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Critical aspects in the application of the principles of good laboratory practice (GLP)

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Summary. - The principles of good laboratory practice (GLP) are very flexible and an accurate interpretation is required in the application phase. Each test facility has to apply the principles of GLP within its own laboratories, taking into account both the cultural and the organisational aspects. Furthermore, the GLP quality system, as all quality systems, is a dynamic, not a static one. Continuous improvement, depending on the evolving state of the art, is essential. As a consequence, there are many difficulties as well as many different ways in applying the principles of GLP. The cultural aspects play an essential role. The knowledge, experience and fully adherence to the GLP principles, combined with the knowledge of the problems linked to the conduct of various types of non-clinical laboratory studies as well as continuous discussion with representatives of regulatory authorities are mandatory in order to select the correct and adequate methods of application.

Key words: OECD, good laboratory practice, quality assurance, regulatory studies, non-regulatory studies, multi-site studies.

Riassunto *(Aspetti critici nell'applicazione della buona pratica di laboratorio)*. - Nel leggere i principi di buona pratica di laboratorio (BPL) emerge chiaramente il loro alto grado di flessibilità e, quindi, l'intrinseca necessità di una loro interpretazione in fase applicativa. Ciascun Centro di saggio (CdS) è chiamato ad applicare i principi di BPL in un contesto proprio e unico, sia da un punto di vista organizzativo e strutturale che da un punto di vista culturale. Inoltre, il sistema di qualità BPL, come tutti i sistemi di qualità, è un sistema dinamico che necessita di un miglioramento continuo in relazione al continuo divenire dello stato dell'arte, sia tecnico-scientifico che normativo, in cui un CdS si trova ad operare. Di conseguenza, molte sono le difficoltà e le problematiche che emergono nella fase applicativa dei principi di BPL e diverse sono le possibili interpretazioni applicative. Rimane fondamentale l'aspetto culturale inteso come conoscenza, esperienza ed adesione ai principi stessi che, insieme alla consapevolezza delle problematiche legate alle varie tipologie di studi e al confronto continuo con i rappresentanti dell'ente regolatorio, sono alla base della selezione di modalità applicative idonee e conformi alla norma.

Parole chiave: OECD, buona pratica di laboratorio, assicurazione di qualità, studi regolatori, studi non regolatori, studi multisito.

Introduction

Inherent in the principles of good laboratory practice (GLP) are two critical aspects which have caused many of the problems encountered during the application phase, *i.e.*, first, rather than rules they are guidelines, principles that require interpretation during their implementation in a real situation; secondly, they demand continuous improvement in order to maintain the defined quality system. The need to interpret the principles of GLP implies flexibility and expertise on behalf of those responsible for their implementation within a test facility (TF). Cultural aspects, along with knowledge and a complete understanding of and adherence to the principles of GLP, are fundamental in order to guarantee a pragmatic approach during application of the principles and then the adoption of adequate solutions.

In view of the various types of operation, processes and organisational aspects, the possible solutions are manifold. It is often difficult to find a suitable solution from many possibilities, which can be best integrated into an individual organisation, both in organisational/ operational and economic terms. The need for continuous improvement is linked to the progress of technical and scientific knowledge, that results in a continuous updating of the rules, as well as to a broadening of the scope of the principles of GLP and to the ongoing process of international harmonisation. From this comes a continuous change in the state-of-the-art in which a TF operates. Such change represents the only way to ensure maintenance of a defined quality system, provided that it is implemented in a controlled way.

To introduce changes in a controlled fashion means to work closely according to the plan-do-check-action (PDCA) cycle [1]. This allows for innovations, either

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technical/scientific or regulatory, and to analyse the impact of such proposed changes on the organisation as a whole, the introduction of changes, the evaluation of their real impact on the organisation by means of planned verifications and the adoption of appropriate corrective action as necessary.

The last revision of the OECD principles of GLP, adopted in Italy *via* the Decree of 5 August 1999, introduced, for example, new aspects calling for in-depth discussion and analysis among involved parties in order to arrive at a harmonised interpretation [2-5]. This process resulted in a critical review of the actual operational procedures in order to ensure their suitability regarding the new principles of GLP. Also in Italy the adoption of the new principles of GLP has been followed by various initiatives to promote discussion among the interested parties, primarily those responsible for quality assurance (QA) functions and the regulatory authority representatives responsible for GLP compliance monitoring.

