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Condensed from presentations and discussions at the DIA Workshop "The Revised OECD Principles of Good Laboratory Practice," September 3–4, 1998, Brussels, Belgium.

*The opinions expressed are those of the authors and do not necessarily reflect the positions of the respective monitoring authorities or companies.

This paper is the condensed result of the presentations and discussions held at the DIA Workshop "The Revised OECD Principles of Good Laboratory Practice," held September 3 and 4, 1998, in Brussels. The workshop brought together inspectors from compliance monitoring authorities and quality assurance units in industry, as well as study directors working according to the rules of Good Laboratory Practice (GLP). They discussed a number of issues important to the successful implementation of the revised Principles of Good Laboratory Practice of the Organisation for Economic Cooperation and Development (OECD), were informed about the changes which had taken place in this set of rules, debated areas of controversy, and looked at opportunities in the revised principles to improve the quality of safety studies. Specific areas covered included the new definitions given in the revised principles and their pragmatic application, the question of whether the new position of the principal investigator would offer any benefits to the procedures in the pharmaceutical industry, the issue of what constitutes a short-term test and how a test facility and its quality assurance unit could sensibly deal with it, and the impact of information technology, including the possibility of electronic signatures on Good Laboratory Practice and its implementation in the future. There are no easy solutions or handy recipies for any of the issues tackled in these discussions, nor were they expected. The result of the workshop was a better understanding of the various viewpoints that could be taken when it comes to interpreting and implementing the Principles of Good Laboratory Practice. The rules governing this quality system are general terms which must be adapted in a pragmatical manner to widely differing situations, and a workshop such as this can help to bridge the gaps between this wide array of disciplines working under GLP. In this, the DIA Workshop on the "The Revised OECD Principles of Good Laboratory Practice" succeeded in full measure.

Key Words: Study; Definitions; Responsibilities; Short-term studies; Sponsor; Principal investigator; Information technology; Validation

PRELIMINARY REMARKS

THIS PAPER IS THE condensed result of the presentations and discussions held at the DIA Workshop "The Revised OECD Principles of Good Laboratory Practice," held September 3 and 4, 1998, in Brussels. The workshop brought together inspectors from Good Laboratory Practice compliance monitoring authorities and from quality assurance units in industry, as well as study directors actively involved in the implementation of the revised OECD GLP Principles (1). The workshop was well received, and the lively discussions pointed to an obvious need for more public exchange of opinions and views. There was the unanimous opinion within workshop faculty that a summary publication should be undertaken with the goal of further disseminating the views and opinions expressed on the issues discussed, thus further propagating these discussions. The present paper attempts to bring the changes, the chances, and the controversies surrounding the revised OECD Principles of GLP to the fore, with a view of also fostering harmonization in their application through continuing discussion.

INTRODUCTION

The GLP principles had originally been developed from, and modeled to, the conduct of (chronic) toxicity studies in animal test systems. The extension of GLP principles to other types of studies, notably to field studies, the application of these principles to the online recording of data and the concomitant necessity for validation of the respective information technology systems, as well as the "fragmentation" of studies with parts contracted-out and recontracted-back were among the developments in the field of "health and environmental safety testing" that made it necessary to discuss possible differences in the interpretation of certain aspects of the GLP principles. Commonly agreed interpretations were thus developed under the auspices of OECD in consensus

workshops, and were subsequently published in the OECD Series of Consensus Documents. The progress and developments, however, reached a stage where it was considered necessary to revise the original OECD Principles, in order to integrate such common interpretations, to incorporate GLP in the new fields of application, and to incorporate new ways to cope with the ever greater complexities of study conduct. There had been controversial points in the "old" principles, issues that had either not been resolved despite prolonged discussions or that had arisen as controversial points already in the primary development of GLP. Some of the changes in the revised principles were made with the intention of resolving such controversial issues. Other changes had been introduced in response to the changed "study environment" or simply to incorporate issues resolved to satisfaction in consensus documents. In summary, major changes have been introduced in the revised principles which call for implementation and for renewed consensus interpretations.

