QUASAR

Quality Assurance and Research

Issue No. 81 ISSN 1463-1768 October 2002

'Our man in Tokyo' together with JSQA officers at the JSQA Annual Meeting held in Japan. Back row, left to right: Dr Takeshi Hashizume (Auditor, GLP Division), Mr Kazuya Tanizaki (Board Member, GCP), Ms Naoko Mizuno (Board Member, GLP), Mr Shinnji Hara (Board Member, GCP), Dr Akira Nomura (Board Member, GLP), Mr Yutaka Nakae (Auditor, GCP Division). Front row, left to right: Mr Kiyoshi Masani (Vice President, GLP Division), Dr Tomoji Yanagita (JSQA Past President), Dr John Wenn, Ms Yoko Nakamura (JSQA President), Mr Masayuki Takezawa (Vice President, GCP Division).

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Committee News

GLP Committee page on the BARQA website

Recent visitors to the GLP Committee webpage may have noticed that some of the material was out of date. I am pleased to say that the redundant material has now been removed and what is left is current! The Committee undertake to keep this site current and will post useful GLP items throughout the year following discussions at future committee meetings.

If you would like to visit this website and haven't yet done so it can be accessed in the following manner:

- Log on to the BARQA website (www.barqa.com)
- Select Areas of Interest
- Select GLP Committee

Cosmetic update to OECD document

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, No. 13: The Application of the OECD Principles of GLP to the Organisation and Management of Multi-site Studies.

This document was updated on June 25th 2002 to facilitate cosmetic changes to the page which references other documents in the series. The content of the document remains unchanged. This latest version cancels and updates the same document of March 11th 2002.

Interpretative issues

The GLP Committee have recently received a question from a member in Greece asking if ELISA is acceptable as an analytical technique for residue and bioequivalence studies conducted in GLP environment.

The Committee suggests that ELISA assays are widely used in the GLP environment and so with appropriate documentation there should be no problem.

Documentation would include a justification for the method, an approved methodology for the specific test item, SOPs covering the equipment and any associated computer systems, a definition of the raw data, user training, and validation of the method itself for the specific test item – robustness, reproducibility, limit of detection, etc., validation plans, testing results, etc., would also be required to support any computer system used.

Fundamentally, so long as an assay method is demonstrably 'fit for purpose', it will be acceptable under GLP.

For further interpretative issues contact the GLP Committee via the chat line, by writing to us or seek us out at the Manchester meeting (more than likely to be found near the bar!).

GLP training video

One of the major initiatives the GLP Committee has undertaken seems to have been semi-dormant for quite a while, but at last has really taken off. With the generous sponsorship of a number of companies, the Committee is now actively working in partnership with John Hemson to produce an updated GLP training video. A sneak preview may even be possible at the Annual Meeting in Manchester!

Calling all foreign correspondents

The appeal in July's edition of *Quasar* for foreign correspondents brought us some contacts but the Committee would still welcome more non-UK thoughts on the world of GLP. Please contact any member of the GLP Committee if you have something to share.

OECD Monograph No. 13

ROUND TABLE DISCUSSION BY SSFA AND GIQAR

The application of the OECD principles of GLP to the organisation and management of multi-site studies

INNOVATIVE ASPECTS AND INTERPRETATIONS IN THE APPLICATION PHASE*

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PRELIMINARY REMARKS

This paper is the result of the round table discussion organised by the SSFA/GIQAR (Society for Applied Pharmacological Sciences/Italian Group of Quality Assurance in Research) working group on Multi-site studies, held on June 12th 2002 in Pomezia (Rome).

The round table brought together auditors from quality assurance units in industry, inspectors from good laboratory practice compliance monitoring authorities, as well as Study Directors, principal investigators and management representatives.

A background document, prepared by the GIQAR working group on multi-site studies, was used as the starting point for discussion. The aspects of the OECD Monograph No. 13 considered critical, in terms of interpretation and/or application, were discussed in detail in order to reach harmonisation between all the involved parties.

The issue of non-certified sponsor and contract archives was included in the background document and then discussed during the round table.

Key words: multi-site studies, GLP – Good Laboratory Practice, quality assurance, archives, GIQAR.

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

The authors wish to thank RTC, Research Toxicology Centre SpA, for supporting the initiative (site, logistic, costs).

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The comments based on the round table discussion results are in italics. The sections were numbered in order to facilitate the reading of the document.

