Good laboratory practice 30 years on: challenges for industry

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Summary. The principles of good laboratory practice (GLP) have undergone little change since they were established 30 years ago. Conversely, there have been huge advances in science and technology during this time. Test facilities (TF) have been challenged to utilise these advancements and thus enhance the quality of their programmes of non-clinical safety testing. As a consequence, practices are very different today compared with the late 1970's. The scientific advancements have also extended the boundaries of GLP principles and TF must maintain an awareness of the scope of GLP. TF now typically operate on a global basis and strive for harmonised systems, processes and procedures. This is particularly challenging when national monitoring authorities (MA) have different expectations and interpretations of the GLP principles. Other industry challenges that have emerged in recent years include the management of multi-site studies and the independence of the quality assurance (QA) unit.

Key words: good laboratory practice, test facilities, interpretation, globalization, technology, risk assessment, inspections.

Riassunto *(Trenta anni di buona pratica di laboratorio. Le sfide per l'industria)*. I principi di buona pratica di laboratorio (BPL) sono cambiati di poco da quando sono stati formulati trenta anni or sono. D'altro canto, nello stesso periodo le scienze e la tecnologia hanno fatto passi enormi. I centri di saggio (CdS) hanno dovuto adattarsi a tale progresso per incrementare la qualità dei loro programmi per gli studi di sicurezza non clinici. Di conseguenza, le attività sperimentali sono oggi assai diverse da quelle condotte alla fine degli anni '70. Il progresso scientifico ha anche ampliato i confini dei principi di BPL e pertanto i CdS devono mantenere una costante consapevolezza in merito al loro effettivo campo di applicabilità. Di norma, oggi i CdS operano su una base globale e mirano all'armonizzazione di sistemi, processi e procedure. Ciò risulta particolarmente difficoltoso quando le varie autorità di monitoraggio (MA) nazionali hanno aspettative ed interpretazioni diverse dei principi di BPL. Altre sfide che l'industria ha dovuto recentemente affrontare riguardano la gestione degli studi multisito e l'indipendenza della unità per l'assicurazione di qualità (AQ).

Parole chiave: buona pratica di laboratorio, centri di saggio, interpretazione, globalizzazione, tecnologia, defi nizione del rischio, ispezioni.

INTRODUCTION

Industry was challenged when the first good laboratory practice (GLP) regulations were introduced in 1978 and industry are still faced with a number of challenges. The challenges of today are again the consequences of change; this time not in terms of implementing new regulations, but in terms of applying the regulations in the modern day environment, an environment that is constantly changing. The GLP principles, despite being a little dated remain fundamentally sound and so can still be applied in the modern day environment. On the one hand, industry must consider the principles before applying new science, technology and strategy, whilst on the other hand, the GLP monitoring authorities (MAs) should recognise the impact of change on the quality of data that should allow for a pragmatic approach without compromising compliance.

Advances in science has led to new study types, new study designs, increased interest in biological entities, increased scientific methodology and the ability to measure more parameters. The GLP principles could be perceived as a barrier for such changes due to the risk or effort required to transfer novel research techniques into the safety testing environment. Industry should not move too quickly ensuring that appropriate validation has taken place and the GLP MA should readily accept valid models for safety testing.

Advances in technology have been of great benefit to the industry, for example, allowing data to be captured electronically and in a number of formats.

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These changes have enhanced the quality of data and should promote the application of risk management criteria; however this is somewhat constrained by the GLP principles, *e.g.* the requirement for quality assurance (QA) to audit every final report.

The advance in science and technology has also influenced the organisation and strategy of test facilities (TF). With improvements in communications and development of specialist areas, the industry can now fully act on a global basis rather than as a number of separate entities operating within the same organisation. The challenge here is how to harmonise procedures where there are parochial GLP MA interpretations. The improvement in communications and capacity to perform specialised or focused areas of work has also contributed to a significant increase in multi-site studies. Multi-site studies present more compliance risk than single site studies due to their complex nature.