In every change, however, lies not only the potential to improve the quality system of GLP and to facilitate the conduct of studies and the tasks of quality assurance, but there also looms the potential for further controversies about the value of the "old ways" in comparison to the "new" ones and about the interpretation of new rules and the value of the added possibilities. The GLP principles had their origin in those studies which form the major part of the preclinical safety documentation for a pharmaceutical data submission. The development of GLP into, and development of tools from, ecotoxicological and field studies led to the incorporation into the GLP principles of notions that had not been considered before in the context of (mammalian or *in vitro*) toxicology studies in the pharmaceutical industry. Thus, the application of such "new" concepts and possibilities could be regarded as much as a chance to cope with increasing globalization of toxicity testing as it could give rise to controversial opinions about their true value for pharmaceutical toxicity testing. The workshop in Brussels did not attempt to provide final answers or ultimate solutions to such questions, but aimed at a discussion of their facets and possible, practicable (and practiced) ways to deal with them.

DIFFICULTIES WITH DEFINITIONS

Definitions may be considered the linguistic counterpart to mathematical axioms. From these not further reducible entities, the logical construction of the whole set of principles is started. Definitions are necessary to provide everybody with building blocks as harmonized and equally accepted as possible, but their formulation by reduction of the vast area of specific details and delineated by exceptions-to-the-rule down to the general, simple and straightforward one-sentence-definition can suddenly give rise to uncertainties. One does not need to invoke the OECD definition of short-term studies which experts finally agreed on (and which will be dealt with later), but a number of other definitions may also give rise to controversies in their everyday application.

While there are definitions for study initiation and study completion, and for experimental starting date and experimental completion date, there is a certain lack of logical connection between them. On the one hand, it is obvious that "a written (study) plan should exist prior to the initiation of the study," since study initiation is defined as the date on which the study director signs this study plan (which, therefore, logically, must exist at this time). On the other hand, there is no obvious, formal connection between study initiation and the experimental starting date, such as a paragraph indicating that this latter date should follow the former one, or that experiments (data collection) should be performed only after the initiation date. The intention, however, was certainly that a study plan should exist prior to the start of study activities in order to conduct the study in an orderly and planned fashion. This logical connection, however, can only be inferred from the fact that the study plan should contain, among other information, the proposed experimental

starting date. But with this term, the next difficulty seems to arise. The "experimental starting date" is defined as the date on which the first study-specific data are collected from the test system. This definition, although concise and logical, leaves a further, practical question unanswered: which data should be regarded as "study-specific"? Do health checks after the arrival of animals or the weighings used for stratification and randomization belong to this category? Does the acclimation period generate study-specific data, or does only the first application of the test item do so? The same practical questions arise with the "experimental completion date," where opinions clash between regarding the necropsy date as the last occasion on which study-specific data are collected and regarding only the last reading of the last slide by the pathologist as constituting the true end of the experimental phase. From one possible interpretation of the principles the latter opinion would seem to dominate, as the reading of slides also could be regarded to constitute "original observation," while from another, possibly more pragmatic point of view, the necropsy as the end of the in-life phase of a toxicology study could be regarded as the end of experiments (with a possible extension to the cutting, embedding, sectioning, and staining operations, until the final slide preparation), since reading the slides may not be viewed as "experimenting" anymore, but could be regarded rather as "interpreting the data" (ie, tissue sections) by the pathologist. This activity may be compared to the study director, who, on writing the final study report, is interpreting the data output from hematology, clinical chemistry, and urinalysis determinations, which at this stage are no longer experimental activities.

What is true for a carcinogenicity study, however, may be wrong for an analytical chemistry study; what can be applied to an *in vitro* genotoxicity study could be completely out of question for a teratology study. Therefore, it would seem to be important to interpret these definitions flexibly and with well-considered regard to the study type and the "experimental" activities connected with it. This need for flexibility and pragmatism illustrates furthermore the reason for, and the urgent necessity of, the OECD requirement that inspectors in monitoring authorities should be knowledgeable in the studies they have to inspect and the GLP conformity of which they have to judge. Only by a certain knowledge of the problems in the conduct of such studies will they be able to appreciate the pragmatic solutions for the dificulties with definitions illustrated above.