INTRODUCTION

Conducting a study as a multi-site study must not be viewed as an obligation but as one of the possible options. Even if some of the phases are delegated to other sites, the possibility of managing the phases carried out in other sites as separate and independent studies, each with its own protocol, Study Director (SD) and final report remains open.

Therefore, there is no change with regard to the situation previously described by GIQAR in the document 'A critical analysis of the Law of 5 August 1999, provisions regarding inspection and verification of Good Laboratory Practice, in implementation of Directives 1999/11/CE and 1999/12/CE' ('Analisi critica del decreto 5 agosto 1999, disposizioni relative all'ispezione e verifica della buona prassi di laboratorio in recepimento delle direttive 1999/11/CE e 1999/12/CE'), published in *Cronache Farmaceutiche*, no. 1, January-February 2000.

The sponsor has the choice/decision of opting for the conduction either of a multi-site study or of several separate studies. This OECD document refers solely to multi-site studies.

The purpose of this paper is to analyse the document and provide further guidance as to its application.

CONTENTS

INTRODUCTION

The planning, performance, monitoring, recording, reporting and archiving of a multi-site study present a number of potential problems that should be addressed to ensure that the GLP compliance of the study is not compromised. The fact that different study activities are being conducted at different sites means that the planning, communication and control of the study are of vital importance.

Although a multi-site study will consist of work being conducted at more than one site (which includes the test facility and all test sites), it is still a single study that should be conducted in accordance with the OECD Principles of GLP. This means that there should be a single study plan, a single Study Director and, ultimately, a single final report. It is therefore essential that, when the study is first planned, personnel and management at the contributing sites are made aware that the work they will perform is part of a study under the control of the Study Director and is not to be carried out as a separate study.

It is imperative that the work to be carried out by the various sites is clearly identified at an early stage of planning, so that the necessary control measures can be agreed upon by the parties concerned before the study plan is finalised.

1. There is no obligation to insert in the protocol all the sites that will be involved in the study, since this is not always possible. The choice of carrying out activities at an external site and the selection of such sites can also be made while the study is in progress. In line with normal practice, a change in the study protocol will inevitably lead to the issue of a protocol amendment.

Many of the problems associated with the conduct of multi-site studies can be prevented by clear allocation of responsibilities and effective communication among all parties involved in the conduct of the study. This will include the sponsor, the Study Director, and the management, the Principal Investigator(s), Quality Assurance and study personnel at each site.

All of these parties should be aware that when a multi-site study is conducted in more than one country there might be additional issues due to differences in national culture, language and GLP compliance monitoring programmes. In these situations it may be necessary to seek the advice of the national GLP compliance monitoring authority where the site is located.

2. One example is the use of a non-certified site (§ 13) or a site not included in the programme of monitoring of compliance with good laboratory practice (GLP) by the pertinent regulatory authority. In this case, it would be prudent to contact the pertinent regulatory authority in advance, in order to confirm the correct method of action/request (for example, to notify the local regulatory authority in advance of the utilisation of a non-certified site, if this is required under the local regulations). The responsibility for this aspect must be defined at the study planning stage (sponsor or management of the test facility).

The pertinent regulatory authority could be that for the residence of the site and/or for the site where the test facility management resides. It is preferable to contact the pertinent regulatory authority for the site where the Study Director resides.

The guidance contained within this document should be considered during the planning, performance, monitoring, recording, reporting and archiving of any study that will be conducted at more than one site. The guidance applies to all types of non-clinical health and environmental safety studies.

MANAGEMENT AND CONTROL OF MULTI-SITE STUDIES

A multi-site study means any study that has phases conducted at more than one site. Multi-site studies become necessary if there is a need to use sites that are geographically remote, organisationally distinct or otherwise separated. This could include a department of an organisation acting as a test site when another department of the same organisation acts as the test facility.

3. The definition of 'multi-site study' does not exist in the GLP principles. The last sentence of the paragraph indicates one site as a 'test facility' whereas in GLP 'test facility' means all sites involved in the study. (The draft consensus document was in accordance with GLP.) N.B. our comments refer to the GLP definition of test facility.

A phase is a defined activity or set of activities in the conduct of a study.