A specific challenge for the quality assurance (QA) unit is maintaining its independence. The auditees perception of QA being the 'police force' has been replaced by QA now being considered a partner. This has greatly enhanced compliance as auditees more readily seek consultation and advice from QA. QA must ensure that the relationship does not impact on their ability to monitor in an objective, independent manner.

The industry is faced with a number of challenges related to the conduct of non-clinical safety studies. Among the main challenges are the incorporation of new science/technology into the safety testing environment, globalisation in the face of parochial GLP interpretations, the management of multi-site studies, independence of the QA unit and the scope of the GLP regulations themselves.

SCIENCE AND TECHNOLOGY AS A CHALLENGE FOR TF

In 1978 the GLP regulations were introduced by the US Food and Drug Administration (FDA) [1]. This created a new challenge for industry – the industry needed to understand these regulations, interpret the regulations, implement them and comply with them. The introduction of the GLP regulations also marked the birth of the GLP QA unit. Newly appointed QA managers held meetings to seek a better mutual understanding of the regulations. These meetings led to the formation of national QA groups, for example, the UK Quality Assurance Group which is now the British Association of Research Quality Assurance (BARQA).

Following on from the FDA regulations, the OECD published the OECD principles of GLP in 1982 and this was followed by several countries issuing national GLP regulations based on the OECD principles [2]. TF management, aided by QA and national QA groups implemented the requirements of the GLP principles.

The GLP principles are still in place today. These are now the international standard for non-clinical safety testing and the OECD have greatly helped in terms of international harmonisation and the mutual acceptance of data (MAD) [3-5]. Although this is the case, the principles themselves were written relative to the environment of the time and have undergone little change over 30 years. During this time, science and technology have seen huge changes. This has presented both an opportunity and a challenge for TF management.

TF have taken advantage of scientific/technological advances in their non-clinical safety testing programmes. For example, technology now allows data to be captured, processed and reported electronically. Use of such technology has greatly increased the quality of data. If you compare data from 15-20 years ago with that generated today, there is a striking difference in terms of quality and yet the older data were acceptable and compliant with the GLP principles, principles that have not changed that much over the years. This is a key message for the MA, that data quality has improved significantly over the years and this should be reflected in the inspection approach of the MA. There should be a different approach to that adopted in the late 1970's with a focus on the bigger picture and an appreciation that there is more than one way of applying the GLP requirements.

Advances in science and technology have also created challenges for test facilities. From the scientific perspective, since the introduction of the GLP principles there has been new study types, changes in study designs, increased methodology and the ability to measure more parameters.

There is a dilemma for industry when novel techniques are being considered. Sometimes there is a reluctance to bring them into the GLP arena particularly if they are replacing established techniques. The time and effort needed to transfer the technique might be considered a burden. On the other hand, there may be a temptation to introduce new techniques or methodology too quickly without taking into full account the GLP principles. For example, new assays or computerised equipment might not be sufficiently validated; standard operating procedures (SOP) may not be in place and people not adequately trained. Assurance that methods and equipment are fit for purpose is essential in today's environment as industry places so much reliance on the systems once they are up and running.

Some analytical methods are now very sensitive and this in itself can create issues. Sometimes small traces just above the lower limit of quantification might be picked up in control samples. Many TF now include naive samples as well as controls to try to explain any apparent contamination. Sometimes such contamination cannot be easily explained, but it should be remembered that apparent contamination at such levels could be insignificant compared with the degree of general biological variation within non-clinical safety studies.

There is an increasing interest in biological entities and this creates a number of challenges. There could

be different interpretations on the definition of test item/test item carrier mixture and what measures need to be taken to appropriately characterise these entities. Specialised immunological assays are sometimes required in studies and demonstration that the assays are fit for purpose can create difficulties.

Moving from science to technology, the latter has helped the industry in several key areas. The first is to streamline processes and systems, for example, by automation of sample processing and by electronic capture and processing of data. These processes have significantly increased the quality of data in recent years. Due to the increased data quality, risk management principles should be encouraged to focus on the key areas of risk.

Industry must remember that the systems and processes should be appropriately validated before implementation. Also, in the areas where there is human intervention, robust quality control (QC) procedures should be put in place.