Another definition problem arises with changes in the study plan: While in the "old" principles, changes to the study plan could formally only be made by amendments, the "new" principles formalize the distinction between "amendments" and "deviations." Although the definitions of these two possibilities for execution of changes in the study plan seem clear-cut, there might be practical difficulties in the application of these definitions to the "real world." First of all, common-sense logic seems to tell us that every change in a study plan is a deviation from its original intentions; in this sense, the difference between deviations (in the OECD-sense) and amendments are that there are deviations which have only to be taken notice of and deviations which necessitate a formal amendment. But can, for example, the shift of the date for the conduct of some specific activity, fixed in the study plan for Wednesday, to Thursday, really be cause for an amendment? Not even a deviation would have had to be acknowledged by the study director had the plan just called for this activity to be performed "during week xy of the study"! Or would it have to be an amendment if the study director decided for this shift on Monday, thus "planning" it in the sense of the definition, but be regarded as a deviation only if the shift became necessary due to a sudden computer failure on Wednesday morning, making ("unplannedly") the execution of this activity impossible? Again, the principles provide the basic definition only, but it is the study directors and the quality assurance personnel who have to come to a consensus and agree to a common interpretation within their test facility. There may again

be good reasons for setting the borders between amendments and deviations somewhat differently in different test facilities or even within a test facility for different studies, but the foremost need is in a clear policy of the test facility for the application of the "change instruments" deviation and amendment, which has to allow for consistency in their use.

Such common understandings between GLP partners, or their policies, will also be of great help in the implementation of some of the "looser terms" as, for example, the "timely manner" in which the quality assurance unit is to be informed of changes in the scheduling of study activities.

THE PRINCIPAL INVESTIGATOR—NECESSARY OR NUISANCE?

GLP was originally developed under the notion of "one test facility—one study director—one study—one report," derived from the manner of conducting "simple" toxicity studies, and the accountability provided by a *single* study director who plans, oversees, and controls the conduct of the study and is responsible for the results of a study is one of the most important aspects of the GLP principles. In reality, however, certain types of studies could not be fitted into this scheme, notably field studies with pesticides. There, the study director would sit in his office or laboratory in one country, while parts of the study he/she was supposed to direct and personally supervise were carried out on a certain number of field plots, situated in one or more countries around the globe. In this situation, the study director could certainly not him- or her-self supervise all parts of the study, as he/she could do with a classical toxicological study, where everything is performed within the same test facility (if not within the same building or even on the same floor). Thus, the position of the "principal investigator" (PI) was created, first described in a OECD Consensus Document on Field Studies (2), and finally legalized in the revised principles. According to the new definition of the PI, some of the study director's responsibilities may thus be delegated to a PI in those cases where the study director cannot exercise immediate supervisory control over any specified phase of the study.

While for field studies this concept certainly brought about a very welcome alleviation of the study director's burden by distributing some of the responsibilities onto other, better situated, shoulders, the need for this concept may not be obvious in the same way for the pharmaceutical industry. There, the "classical" conduct of a study has been much more prominent, where the study director is normally able to completely control the whole study. Even when, in order to speed up the development process of regulatory toxicology studies, studies were subdivided into various phases (eg, *in-life*, toxicokinetics, formulation analytics, histopathology, etc.) which were conducted in different places, and which thus employed something like a multisite approach, the involvement of collaborating investigators with defined functions could be handled by the study director within the framework provided by the "old" principles. In such a case, where these (internally or externally situated) investigators performed the investigations according to a detailed study plan and according to standard operating procedures (SOPs), where the sponsor's quality assurance unit could conduct the appropriate inspections, and where the study director could exercise some kind of control over all parts of the study (see Figure 1), the appointment of a PI may not be considered necessary. On the contrary, it might be seen as a nuisance, since such an appointment would create additional hierarchical levels within the structure of study control, and might thus introduce further communication problems.