4. The definition of 'phase' does not exist in the GLP principles.

The decision to conduct a multi-site study should be carefully considered by the sponsor in consultation with test facility management assigned by the sponsor before study initiation. The use of multiple test sites increases the complexity of study design and management tasks, resulting in additional risks to study integrity. It is therefore important that all of the potential threats to study integrity presented by a multi-site configuration are evaluated, that responsibilities are clear and that risks are minimised. Full consideration should be given to the technical/scientific expertise, GLP compliance status, resources and commercial viability of all of the test sites that may be used.

5. The first sentence of this paragraph seems to be in conflict with the last one of paragraph § 8. However this conflict is more apparent than real; in fact, during the decision process to conduct a multi-site study, the sponsor should consult the test facility management. For this reason also in paragraph § 8, concerning study management, it is emphasised that the test facility management is involved in the decision process.

Certainly the sponsor has the final responsibility for conducting a multi-site study and has also the task to facilitate the communication among the sites involved in the study.

Communication

For a multi-site study to be conducted successfully it is imperative that all parties involved are aware of their responsibilities. In order to discharge these responsibilities, and to deal with any events that may need to be addressed during the conduct of the study, the flow of information and effective communication among the sponsor, management at sites, the Study Director, Principal Investigator(s), Quality Assurance and study personnel is of paramount importance.

The mechanism for communication of study-related information among these parties should be agreed in advance and documented.

6. The information/communication flow could be defined in the study plan or in a separate document. A standard operating procedure (SOP) should define and detail how to manage the communication and information process among sites.

The Study Director should be kept informed of the progress of the study at all sites.

7. The communication system should be defined in the study plan or in a separate document: which type of information, the frequency and vehicle of communication from the Principal Investigator to the Study Director. (In other words the format of the 'study status report' should be defined.)

Study management

The sponsor will assign a study to a test facility. Test facility management will appoint the Study Director who need not necessarily be located at the site where the majority of the experimental work is done. The decision to conduct study activities at other sites will usually be made by test facility management in consultation with the Study Director and the sponsor, where necessary.

8. The sponsor could decide to appoint the Study Director at the sponsor site. The decision to conduct activities at different sites is a responsibility shared between the sponsor and the test facility management, ratified by approval of the study plan and subsequent amendments. See also § 5.

With regard to the first sentence see § 3.

When the Study Director is unable to perform his/her duties at a test site because of geographical or organisational separation, the need to appoint a Principal Investigator(s) at a test site(s) arises. The performance of duties may be impracticable, for example, because of travel time, time zones, or delays in language interpretation. Geographical separation may relate to distance or to the need for simultaneous attention at more than one location.

9. Note: There is the possibility to conduct multi-site studies without the Principal Investigator (PI). Nevertheless this option seems not to be easily feasible when test sites from different companies are involved in the study. (see § 16).

Test facility management should facilitate good working relationships with test site management to ensure study integrity. The preferences of the different groups involved, or commercial and confidentiality agreements, should not preclude the exchange of information necessary to ensure proper study conduct.

10. Test facility management should be aware of its own responsibilities and should not hamper. but should facilitate the drawing up of agreements/contracts among sites.

It is desirable that confidential agreements between test site-sponsor and/or test site-test facility management should be drawn up at the time of test sites selection.

Roles and Responsibilities

Sponsor

The decision to conduct a multi-site study should be carefully considered by the sponsor in consultation with test facility management before study initiation. The sponsor should specify whether compliance with the OECD Principles of GLP and applicable national legislation is required. The sponsor should understand that a multi-site study must result in one final report.

11. This information should be defined in the study plan and/or in a separate document/agreement.

The sponsor should be aware that, if its site acts as a test site undertaking a phase(s) of a multi-site study, its operations and staff involved in the study are subject to control of the Study Director. According to the specific situation, this may include visits from test facility management, the Study Director and/or inspections by the lead Quality Assurance. The Study Director has to indicate the extent to which the study complies with GLP, including any work conducted by the sponsor.

12. Note: If a sponsor becomes a 'test site', its operations and staff should be controlled by the Study Director of the contract research organisation (CRO) to which the study has been contracted. These controls are not necessarily desirable or productive, since the sponsor has the final responsibility for the submission of the study to regulatory authorities. See also § 15.