The most frequently debated issues were addressed and examined also at an *ad hoc* round table discussion organised by the Italian group of quality assurance in research (GIQAR) [5].

In this paper only a few examples are given of the critical aspects which should be faced during implementation, not all of which are linked to the revised principles of GLP, namely, adequate separation between regulatory and non-regulatory studies, multi-site studies, use of external sites and responsibility and dates relevant to the study.

Adequate separation between regulatory and non-regulatory studies

In order to avoid misunderstandings it should be stated first that by regulatory studies it is meant studies which fall within the scope of GLP, whilst non-regulatory studies are those studies which are outside the scope of GLP. For non-regulatory studies, the adherence to the principles of GLP is not mandatory; such studies are therefore not subject to inspection by the designated regulatory authorities.

In many organisations, whether national or international, contract research organisations (CRO) or sponsors, both types of study, regulatory and non-regulatory, are carried out in the facility itself (own laboratories, own animal facilities, etc.). An adequate separation in the conduct of these two different types of study creates several problems in the implementation of the principles of GLP. Various solutions can be envisaged, three of which are described and discussed hereafter, all being equally valid in the extent of compliance with GLP, *i.e.*: complete separation and separate organisation; complete separation and same organisation; no separation at all.

Complete separation and separate organisation

This would appear to be the less problematic solution to implement, as a completely separate organisation is used for the conduct of regulatory studies. A separate organisation could be: laboratories/operational areas located in a completely separate building/company; laboratories/operational areas completely separate, even if located in the same building (*e.g.*, two different departments). In either case the adequate separation between the two types of study is automatically assured by the physical, operational and organisational separation.

Complete separation and same organisation

This is where regulatory studies are carried out within the same TF (laboratory, animal facility, etc.) as the non-regulatory work. In such a case, adequate separation can be ensured, for example, by the temporal separation of the two kinds of studies. It will, however, be essential to define the method of conduct and separation of these two types of studies, to provide, *e.g.*, suitable labelling of materials, equipment, locations and documentation in order to ensure separation between the two activities and avoid misunderstandings and potential errors during the conduct of the studies. This option is the most complex to manage and control operationally. It requires that the personnel, the facility and the organisation adopt two different quality standards according to the activity concerned. This is a route which can be followed particularly where the number of regulatory studies is limited compared to the volume of non-regulatory work. It must not be forgotten, in this context, that quality has a cost; hence, for an organisation which performs only few regulatory studies according to the principles of GLP, this could be the ideal solution in terms of both quality and cost.

No separation

This last option involves the coexistence, both physical and temporal, of regulatory and non-regulatory studies or activities within the same TF (same laboratory, animal house, etc.). This third route to quality requires the adoption of one standard of quality alone, *i.e.*, the one which is most restrictive and which results in the integration of the diverse systems and levels of quality existing within an individual organisation. Such an option is almost mandatory for those organisations where the majority of the studies and activities conducted fall under the scope of the principles of GLP.

The adoption of a single standard of quality requires careful attention and appropriate interpretation of the rules, which would not be applicable to non-regulatory studies in many circumstances. The possible differences

in interpretation and application of the principles must be duly reflected in the internal standard operating procedures (SOP). These differences should be limited essentially to aspects of management of the appropriate studies and therefore to senior management, study directors, principal investigators and QA unit. The experimental methods must, however, be the same for the technical staff. This would appear to be a *conditio sine qua non* for the adoption of one quality standard which ensures compliance with the principles of GLP.

A useful example for understanding the acceptability of an integrated quality system and, therefore, a GLP system as a unique quality standard where the principles of GLP are the most stringent, is the archive. Such a facility, in terms of GLP, must ensure the appropriate storage of the material generated throughout the course of a study. This material must be maintained so as to allow for easy archiving and retrieval; it must be accessible only by authorised persons and any transfer and access to the material must be documented. The questions which emerge as regards the organisation of a GLP archive will certainly include the following: should such an archive contain only material relevant to GLP studies and activities? Is it possible to include in the same archive material related to non-regulatory studies or activities? Is it possible to place material from different origins within the same archive? One of the possible interpretations of the rules could be the following: in a GLP archive material related to non-regulatory studies or activities can also be stored, provided that the conditions required for studies or activities performed according to the principles of GLP apply to all the material present.