Depending on the complexity of the task, or the specialized knowledge necessary to perform this part of the study, the use of a PI might, however, be regarded as an optimal solution. Whether these out-sourced activities would be supervised by a PI or simply by a participating investigator as "principal scientist," the matter of study control could probably be resolved without difficulties if

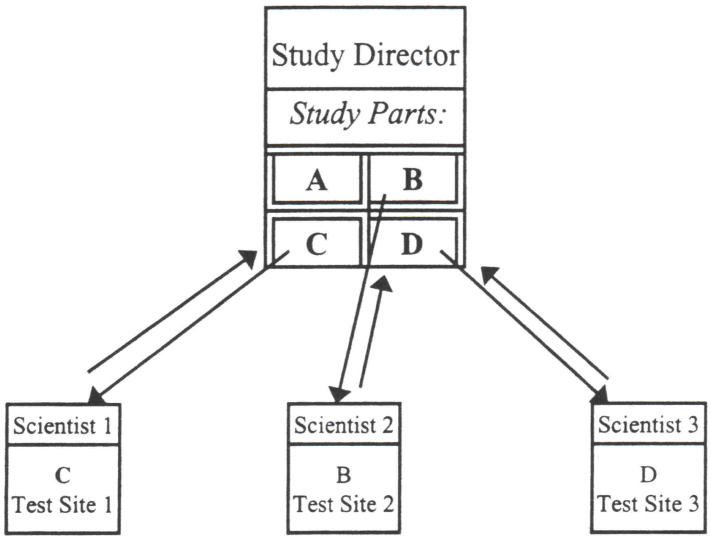

FIGURE 1. Schematic representation of the conduct of a toxicology study with some activities performed outside the immediate test facility of the study director, but with complete control exercised over these study subparts by the study director.

the study director is situated at the sponsor's site and the PI or the "principal scientist," respectively, is located in a contract research organization (CRO), since the CRO may not oppose the request that the sponsor's quality assurance unit should play a certain role in the supervision of the delegated part of the study, in order to be able to provide a full quality assurance statement covering the whole study.

The situation, however, becomes more complicated from a practical point of view, when not only some small subparts or phases of a study are performed by somebody outside the sponsor's facilities, but when a whole study is contracted-out to a CRO. Obviously, the study director in this case must be located at this CRO, while a study monitor will exercise some additional control on behalf of the sponsor. If, subsequently, some phases other than the *in-life* part of this study, for example, analytical chemistry, toxicokinetics, or histopathology, are back-sub-contracted to test sites at the sponsor's facilities (see Figure 2), the problem of both the study director's and the CRO quality assurance unit's supervision over the participating investigators at the sponsor's facilities will arise. The sponsor may, for example, not be willing to accept being inspected by the quality assurance unit of the CRO, or it may even refuse to report the inspection results of its own quality assurance unit, relating to the delegated phases of the study, to the study director. This then leads to the question of whether a study director indeed could take on the full responsibility for a study which is including parts that he/she has not been able to supervise, for which his/her quality assurance unit has not had the opportunity to perform the necessary inspections, and for which his/her own quality assurance unit would, at least theoretically, have to formally exclude this part from the quality assurance statement? Could, in such an instance, the situation be improved through the appointment of a PI? On the first, superficial look this could indeed be considered a valid solution. For a better understanding of this problem, however, the interactions between the study director and the PI as well as of the respective quality assurance units must be taken into account.

The role of the PI at a test site is to direct

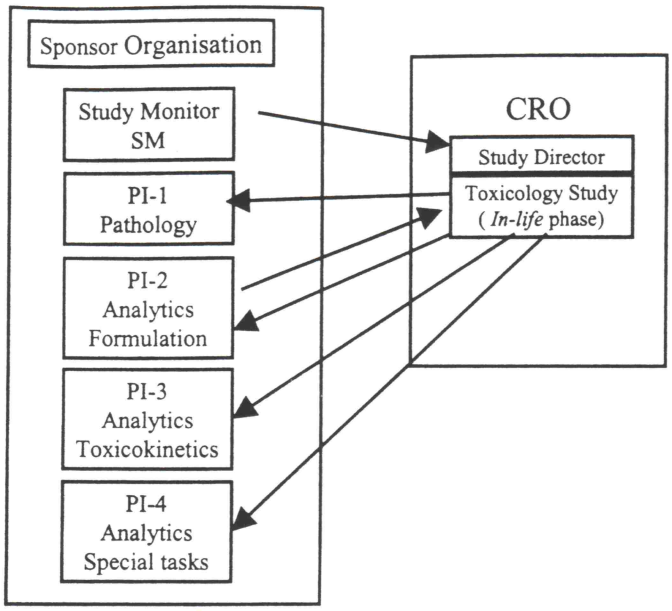

FIGURE 2. Toxicology study conducted at a CRO, with some specific parts of the study carried out within the sponsor's test facilities, over which the study director has only limited ability to control the study.