Test Facility Management

Test facility management should approve the selection of test sites. Issues to consider will include, but are not limited to, practicality of communication, adequacy of Quality Assurance arrangements, and the availability of appropriate equipment and expertise. Test facility management should

designate a lead Quality Assurance that has the overall responsibility for quality assurance of the entire study. Test facility management should inform all test site quality assurance units of the location of the lead Quality Assurance. If it is necessary to use a test site that is not included in a national GLP compliance monitoring programme, the rationale for selection of this test site should be documented. Test facility management should make test site management aware that it may be subject to inspection by the national GLP compliance monitoring authority of the country in which the test site is located. If there is no national GLP compliance monitoring authority in that country, the test site may be subject to inspection by the GLP compliance monitoring authority from the country to which the study has been submitted.

13. If we consider that the test facility management is responsible (approver) for the selection of test sites, and for the appointment of the lead quality assurance (see also § 29), then this implies a potential conflict of interest. In reality the sponsor takes these decisions and will always do so as, justifiably, it has the ultimate responsibility for the study with regards to regulatory authorities.

Approval of test sites by test facility management should be understood as involvement in the decisional process and ratification of the choice. This is documented by approval of the study plan. A SOP should set out the conditions for selection of test sites.

If a non-certified test site is used, the rationale for this choice should be documented in writing. See also § 2.

Test Site Management

Test site management is responsible for the provision of adequate site resources and for selection of appropriately skilled Principal Investigator(s). If it becomes necessary to replace a Principal Investigator, test site management will appoint a replacement Principal Investigator in consultation with the sponsor, the Study Director and test facility management where necessary. Details should be provided to the Study Director in a timely manner so that a study plan amendment can be issued. The replacement Principal Investigator should assess the GLP compliance status of the work conducted up to the time of replacement.

14. The appointed PI at the test site is responsible for ensuring compliance with the principles of GLP for the delegated phases. The PI will prepare and sign the GLP compliance statement for the delegated phase in which will be indicated the extent to which the phase complies with GLP principles.

The replacement of a PI should be documented in an amendment to study plan.

Study Director

The Study Director should ensure that the test sites selected are acceptable. This may involve visits to test sites and meetings with test site personnel.

15. See § 12.

This could imply a conflict of interest. Certainly it is more appropriate for the sponsor to determine acceptability of test sites, especially if the test site is a competitor of the site where the Study Director is located, or is at the sponsor site. Furthermore the existence of 'commercial or confidentiality agreements' (§ 20) cannot be ignored.

The Study Director could state the acceptability of a test site by only reviewing the documentation without any inspection at the site.

(It could be unnecessary for the Study Director to visit a test site involved in the study, although he should review information and documentation for the test site such as GLP certificate, curriculum vitae of the Principal Investigator, etc.)

When an uncertified test site is involved in the study, monitoring by the Study Director and lead quality assurance should be defined in advance.

Note: any test sites which are not certified (see also § 2) should be mentioned in the GLP compliance statement signed by the Study Director.

If the Study Director considers that the work to be done at one of the test sites can be adequately controlled directly by him(her)self without the need for a Principal Investigator to be appointed, he/she should advise test facility management of this possibility. Test facility management should ensure that appropriate quality assurance monitoring of that site is arranged. This could be by the test site's own Quality Assurance or by the lead Quality Assurance.

16. The complete and direct control of activities carried out at a separate site by the Study Director could be acceptable only when the test site is part of the same company or organisation. In other circumstances, this option could not easily be followed.

Certainly in such cases, considering the complexity and critical state of this option, the relevant responsibilities of all parties involved should be defined in detail.

This option seems more suitable for field studies than for standard toxicological studies.

The Study Director is responsible for the approval of the study plan, including the incorporation of contributions from Principal Investigators. The Study Director will approve and issue amendments to and acknowledge deviations from the study plan, including those relating to work undertaken at sites. The Study Director is responsible for ensuring that all staff are clearly aware of the requirements of the study and should ensure that the study plan and amendments are available to all relevant personnel.

17. It is difficult for the Study Director to comply with the requests in the last sentence of the paragraph. It seems to be more appropriate for a Principal Investigator acting as Study Director at the test site (§ 22).

In the study plan or in a separate document it should be reported who is responsible at each site for the distribution of the study plan and related amendments as well as that any deviation from the study plan should be reported by the Principal Investigator to the Study Director.

It is necessary to have a distribution list for the study plan (and related amendments) with acknowledgement of receipt.

The Study Director should set up, test and maintain appropriate communication systems between him(her)self and each Principal Investigator. For example, it is prudent to verify telephone numbers and electronic mail addresses by test transmissions, to consider signal strength at rural field stations, etc. Differences in time zones may need to be taken into account. The Study Director should liaise directly with each Principal Investigator and not via an intermediary except where this is unavoidable (e.g. the need for language interpreters).

