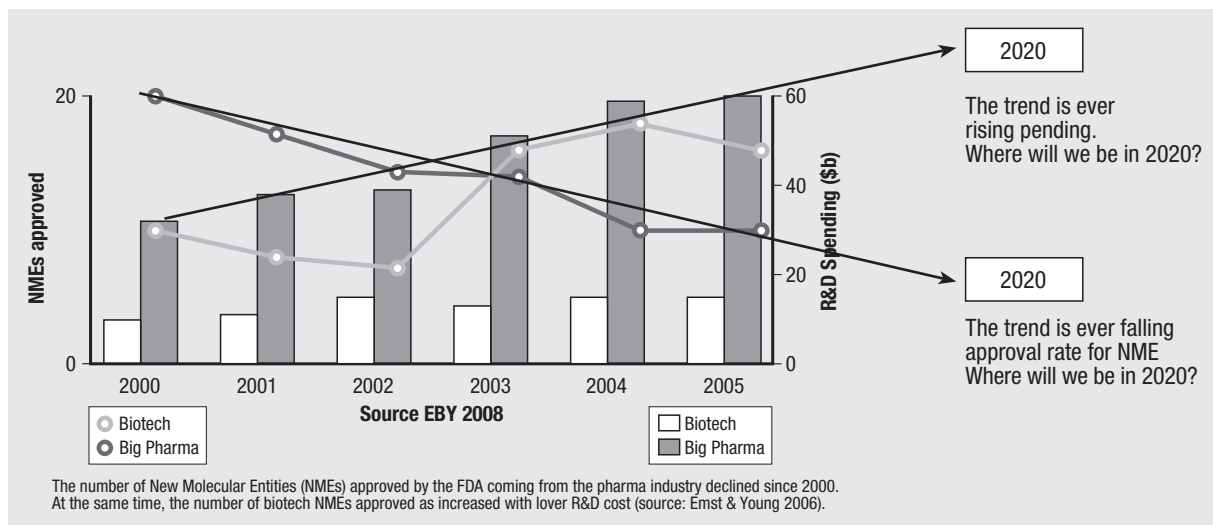


Fig. 2 | R&D spending and success rate from 2000-2005 (Reproduced with kind permission).

What can pharmaceutical management do about this? Two things: look for a new R&D development model and find ways of spending money more effectively. Here I will consider the financial side first before looking at a possible paradigm shift.

While waiting for a paradigm shift in the way we do R&D, we need to get a real grip on spending and find out how we can spend less and more wisely. So, where is this colossal amount of money being spent? About 80% goes on clinical trials, 50% on phase III studies and 30% on phase I and II studies. Thus, the part relating to GLP (about 10%) is “small beer”....or is it?

Let us next look at the success rate in the different phases of R&D. Suppose we start with 10 000 NME. Only about 12 get into GLP studies. However, to go from the chemist’s bench to the GLP toxicology department only costs us about 5% of the total 820 M US \$. How many of the 12 NMEs in toxicology survive to reach phase I clinical trials? If we are lucky half will survive, and half will fail. So we arrive in phase I clinical with 6 NME. The failure rate at phase I is about 33%. Thus 4 NME go into phase II. Half of these will fail, so only 2 NME get into phase III and finally, half of these fail, so 1 NME gets to the market (for the accountants amongst the readers, who have been totting up the percentage cost as they have been reading, the remaining 5% of spending goes on the regulatory submissions documents, troubleshooting and so on).

One of the words most frequently use in the previous paragraphs is “fail”. Companies are not very forthcoming about failure, but data suggests that the cost of failure is as high as 50% of the total R&D spending [8].

A little earlier on I called GLP studies “small beer” compared with clinical trials. But, let us look again at this in view of the cost of failure. If we could halve the failure rate (therefore halve the cost of failure) of clinical trials we would save 40% of our R&D spending. Or, put another way, if GLP studies could predict better which candidate NMEs were likely to be successful in clinical trials we would save an awful lot of money, maybe enough to keep the big pharmaceutical businesses going until a new R&D model brings them succour. This is a financial reason why all studies upstream of clinical should be of the highest quality, both GLP studies and research studies, because we also need better prediction for the candidates going into the GLP arena, even though the cost of failure is less here.

For financial reasons, pharmaceutical management is beginning to see the benefits of opting for the highest quality in R&D studies at all stages of the R&D process. Management would like to have an integrated quality approach throughout the company [9]. Integrating, but not combining GLP, GMP and GCP, using ISO as platform is beginning to occur. Remember that quality is viewed by management as a balance between compliance, cost and time (that famous triangle you will all have seen in books about quality). GLP supplies the compliance

component in non-clinical safety studies; management has to worry about quality across the board (including cost and time – which are intimately intertwined). Thus, approaches that optimise systems and processes are at last gaining interest. In addition, GLP is viewed by enlightened management as being only part of pre-clinical quality. It is no accident that quality in early research has now become an issue. Remember, “garbage in – garbage out” applies to all steps in the R&D process. Hence we have very recently seen the World Health Organisation (WHO) initiative on *Quality practices in basic biomedical research (QPBR)* [10]. A more holistic approach will impact the future organisation of GLP consultancy and training. One will borrow from other systems of quality management with increased reliance on risk analysis, process approaches, and qualification and validation techniques.