the work on the delegated phase of the study and to ensure that this phase is conducted in compliance with GLP principles and in accordance with the study plan and all relevant SOPs. The PI should ensure that all raw data generated are fully documented and recorded, and that all raw data, records, and specimens are adequately maintained to assure data integrity, and that they are transferred in a timely manner to the study director or as directed in the study plan. The PI should also sign and date a report of the delegated phase(s) indicating acceptance of responsibility for the validity of the data and extent of compliance with GLP. Where a PI acts on behalf of the study director, then the test facility management, the test site management, and the study director also have defined additional responsibilities. Test facility management (ie, person[s] to whom the study director reports) has the ultimate responsibility that the test facility and all associated test sites operate in compliance with GLP. This also includes the responsibility for the existence of clear lines of communication between the study director, PI(s), the quality assurance unit, and study personnel. Test site management should assure the study director (in writing) that the requirements of Section II, 1.1 (Test facility management's responsibilities) of the revised OECD GLP Principles are met for the appropriate phase(s) of the study. The study director should ensure that the study plan and the final report identify and define the role of any test site(s) and PI(s) involved in the study. He/she should also ensure that the approved study plan, including any amendments, are available to the PI(s) and to the responsible quality assurance units(s). The study director's responsibility for the overall conduct of the study and for GLP compliance, however, cannot be delegated to the PI. Furthermore, the test site quality assurance unit, if applicable, has to report any inspection results in writing not only to its own test site management and PI, but also to the study director.

This latter obligation will certainly give rise to controversies in the very complex situation depicted in Figure 3 where supplemen-

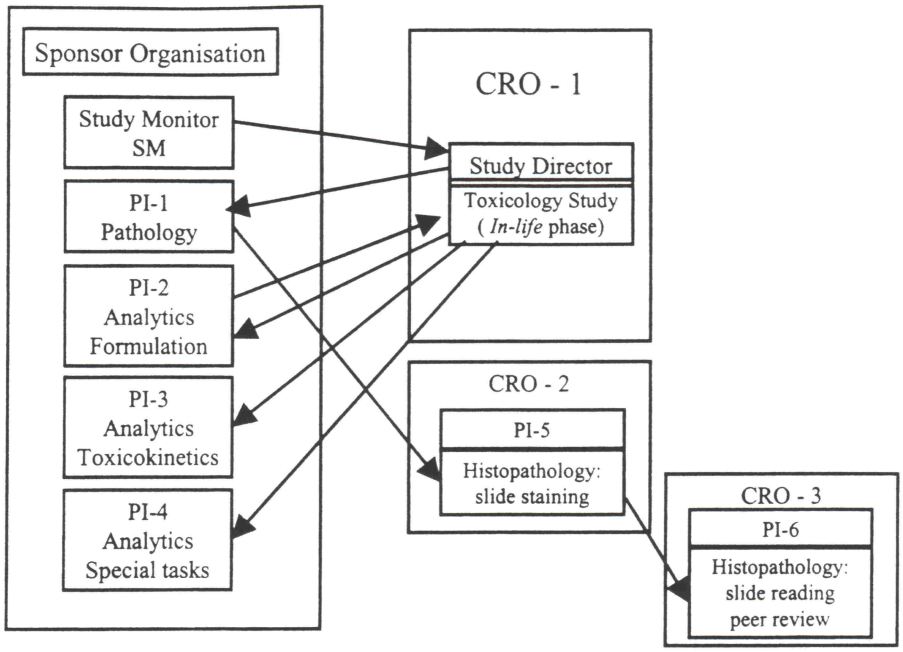

FIGURE 3. Schematic representation of the very complex situation where multiple CROs are employed: The study director at CRO 1 has only limited ability to control the activities performed at the test facilities of the sponsor which will become even more limited for the activities performed at CROs 2 and 3 (which may be competitors of CRO 1 in other respects).