18. Preliminary contacts between Principal Investigator(s)-Study Director during study plan definition should be enough to automatically validate the appropriate process. The sentence '... set up test and maintain appropriate communication system ...' does not necessarily require supporting written documentation.

Throughout the conduct of the study, the Study Director

should be readily available to the Principal Investigators. The Study Director should facilitate the co-ordination and timing of events and movement of samples, specimens or data between sites, and ensure that Principal Investigators understand chain of custody procedures.

19. A SOP should describe the mechanism of material/documentation movements between test sites and the related responsibilities.

All steps for delivering of materials and the related responsibilities should be documented (responsibility tracking).

The Study Director should liaise with Principal Investigators about test site quality assurance findings as necessary. All communication between the Study Director and Principal Investigators or test site quality assurance in relation to these findings should be documented.

The Study Director should ensure that the final report is prepared, incorporating any contributions from Principal Investigators. The Study Director should ensure that the final report is submitted to the lead Quality Assurance for inspection. The Study Director will sign and date the final report to indicate the acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with the OECD Principles of Good Laboratory Practice. This may be based partly on written assurances provided by the Principal Investigator(s).

20. It is impractical for a Study Director to ascertain GLP compliance for activities performed at different test sites without direct oversight. The Study Director should accept assessments by the other sites' staff (management, Principal Investigator, quality assurance).

The Principal Investigator will assure GLP compliance at his own site according to GLP section II, § 1.3 (see also § 14 e 22).

In practice, each test site will supply both a GLP compliance statement signed by the relevant Principal Investigator, and a quality assurance statement (protocol review, list inspections performed, audit of reports, etc.). These documents could either be appended to the final report or referenced in the GLP compliance statement and quality assurance statement of the final report. In any case the original Principal Investigator and quality assurance statements must be archived in the study file.

At sites where no Principal Investigator has been appointed, the Study Director should liaise directly with the personnel conducting the work at those sites. These personnel should be identified in the study plan.

21. See § 16.

Note: It is not specifically required that a Study Director should be appointed at a certified site. It is permitted to appoint a 'freelance' Study Director (see also § 8). However, the Study Director should have appropriate qualifications, training and experience according to GLP.

Principal Investigator

The Principal Investigator acts on behalf of the Study Director for the delegated phase and is responsible for ensuring compliance with the Principles of GLP for that phase. A fully co-operative, open working relationship between the Principal Investigator and the Study Director is essential.

22. As the Study Director may not be located at the site where the majority of the experimental work is done, the Principal Investigator could have the responsibility for the major part of the study.

The Study Director should evaluate any contribution by the Principal Investigator, co-ordinate the different sites, manage and assume the responsibility for the overall conduct of the study.

Nevertheless, the Principal Investigator is responsible for GLP compliance of the delegated activities performed at the test site (see also § 20).

There should be documented agreement that the Principal Investigator will conduct the delegated phase in accordance with the study plan and the Principles of GLP. Signature of the study plan by the Principal Investigator would constitute acceptable documentation.

23. Signature of the study plan is an option not a condition; the agreement could be ratified in a specific document. Additionally, obtaining the signature of the Principal Investigator on the study plan could prove to be a logistical problem.

Deviations from the study plan or Standard Operating Procedures (SOPs) related to the study should be documented at the test site, be acknowledged by the Principal Investigator and reported to and acknowledged by the Study Director in a timely manner.

24. Reporting SOPs deviations to the Study Director should be limited to only when strictly necessary.

When the same SOP is used at different sites performing the same experimental procedure, the deviation from the SOP in one site should be communicated to the Study Director; therefore the Study Director could evaluate the impact of the deviation on the study data.

Conversely, if the delegated phase is independent from other phases conducted at other test sites, reporting SOP deviations seems to be unnecessary.

The Study Director, in fact, will not necessarily know the SOPs of each test site in detail, and does not approve them formally (it is up to the management of the test site to approve the SOPs used at the test site). Moreover, the Study Director may well not have the expertise or competence to evaluate SOPs used during delegated experimental phases conducted under the responsibility of the Principal Investigator.

For these reasons, reporting of SOPs deviation to the Study Director, could be useful, but could also create situations of potential conflict of interest and problems of confidentiality.