Communications is a key area that has helped to change the strategy and organisational structure of TF. This has had two main consequences, namely, 1) globalisation and the associated harmonisation and 2) the increased number of multi-site studies.

GLOBALISATION AND HARMONISATION AS A CHALLENGE FOR INDUSTRY

Industry has changed in the way it conducts business. It is a reality that companies are now global in terms of structure, organisation and operation. They deliver GLP on a global basis. Globalisation results in a streamlined organisation that can work efficiently and effectively. This is due to global management oversight, resource optimisation, minimising duplication of functions and the harmonisation of processes, systems and procedures. Harmonisation can be a challenge since national GLP MA have parochial GLP interpretations, making it difficult to comply with the expectations of all relevant GLP MA. The GLP principles have always stated what must be done; the how it is to be done was and still is open to interpretation. Compliance monitoring inspectors have been heard to say that they expect to see this or to see that; industry's perception is that on occasions there is a lack of willingness to see alternatives or the bigger picture. It is understood that interpretation is often influenced by culture, attitudes and behaviours. Different opinions can be seen at all levels – within organisations, within countries and between different countries. This is not helped by the ever changing environment. Industry and MA all need to change and move with the times.

A few examples of the expectations of different MA are given below:

- some MA insist that test item characterisation is conducted in accordance with GLP and that exceptions should be in the compliance statement; others consider this to be outside of the scope of the study and therefore a standard such as good manufacturing practice (GMP) would be equally acceptable;
- some MA expect critical phase inspections on every study; others would allow all procedural inspections on a short-term study to be covered by a process-based regime;
- MA have different views on the reporting of terminated studies on test items with no human exposure. Some expect a final report while others would accept a summary report;
- for multi-site studies, if data is returned to the study director (SD) for archiving, some MA require the test site to retain a photocopy of all study data. Other MA accept retention of the protocol and report only;
- some MA do not permit data to be removed from the archive once lodged; others would allow removal under controlled procedures;
- at least one MA expects data to be paginated before archiving; others do not;
- some MA expect an independent review of the QA unit, others do not.

It is recognised that there is now greater awareness of the different interpretations and a number of initiatives are underway that reflect this. The Japanese Society of Quality Assurance is leading an initiative to identify differences in expectations between the US, UK and Japanese MA. The FDA is investigating GLP modernisation and it is encouraging that industry associations such as Society of Quality Assurance (SQA) and PhRMA are being consulted.

Globalisation and changes in company strategy has lead to an increase in the number of multi-site studies. Multi-site studies can present a compliance risk due to their complex nature and multiple interfaces.

MULTI-SITE STUDIES AS A CHALLENGE FOR INDUSTRY

In recent years, TF have gained a better understanding of multi-site studies. The guidance in the OECD Consensus Document on multi-site studies [6] has helped in this respect. Despite this better understanding, compliance issues continue to be identified by GLP MA. Multi-site studies can have numerous permutations relating to the number, types and compliance status of test sites. The TF and test site(s) involved in a study could have different interpretations on how a multi-site study should be managed and some of these differences may or may not arise from different MA expectations. All parties involved must have a clear understanding of the "rule of ones". Although a multi-site study takes place in a number of locations it is a single study and therefore must have one study number, one SD, one protocol and one final report. Some common deficiencies relating to multi-site studies arise due to:

- the principal investigator (PI) having little or no involvement in protocol preparation;

- the protocol not being distributed to all parties involved;
- no formal acceptance of responsibilities by the PI;
- insufficient communication between remote parties;
- ineffective QA monitoring of the entire study;
- test Site QA findings not communicated to remote SD.

INDEPENDENCE OF THE QA UNIT AS A CHALLENGE FOR INDUSTRY

There is an industry challenge associated with QA; that is for the QA unit to maintain its independence. The QA unit and the auditees have always had the common goal to help assure safety data is reliable, valid and of sound integrity. In the past, QA and the auditees may not have agreed how best this could be achieved and the relationship could be somewhat strained. This situation has changed in that many TF have recognised the benefit for the business and QA to partner in the delivery of quality and compliant facilities and studies. QA is no longer considered to be a police force. This has improved compliance as auditees actively seek consultation and advice from QA, this being very important in the modern day environment. The QA unit, however, must not overstep the mark. In particular, it must not become part of the process which it is monitoring. There must be no conflicts of interest and the QA unit must be able to monitor in an objective manner.