tal activities are performed on behalf of the sponsor and its PI in CROs other than the one where the main *in-life* phase is conducted and where the study director is located. Conflicts of interest can be envisaged here when these additional CROs (CRO-2 and CRO-3) are market competitors to the "main" CRO (CRO-1), but will be obliged by the GLP Principles to "effectively communicate" with the study director, who has the overall responsibility. It is exactly in this latter situation where the use of this "new" construction with the appointment of a PI could be considered an improvement over the "old" ways. With the definitions of test site, PI, and test site management, and of their respective GLP responsibilities in parts of a GLP study, the situation has become clarified with respect to these issues, and thus it should be possible to enhance the overall integrity of a study. Whether and to what extent the idea of the PI and the test site will be fruitful, and will be introduced in pharmaceutical test facilities may differ from company to company. The possibility of formally delegating some parts of the study director's responsibilities, however, could certainly be looked at as one of the opportunities offered by the revised principles.

SHORT-TERM STUDY: HOW SHORT SHOULD, AND HOW LONG COULD, IT BE?

One of the most contentious and hotly debated issues in GLP principles has been, is, and will be, the interpretation of the requirements of the principles with regard to short-term studies. Although the GLP principles can be considered a general code of conduct covering all experimental disciplines, their

application to specific sectors may well raise particular concerns and require *ad hoc* approaches. This is true for many aspects of GLP, but especially so for the so-called "short-term" studies. As defined in the 1997 revised OECD principles, the expression "Short-Term Study" means a "study of short duration with widely used, routine techniques." From this viewpoint short-term studies may include both physical-chemical and biological tests. The former cover chemical characterization and physical parameters on the basis of which, primarily, the environmental behavior of a test article, and the physical risk posed by it, can be predicted. On the other hand, the latter go from acute toxicity studies to genetic and ecotoxicological studies. If one considers that over 60 properties are the target of short-term tests, it is not surprising that so much importance has been attached to them in the context of GLP. The special treatment of this type of study regarding compliance with GLP principles can be considered warranted under two different aspects. On the one hand, the "administrative" workload, connected with the necessity of writing and approving study plans and study reports for each single study, would seem excessive for studies "with widely used, routine methods," the results of which might consist of a single figure only (eg, a melting point). On the other hand, the "short duration" of the "critical phase(s)" and the frequent performance of such studies might make it impossible for the quality assurance unit to effectively monitor the GLP compliant conduct of each of these studies.

The specific concerns that plague short-term studies can be summarized as follows:

- Where is the borderline between short-term and long-term studies?
- Are short-term studies considered to be less scientific, and why so?
- When are general study plans and standardized final reports sufficient (and necessary)?
- What criteria are applied by quality assurance units to monitor short-term studies? and
- Who decides on the frequency of quality assurance inspections of short-term studies?

It goes without saying that two of the major characteristics of short-term studies, that is, the fact that multiple studies can be carried out simultaneously and that test guidelines can be rather simple, can create the false impression that such studies are "less scientific" or "less important." They may thus receive less attention from the study director, the technical staff, and the quality assurance personnel. Due account being given to the peculiarities of short-term studies, the OECD Principles of GLP recommend a standardized approach that can be summarized as follows:

- Short-term studies may be preferentially subjected to process-based inspections; there is thus no need for the quality assurance unit to inspect all individual short-term studies,
- The frequency with which the quality assurance unit inspects such studies should be clearly delineated in the relevant SOPs, and a rationale should be given for the choice of the particular frequencies,
- The study plan may be general enough to treat the repetitive aspects of short-term studies, while supplements should be added to cover the specific aspects of the single, individual studies, and
- A standardized final report is also acceptable, provided that there are study-specific extensions. In any case, the quality assurance unit must audit every final report in order to be able to assure the integrity of the raw data and the study.