This requirement could be referenced to the OECD GLP guidance document 'Consensus document on the application of the GLP principles to field studies'. It should be noted here that not all multi-sites studies are field studies, and thus some provisions may not apply.

The Principal Investigator should provide the Study Director with contributions which enable the preparation of the final report. These contributions should include written assurance from the Principal Investigator confirming the GLP compliance of the work for which he/she is responsible.

25. This information should be defined in the study plan and/or in a separate document/agreement.

The Principal Investigator should ensure that all data and specimens for which he/she is responsible are transferred to the Study Director or archived as described in the study plan. If these are not transferred to the Study Director, the Principal Investigator should notify the Study Director when and where they have been archived. During the study, the Principal Investigator should not dispose of any specimens without the prior written permission of the Study Director.

26. This information should be defined in the study plan and/or in a separate document/agreement.

Study Personnel

The GLP Principles require that all professional and tech-

nical personnel involved in the conduct of a study have a job description and a record of the training, qualifications and experience which support their ability to undertake the tasks assigned to them. Where study personnel are required to follow approved SOPs from another test site, any additional training required should be documented.

27. A SOP should describe how to manage SOPs from other sites and how to record any additional training.

If SOPs from another site are followed, this should be documented in the study plan or in a separate document. (It should be documented the list of the SOPs in use.)

There may be some sites where temporarily employed personnel carry out aspects of study conduct. Where these persons have generated or entered raw data, or have performed activities relevant to the conduct of the study, records of their qualifications, training and experience should be maintained. Where these individuals have carried out routine operations such as livestock handling subject to supervision by more highly qualified staff, no such personnel records need be maintained.

28. Examples in which no personnel records (training records and curriculum vitae, etc.) need to be maintained could be found in studies evaluating residuals of veterinary drugs in farm animals:

- *Farm staff involved in facility cleaning procedures.*
- *Slaughterhouse staff involved in slaughtering procedures.*

QUALITY ASSURANCE

The quality assurance of multi-site studies needs to be carefully planned and organised to ensure that the overall GLP compliance of the study is assured. Because there is more than one site, issues may arise with multiple management organisations and Quality Assurance programmes.

29. The function of lead quality assurance is not set out in the GLP principles, which only refer to the existence of a quality assurance programme for the test facility, which actually means all the sites involved in a study (section I, § 2.2.8 of GLP). Nor is the definition of lead quality assurance present in GLP.

In real terms, it is the sponsor who appoints the lead quality assurance (see also § 13). To avoid any conflict of interest, it would seem more appropriate for the sponsor to appoint the lead quality assurance at his own premises (which would, however, be difficult to apply where the sponsor's facility is not 'GLP-compliant').

It should be noted that several different quality assurance systems may be operating.

Responsibilities of Lead Quality Assurance

The lead Quality Assurance should liaise with test site quality assurance to ensure adequate quality assurance inspection coverage throughout the study.

30. It follows that the quality assurance unit of each site must provide the lead quality assurance (preferably through the Principal Investigator) with a copy of the quality assurance programme related to the study. This would allow the lead quality assurance to:

- *Ensure that an overall quality assurance plan is available.*
- *Ensure that there are no critical activities not monitored by a quality assurance unit.*
- *Avoid duplication of quality assurance activities.*

Particular attention should be paid to the operation and documentation relating to communication among sites. Responsibilities for quality assurance activities at the various sites should be established before experimental work commences at those sites.

31. To be defined in the protocol and/or in a separate agreement/document. See also § 30.

The lead Quality Assurance will ensure that the study plan is verified and that the final report is inspected for compliance with the Principles of GLP. Quality assurance inspections of the final report should include verification that the Principal Investigator contributions (including evidence of quality assurance at the test site) have been properly incorporated. The lead Quality Assurance will ensure that a Quality Assurance Statement is prepared relating to the work undertaken by the test facility including or referencing quality assurance statements from all test sites.

32. If the lead quality assurance is appointed at a site other than the one where the Study Director is located, the responsibilities of the quality assurance unit involved should be carefully defined in order to avoid duties being duplicated (for instance, the lead quality assurance may not have to check the study protocol, since this is done by the quality assurance of the site where the Study Director is located and this phase is under his responsibility. The same is true for the final report).

Responsibilities of Test Site Quality Assurance

Each test site management is usually responsible for ensuring that there is appropriate quality assurance for the part of the study conducted at their site. Quality assurance at each test site should review sections of the study plan relating to operations to be conducted at their site. They should maintain a copy of the approved study plan and study plan amendments.