We can now turn our attention to the paradigm shift in the pharmaceutical R&D model. From what we see above about the financial situation, no-one doubts that a new R&D model is necessary. The problem is finding one.

Early in 2008, the American Association for the Advancement of Science held a meeting in Boston with the participation of several RA. Amongst the announcements was an initiative, supported by the RA in the USA, to launch an immense cellular toxicology research project. Reported in *Le Monde* the initiative, and others like it, may be set to revolutionise the R&D model and would have a significant impact on GLP consultancy and training [11].

In summary, the suggestion is that human cell lines could one day replace the vast majority of animal models used today. The human cell lines (kidney cell lines, hepatic cell lines, pancreatic cell lines etc.) would be exposed to NME and their reactions measured at a genome level. The tests could be very highly automated and this would have a massive effect on the speed at which research is performed before getting to clinical trials. It would, therefore, also have a gigantic effect on reducing the cost of R&D. To get a grip on the numbers, it is postulated that although it would mean replacing tens, or hundreds, of standard rodent tests by tens of thousands of *in vitro* tests, thousands of the latter could be performed each day [12]. This would transform all the present “time to market” standards and give a second wind to the flagging pharmaceutical R&D scenario.

With these types of methods relying significantly on automation we will also see an even more extensive use of computers and a concomitant increase in reliance on qualification and validation skills. However, tests will require careful validation before they are accepted by RA as substitutes for animal studies, but the fact that the initiative is backed by the regulators is extremely encouraging.

The impact on GLP consultancy

Apart from consultants needed for the general maintenance of GLP compliance and for the exten-

sion of GLP to areas such as analytical laboratories or laboratories new to GLP (developing countries), new consultancy services will be needed to provide expertise in the following areas:

- systems and process approaches, including process mapping and modelling. Some of this expertise is already available from those dealing with other reference standards such as International Standards organization (ISO) or total quality management (TQM);
- risk assessment and analysis. Using techniques developed for good manufacturing practice (GMP) and with reference to International Committee on Harmonisation (ICH);
- cost-effectiveness studies;
- *in vitro* techniques, including methods for study validation;
- qualification and validation of automated systems.

The impact on GLP training

There will still be a need for basic training and training to accompany personnel embarking on GLP for the first time. However, future training will need to be adapted to the techniques indicated above. Hence, there will be an increasing need for training in quality management in more general terms as the principles of GLP and standards for early research, such as QPBR, get closer together and are used by the same persons. This type of training will require insight into:

- process mapping and process improvement;
- risk management;
- quality indicators and metrics;
- techniques of audit based on risk analysis;
- responsibilities of management linked to business risk;
- *in vitro* techniques, including their validation;
- extension of computerised systems and validation to automation.

In addition to the type of training that will be needed in the future it is highly likely that the way it is delivered will change. No doubt there will always be room for training in classroom groups. The possibility of reaching out to a live expert and peppering her/him with questions and participating in debate is always a wonderful learning experience. In-house training, with the possibility of tailoring programmes to meet individual company needs (and incidentally save on travel) will become more popular. However, as training budgets are being limited and the training needs are being extended, two developments will become apparent. The first is for training programmes which can serve as certification, allowing staff to demonstrate the level they have attained, with the view to servicing their professional development. The second is the need to provide individualised training at distance leading, no doubt, to the growth of Internet-based training and e-learning programmes. Obviously, these two developments are not mutually exclusive. Indeed, Internet

training, followed by assessment modules, and covered by a certificate, from a *bona fide* learning centre such as a university faculty, is already beginning to show up on our computer screens. Finally, with the acceptance of the fact that quality in early research is as important as GLP, specific training in this field will be developed.

CONCLUSIONS

The above is an entirely personal view of our GLP journey from "foreign country" to present over the last thirty years. I do not expect everyone to agree with my view of history. I expect even fewer people will agree with me about the future. However, whether or not there is agreement about exactly where we are going, what seems absolutely certain is that we must go somewhere radically new. Fundamental changes in the near future are inevitable, as the present situation in R&D becomes more and more unsustainable.

Do changes to the R&D model imply changes to the quality management systems that support the model? Not necessarily, because the fundamentals of the GLP quality system relating to planning, performing, recording, reporting, archiving and monitoring research activities need not change. GLP is a robust standard and will be able to "take on" a new R&D model just as in the past it was able to take on, *e.g.*, the extensive changes which occurred with the sudden increase in the reliance on computerised systems. This is because the GLP standard is an adaptable quality management system with basics that can be applied to many different research scenarios. The OECD has recognised this by promoting the principles that were first applied to classical toxicology to other areas such as field trials, short-term studies, *in vitro* studies etc. GLP principles will need only minor tweaking to cover a new R&D paradigm.

What seems more important in the probable R&D scenario outlined above is that borders between non-clinical safety studies and early research will be far harder to define. Hence, there will be a need either to broaden the scope of the GLP principles (with or without tweaking the text) or to bring on board another quality management standard to cover early research (QPBR would be a candidate). Which of these two routes will be preferred depends upon whether or not the regulators of the future, faced with the new paradigm, continue to make a clear cut distinction between efficacy and safety as is the case with the model actually in use.

What is certain is that the foreign country of the future will be an exacting but exciting place to visit.

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