In addition to this, it is worth stressing that process-based inspections by the quality assurance unit should be designed to suit the specific aspects of the various groups of short-term studies, taking into account, for example, the frequency with which they are conducted, their duration, and the complexity of every single type of study. It is recognized that common sense must be exercised with regard, on the one hand, to the feasibility of

the full application of the GLP principles in special situations, but that the same common sense must be applied when judging the advisability of taking advantage of the provisions for short-term tests. Thus, if a particular test, for example, a single dose, acute toxicity test, is conducted by the score at one test facility, this test facility would certainly be justified in applying (some or all of) the "simplification" measures to this test. If, however, this same test were to be conducted at another test facilty only every other leap year, this test facility would certainly not qualify for any of the special provisions with regard to the application of the GLP requirements for this test. From a GLP point of view, this flexibility in the approach to conducting and monitoring "short-term" studies has, therefore, to be clearly delineated and described in a policy paper or in the quality assurance program in order to create a clear-cut situation; a "case-by-case approach in hindsight," that is, the possibility of declaring in retrospect some single study which has not been properly monitored by the quality assurance unit to be a short-term test and thus to "water down" the requirements of GLP, must be avoided.

Finally, monitoring authorities should inspect short-term studies with the same care as other studies. The guidance provided by such criteria should be sufficient to guarantee the same level of attention and dignity for short-term studies as for more complex and time-consuming studies.

THE BRACKETS AROUND THE STUDY: THE SPONSOR

According to the definition given in the GLP principles, the sponsor is the entity which commissions a study. The sponsor, after this initiating activity, has nothing to do with the actual, experimental conduct of the study, and thus may be regarded as an outsider to GLP. After termination of the study through the signature on the final report by the study director, the report is turned over to the sponsor; what the sponsor does with this report, short of altering its contents, is then again outside the scope of GLP. Although the sponsor, therefore, is outside the reach of GLP regulations (as applied to a study), there are three points where it is directly connected with GLP. First, when submitting the report of a study to a receiving authority, it is mandatory that the study fulfill the requirements of GLP, and the submitting sponsor, although not responsible for the conduct of the study itself, is held accountable for the study's GLP compliance: If the study shows defects in GLP compliance, it may be rejected by the receiving authority, and the sponsor will thus suffer, from having to repeat the study under stringent GLP conditions up to the rejection of the whole application. Second, the sponsor usually provides the test item to the study director, and possesses GLP-relevant information about the test item. Doubts about such analytical data related to the test item (purity, composition, stability) may either lead to just excepting this information from the GLP compliance statement, or to a declaration that these data could be inspected at the sponsor's facilities; if nothing of this kind were mentioned at all, the GLP compliance of the study could be jeopardized. Most directly involved with GLP is the sponsor in the revised principles, since a mandate has been given to both the sponsor and the test facility (most probably the study director), to develop and institute "a mechanism . . . to verify the identity of the test item subject to the study." These aspects of test item identity, purity, and stability have often in the past given rise to controversies between sponsors, test facilities, monitoring authorities, and receiving authorities. With the relatively modest step of including reference to such a verification mechanism and the publication of the advisory document by OECD on "The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP" (3) much of the former problems and tensions between these partners were addressed and thus alleviated, since the responsibilities of the sponsor have been brought to the fore in a clearer

way. On the other hand, there remain certain controversial points, connected with the test item, for example, the question of how to handle test item characterization performed by the sponsor under conditions of other quality systems (GMP, accreditation). It will probably call not only for in-depth discussions between sponsors, study directors, quality assurance personnel, and monitoring authorities, but also for a clear expression of opinion from the regulatory (receiving) authorities whether they would accept such analyses in the frame of a GLP study as compliant. Certainly this is an issue which will have to be resolved in the future.

INFORMATION TECHNOLOGY: THE WAY FORWARD

While the original GLPs had been drafted in an environment largely founded on manual recording and paper data, throughout the period since there has been an extensive increase in the desire to automate many manual processes. As a consequence, computerized systems are now widely associated with most laboratories undertaking health and environmental safety studies.

The revised OECD principles include some important new requirements for all computerized systems associated with the conduct of studies intended for regulatory purposes. Test facility management should establish procedures to ensure that systems are suitable for their intended purpose, and are validated, operated, and maintained in accordance with the GLP principles. Additionally, there is now a responsibility of every study director, as the single point of study control, to ensure that computerized systems used in their study have been validated. Further requirements are associated with these systems being appropriately designed, of adequate capacity, and supported by important SOPs (validation, operation, maintenance, security, charge control, and back-up). Finally, there is the expectation that all "system validation documentation" should be retained in archives for the period specified by the appropriate authorities.