Quality assurance at the test site should inspect study-related work at their site according to their own SOPs, unless required to do otherwise by the lead Quality Assurance, reporting any inspection results promptly in writing to the Principal Investigator, test site management, Study Director, test facility management and lead Quality Assurance.

33. It does not necessarily mean that the quality assurance reports must be sent as they are to external sites, although there is no question as to the obligation of sending the results to management and to the person responsible for the study at his site (Principal Investigator or Study Director).

The responsibilities assigned to quality assurance (QA) by GLP (section II and definitions), including the sending of inspection results, should not be forgotten; they always refer to the QA of the test facility (meaning all the sites involved). No distinction is made between the site QA and the lead QA. Therefore the GLP § 2.2 e) can be understood as referring to the overall QA system, which may also mean that each local QA communicates to its own management and to the Principal Investigator, who pass on the information to the Study Director.

'Reporting results' can also be interpreted in several ways, for example, as immediate communication of any relevant problems concerning the integrity of the study to key functions and the sending of a periodical status report documenting the inspections carried out and their outcome (result in terms of GLP compliance and deviations from the study plan, see also point 24).

Each site will have to set out in its internal SOPs how the results of QA activities at external sites are reported (e.g. periodical quality status of the study).

This is in any case already done with regard to reporting to manage-

ment (every test facility/site in its SOPs specifies how QA reports are distributed, perhaps directly only to the Study Director and to direct superiors whereas the top management receives only periodical reports).

Identifying the Principal Investigator and Study Director as the communication points between sites assures the correct flow of information and satisfactory understanding of their own information by the personnel involved in the study.

Reporting of information should preferably be done through the Principal Investigator. Other different routes may encourage lack of communication. As already discussed in the other points, what the monograph requires is that the Study Director manages the project appropriately and correctly.

If the Study Director cannot guarantee complete control of the activities carried out at a separate, external site, it is better for the Principal Investigator to be responsible for conduct of the studies, including SOPs/SOP deviations at his site.

It should not be forgotten that according to GLP it is the Principal Investigator who is responsible for GLP compliance of the delegated phase (GLP, § 1.3).

As regards the possibility that the site QA is requested by the lead QA to work according to SOPs different from their own, this implies interference with the site quality system and should be considered possible only in terms of identification of the critical phases to be inspected as an interface between sites.

Quality assurance at the test site should inspect the Principal Investigator's contribution to the study according to their own test site SOPs and provide a statement relating to the quality assurance activities at the test site.

34. See § 32.

MASTER SCHEDULES

A multi-site study in which one or more Principal Investigators have been appointed should feature on the master schedule of all sites concerned. It is the responsibility of test facility management and test site management to ensure that this is done.

The unique identification of the study must appear on the master schedule in each site, cross-referenced as necessary to test site identifiers. The Study Director should be identified on the master schedule(s), and the relevant Principal Investigator shown on each site master schedule.

35. In addition to the information required by GLP for any type of study, the master schedule sheet (MSS) at the site where the Study Director is located should include also:

- *All the other sites involved in the study*
- *The Principal Investigator for each site*
- *The study code identification for each site where this is different from that stated in the study plan (i.e. different study numbers)*
- *Start and completion dates for the phase(s) delegated to each site*

In addition to the information required by GLP for any type of study, the MSS at sites where the Study Director is not located should include also:

- *Identity of the Study Director*
- *The study identification code stated in the study plan (where this is different from that used at the site)*

N.B. the study start and completion dates will be those referred for phase(s) delegated to the site.

At all sites, the start and completion dates of the study phase(s) for which they are responsible should appear on their master schedule.

STUDY PLAN

For each multi-site study, a single study plan should be issued. The study plan should clearly identify the names and addresses of all sites involved.

The study plan should include the name and address of any Principal Investigators and the phase of the study delegated to them. It is recommended that sufficient information is included to permit direct contact by the Study Director, e.g. telephone number.

The study plan should identify how data generated at sites will be provided to the Study Director for inclusion in the final report.

It is useful, if known, to describe in the study plan the location(s) at which the data, samples of test and reference items and specimens generated at the different sites are to be retained.

36. To be specified in the protocol or in a separate agreement/document.

It is recommended that the draft study plan should be made available to Principal Investigators for consideration and acknowledgement of their capability to undertake the work assigned to them, and to enable them to make any specialised technical contribution to the study plan if required.