The position adopted by the OECD would appear to confirm this interpretation, i.e., the adoption of one quality standard. In the monograph entitled *Quality assurance and GLP*, in fact, there is a paragraph specifically addressing this issue "QA and non-regulatory studies" [6]. In this paragraph it is stated that "If the non-regulatory studies are not conducted in accordance with standards comparable to GLP, this will usually have an impact on the compliance of regulatory studies…". It is almost as if the OECD is proposing the adoption of a single quality standard, with the aim of eliminating the potentially negative influence of non-regulatory work conducted at a level of quality below that required by the principles of GLP.

Multi-site studies

The Decree of 5 August 1999 clarified several aspects related to the application of the principles of GLP to field studies, by integrating within the principles the concepts first expressed in a specific monograph on this subject [2, 7]. This, however, introduced new difficulties in the interpretation of GLP principles for different types of studies. Nowadays, regulatory studies more frequently require the involvement of one or more test sites in order to complete all phases of the study. This is for several reasons: it could be necessary to select different geographical locations, as in the case of field studies; a test site may not have the technical or scientific capacity, the experience or the facilities to conduct analytical work; the sponsor might wish to carry out analysis of dose preparations in-house, either because a validated method already exists or as a final quality control on the CRO conducting the *in vivo* phase of the study, and the like. In such cases a single study could be subdivided into several studies, one for each test site (one study plan, one study director and one final report for each test site) or it could be considered as one study and then conducted as a multi-site study (one study plan, one study director and one final report, regardless of the number of test sites involved). In the first case, this would require no additional change in the conduct of studies. In the second example, however, a very different and more complex scenario must be faced.

Although a multi-site study includes activities carried out at a number of test sites, it is still a single study which must be conducted according to the principles of GLP. The TF, however, comprises all the test sites where the study will be performed and could also include one or more test sites belonging to the sponsor, or one or more CRO. The situation is even more complex from the practical and managerial point of view, since the study director and the QA of the TF could be located away from the sponsor, for example at a CRO, yet, the very sponsor is also a test site. To ensure an appropriate flow of information, such as communication of the results of QA inspections (deviations from study plan) from the various test sites, including also the sponsor and other CRO, may not be easy or even at all possible.

Regarding QA, the situation is equally complex. For example, if the test facility QA is that of the sponsor, it will be possible, though not easy, to manage an appropriate flow of information concerning the results of audits and inspections from the QA unit of the various test sites. More difficulties will be encountered where the QA of the test facility is located in a test site different from the one where the study director is located, particularly where the QA is at one CRO and the study director at another. Conflict of interest as well as confidentiality issues could arise. In practice, the new principles of GLP permit the delegation of a number of the study director's responsibilities to the principal investigator(s) and then permit the conduct of a study as a multi-site study, maintaining its integrity as one study. Nevertheless, they still allow a study to be conducted as several separate studies, one for each test site.

The conduct of a study as a multisite study must be seen as a new opportunity, *i.e.*, not an obligation, but rather a further element of flexibility within the principles [8]. If, and how, the situation will change as regards studies conducted according to the principles of GLP will be soon perceived, not only in relation to the different interpretation of those conducting the work, but also regarding the issue of the new OECD monograph which is currently being finalised and the regulatory authority perspectives.

Use of external sites

The use of external sites by a TF is closely related to the issue of multi-site studies. External sites rule off suppliers of goods and services which need not comply with the GLP principles, but they include sites where a phase of the study will be performed, along with possible consultants, such as cytogenetists who may be delegated to read slides in their own facility. Sites of this type are hard to include within a national monitoring programme for GLP compliance.

The same problem exists for sites which could request GLP compliance, but which choose not to do so for various reasons, *e.g.*, a university laboratory which is delegated to perform a specific analytical step for which it is a centre of excellence, but which participates in GLP studies only on such occasions. In real life, such situations occur frequently and must be managed appropriately. A TF should carefully assess the choice of test sites and opt, where possible, for those in compliance with the principles of GLP. Where, for any reason, this is not possible, it should nevertheless choose a solution which guarantees the highest level of reliability of data. The use of external consultants (*e.g.*, a consultant cytogenetist) can be regarded as a temporary extension of the test facility [8]. In fact, the management of the test facility could easily ensure direct monitoring by the study director and QA at the external site. Provided that an efficient and effective monitoring is in place, the study director could guarantee GLP compliance for the activities carried out at that site.

Different and more complex is the situation where the external site is, *e.g.*, an entire laboratory. Also in such cases the management of the TF can ensure direct monitoring by the study director and QA, but it will certainly be more difficult for the study director to guarantee GLP compliance of activities conducted at such sites.