The concept of validation is no longer novel to many in the GLP field since many organizations have evolved their approaches over time to meet a minimum need. This has been achieved by way of industry dialogue, attendance at seminars or participation in workshops, and by keeping an awareness of regulatory trends. Validation principles first established under Good Manufacturing Practice and then Good Laboratory Practice have been merged somewhat and now often also provide a best model also for Good Clinical Practice systems.

"What to do to validate" therefore no longer holds any real mystique. Validation has been replaced by new issues focusing on the need to maintain regulatory records in electronic form for prolonged periods of time, and the need to assure the integrity of many such records by electronic signature. In August 1997 the United States Food and Drug Administration Rule 11 on Electronic Records and Electronic Signatures (4) took effect. This single regulation has provided industry and government with the option to use electronic signatures as a legal equivalent to a handwritten signature. Moreover, the rule specifies new requirements for the management and retention of electronic records. Previous widely used options, that is, to first capture data or records electronically and then to print and retain them only as paper copies, are no longer an acceptable practice. For many legacy systems (those introduced prior to August 1997) there is a need to modify or replace them, since maintaining a "hybrid system" (electronic record with handwritten signatures to a paper output) to ensure full compliance is likely to be difficult. These new issues come close on the heels of the recent flurry of testing undertaken to ensure that our systems, applications, and equipment are year 2000 compliant.

The pace of change associated with information technology will undoubtedly mean that these will not be the last challenges for us. By working on these issues together, in-

dustry and government can strive to establish reasonable and achievable standards of quality and regulatory compliance in their joint progress toward the paperless environment.

CONCLUSIONS

The discussions held at this workshop and the experience shared among the participants clearly showed one thing: The revised GLP principles have not been able to solve every problem that had arisen with the "old" ones, but this had not been the intention of the 1997 revision of the principles. Some controversial points and issues remained, and some changes just shifted the problems, while the introduction of concepts new to pharmaceutical test facilities was apt to create new uncertainties. In addition to the adaptations needed for the implementation of the revised principles, there is the problem of an ever growing complexity of organizational structures at all levels and the associated need for new interpretations of these principles of GLP. The revision of the OECD principles has, therefore, to be seen as only a "relay station" on the never ending process of adapting Good Laboratory Practice to the increasing complexity of safety testing. In this environment of adaptation and (re-)interpretation of GLP principles it will be inevitable—as it has been in the past—that different approaches to the implementation of GLP principles will be taken by different countries and different authorities. Thus, there is a quest for harmonization among these various approaches and interpretations, should the revised OECD principles not lose their expressed intention, namely to provide a basis for the mutual acceptance of data, generated in the safety testing of test items, within OECD countries (and the world at large). One possible prerequisite for the success of such a harmonization process could be a much closer interaction between authorities (GLP monitoring and receiving) and test facilities (management, study directors, and quality assurance units) order to identify procedural problems and to work out possible solutions, taking into consideration the experience of the many internationally operating pharmaceutical companies with other solutions to the same (or similar) problem they had to introduce elsewhere. Also, OECD's Mutual Joint Visits Programme is expected to lead to improved harmonization in the implementation and application of the GLP principles, and in the monitoring processes used to assess and ensure GLP compliance of test facilities. In a minor, but not unimportant way, problem-oriented meetings such as this DIA Workshop could further help to achieve this goal, through exchange of views on, and experience with, practical problems and their various possible solutions; and through the possibility of discussions between authorities and test facilities to arrive at pragmatic proposals in contentious areas of GLP.

This DIA Workshop on GLP fulfilled this very objective: By describing the changes made in the revised principles, by investigating the opportunities these changes are offering, and by discussing some of the controversial issues, it succeeded at least in the generation of a mutual understanding of the various positions with regard to the Principles of Good Laboratory Practice, to the possible interpretations of their content, and to possible, pragmatic methods of implementation.

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