The industry/MA relationship is also very important. There can be consultation between MA and industry without compromising the independence of the MA and the MA will still have the ability to inspect TF in an objective manner.

Industry benefits from GLP MA consultation by being able to gather and disseminate regulatory intelligence. The QA unit and the business can then consider any impact in the context of their organisation; there may well be room for manoeuvre and interpretation. The business can then put in place any considered corrective actions or preventative measures in a proactive manner. Compliance should improve and result in a reduction in the number and severity of GLP MA findings, meaning less follow up activities and possibly a reduction in the number of inspections. Building this strong relationship will also help the MA to better understand the business environment. The relationship should be such that TF feel able to challenge specific MA interpretations if they believe they have justification.

SCOPE OF GLP AS A CHALLENGE FOR INDUSTRY

Another challenge for industry in the constantly changing environment is the scope of the GLP principles themselves. This can take on many levels from the national level down to a phase of a study.

The sponsor should be mindful when placing work in a country for the first time. The sponsor should verify the GLP status of the TF and also whether the country in which the facility is based is party to OECD MAD [3-5] and has a national monitoring programme and MA in place. If the country is lacking in these areas there is no guarantee that data submitted to other countries will be accepted by those countries.

At the TF level, part of a GLP study occasionally needs to be performed at a non-GLP facility. This arises when the work is of a specialist nature and no GLP laboratory having the capability can be found. In this case, national monitoring authorities and receiving authorities remain sympathetic providing the study protocol and final report make it clear that no claim of GLP compliance is being made for that part of the study. Some MA allow a claim of compliance to be made, but only under very stringent conditions. Also at the TF level, if an archive is an integral part of a TF, then it is part of a GLP TF. However, it is a common understanding that a standalone contract archive cannot be part of a national GLP Compliance Monitoring Programme as it does not conduct non-clinical safety studies. Despite this situation, it could still be subject to inspection by MA.

At the study level, there may still be different interpretations of a non-clinical safety study; in other words, there could be different opinions on whether or not a particular study type needs to be conducted in accordance with the GLP principles. The receiving authorities (RA) determine which studies must be done in compliance with the GLP principles, but there remain a few grey areas. For example, should studies utilising predictive software be subject to the GLP principles? Another example is when new study types emerge there might be uncertainty regarding their GLP status. This was the case when safety pharmacology studies became more prominent. In addition, when certain findings are discovered during a study, scientific advances now allow TF to run 'spin off' studies to investigate these findings; should all these investigations be performed in compliance with the GLP principles or does it depend on the nature of the investigation?

The standard to which assay method validation should be performed is sometimes raised. It is widely accepted that method validation does not need to be done in compliance with the GLP principles, but that a robust validation process should be in place to assure the validity of the assay used in a GLP study. Assay method validation is not specifically mentioned in the GLP principles, but it is indicated that methods should be fit for purpose.

CONCLUSIONS

Science and technology have moved on since the advent of the GLP principles. As a consequence, the TF environment has changed and continues to change. This brings along new challenges for industry, namely: how to introduce new science and technology into the regulated environment; how to move forward with globalisation and harmonisation

in the face of parochial GLP interpretations; how to ensure the quality and compliance of the increasing number of multi-site studies; how to maintain the close business/QA relationship and industry/MA relationship without compromising independence; how to ensure the GLP principles are applied to all work/study types required by the RA. These challenges are not insurmountable. Although the GLP principles themselves have not changed significantly since the late 1970's, they are still fundamentally sound. The principles can still be applied in the modern day environment providing all parties recognise the need for a pragmatic, flexible approach that does not lose sight of the bigger picture.

Disclaimer

This manuscript does not necessarily reflect the views of the Author's Company.

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