To implement GLP in a laboratory cannot be though improvisation, nor can it be achieved in a short period of time and limited to only one study. This does not mean that non-certified sites cannot conduct given phases of a GLP study; rather, where it is necessary to do this, the use of such sites must be indicated by the study director in the final report as a GLP deviation. Indicating whether there was direct monitoring on behalf of the study director and QA provides the regulatory authorities with all the information necessary to evaluate the reliability and quality of the data submitted.

Responsibility

The new principles of GLP were shaped also taking into account the responsibility aspect, primarily in order to detail responsibility concerning multi-site studies and to clearly identify the TF management and its related GLP responsibility, as stressed by the principles. One modification not related to the introduction of the concept of multi-site studies, which should be evaluated during the application phase and falls within the responsibility of the TF management, is a new phrase prescribing to "ensure that a statement exists which identifies the individual(s) within a facility who fulfil the responsibilities of management as defined by these principles of good laboratory practice". What is meant by such a "statement" in this context? What do the regulatory bodies expect to find in a test facility to meet this requirement? This change appears to be a clarification rather than a new requirement. In reality, the availability of an organisational chart and of job descriptions specific for each function should satisfy this GLP requirement. It is well know, however, how often management can be an entity which is not well defined and how often GLP responsibilities are delegated to an organisation.

The new GLP requirements, therefore, make explicit the need for documentation to be available at the TF which clarifies and defines in unambiguous terms the possible delegation of responsibility within management and the organisation. Essentially, where necessary, besides organisational chart and job descriptions, additional documents and statements are required to clarify the type and extent of responsibility associated with the various functions. This is always with the aim of identifying functions which are directly associated with the responsibilities which the principles of GLP assign to management, such as, *e.g.*, the designation of study directors and principal investigators, approval of SOP and so on.

Study-related dates

This subject is important primarily from the point of view of illustrating the difficulties which can arise from apparently simple or banal requirements. The new principles of GLP include a new definition as regards the dates of starting and completion of experimentation, *i.e.*, "Experimental starting date means the date on which the first study specific data are collected"; and

"Experimental completion date means the last date on which data are collected from the study". These two definitions cannot be interpreted unambiguously. What should be considered as "the first study specific data" for a study? For example, for an *in vivo* study could it be the purchase of the animals, their receipt, the allocation to groups or the first treatment? The purchase of animals, however, could be for more than one study, as could be their receipt. Animals taken from an order related to one study could be used for a different study, and so on. The same questions exist for the date of completion of experimentation. A study ends with the sacrifice of the animals, with the reading of the histological slides, or what else?

For other types of study, *e.g.*, *in vitro* studies, the start and completion dates for the experimentation will obviously mean something different. The same applies to studies which are actually only phase(s) of a study such as the analytical phase of a kinetic study, carried out as a separate study. Each organisation must define and standardise the interpretation of the definition of the experimental starting and completion dates. Their clarification in the internal SOP remains the simplest and most appropriate approach.

Conclusions

The principles of GLP are guidelines rather than rules with the objective of guaranteeing the quality and validity of data generated in safety testing. The final aim is to facilitate the acceptance of data at both national and international levels in the context of regulatory processes where the authorities have to assess the safety of new products. It is clear that there is a high degree of flexibility and thus an intrinsic need for interpretation during their application. Such flexibility is highlighted by the wide use of words such as adequate or suitable and is linked not only to the broad GLP application field, but also to the large number of TF for which these principles are intended and which are responsible for their application. Each TF is in fact asked to apply the principles of GLP in its own context, which is unique both from an organisational point of view and from a cultural perspective.

Moreover, the GLP quality system, as for all quality systems, is a dynamic process which requires continuous improvement in relation to the evolution of the state-of-the-art, both technical/scientific and regulatory, within which a test facility operates. As a consequence, many difficulties and problems arise during the application of the principles of GLP and the possible interpretations are diverse. Cultural aspects remain fundamental, as experience, understanding and adherence to the principles along with knowledge of the problems associated with various types of studies and the interaction with the representatives of the regulatory bodies, are the basis for the selection of pragmatic and appropriate modes of application compliant with the principles. Their implementation should always be based upon defensible decisions in terms of suitability and adherence to the principles of GLP, so that they can be accepted by the regulatory authorities responsible for the GLP compliance monitoring programme.

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