37. N.B. It is not mandatory to circulate the draft protocol to all involved Principal Investigator(s), but it is surely a useful suggestion.

The study plan is normally written in a single language, usually that of the Study Director. For multi-national studies it may be necessary for the study plan to be issued in more than one language; this intention should be indicated in the original study plan, the translated study plan(s) and the original language should be identified in all versions. There will need to be a mechanism to verify the accuracy and completeness of the translated study plan. The responsibility for the accuracy of the translation can be delegated by the Study Director to a language expert and should be documented.

38. A SOP should set out how to translate the protocol and the relative responsibilities. The Principal Investigator may also be delegated to carry out this activity.

PERFORMANCE OF THE STUDY

This section repeats the most important requirements from the Principles of GLP and recommendations from the *Consensus Document on the Application of the GLP Principles to Field Studies* in order to provide useful guidance for organisation of multi-site studies. These documents should be consulted for further details.

Facilities

Sites may not have a full time staff presence during the working day. In this situation it may be necessary to take additional measures to maintain the physical security of the test item, specimens and data.

When it is necessary to transfer data or any materials among sites, mechanisms to maintain their integrity need to

be established. Special care needs to be taken when transferring data electronically (e-mail, internet, etc.).

39. The transfer of materials / data / information between sites should be regulated by a SOP.

Equipment

Equipment being used in a study should be fit for its intended purpose. This is also applicable to large mechanical vehicles or highly specialised equipment that may be used at some sites.

There should be maintenance and calibration records for such equipment that serve to indicate their 'fitness for intended purpose' at the time of use. Some apparatus (e.g. leased or rented equipment such as large animal scales and analytical equipment) may not have records of periodic inspection, cleaning, maintenance and calibration. In such cases, information should be recorded in the study-specific raw data to demonstrate 'fitness for intended purpose' of the equipment.

40. One example concerns the temporary use (for one study) of a complex apparatus (e.g. mass spectrometer) available at a company lab which is not GLP certified and, therefore, usually used for non- regulatory studies.

It is as if the apparatus were hired / borrowed for use in a specific study.

Control and accountability of study materials

Procedures should be in place that will ensure timely delivery of study related materials to sites. Maintaining integrity/ stability during transport is essential, so the use of reliable means of transportation and chain of custody documentation is critical. Clearly defined procedures for transportation, and responsibilities for who does what, are essential.

41. See § 39, § 19 e 42.

Adequate documentation should accompany each shipment of study material to satisfy any applicable legal requirements, e.g. customs, health and safety legislation. This documentation should also provide relevant information sufficient to ensure that it is suitable for its intended purpose on arrival at any site. These aspects should be resolved prior to shipment.

42. To be documented in writing and SOP driven.

When study materials are transported between sites in the same consignment it is essential that there is adequate separation and identification to avoid mix-ups or cross contamination. This is of particular importance if materials from more than one study are transported together.

If the materials being transported might be adversely affected by environmental conditions encountered during transportation, procedures should be established to preserve their integrity. It may be appropriate for monitoring to be carried out to confirm that required conditions were maintained.

43. The correct receipt, including the condition of the incoming material, should be properly documented.

Temperature recording during transportation should be anticipated if this is considered critical to the study.

Attention should be given to the storage, return or disposal of excess test and reference items being used at sites.

REPORTING OF STUDY RESULTS

A single final report should be issued for each multi-site study. The final report should include data from all phases of the study. It may be useful for the Principal Investigators to produce a signed and dated report of the phase delegated to them, for incorporation into the final report. If prepared, such reports should include evidence that appropriate quality assurance monitoring was performed at that test site and contain sufficient commentary to enable the Study Director to write a valid final report covering the whole study. Alternatively, raw data may be transferred from the Principal Investigator to the Study Director, who should ensure that the data are presented in the final report. The final report produced in this way should identify the Principal Investigator(s) and the phase(s) for which they were responsible.

The Principal Investigators should indicate the extent to which the work for which they were responsible complies with the GLP Principles, and provide evidence of the quality assurance inspections performed at that test site. This may be incorporated directly into the final report, or the required details may be extracted and included in the Study Director's compliance claim and Quality Assurance statement in the final report. When details have been extracted the source should be referenced and retained.

The Study Director must sign and date the final report to indicate acceptance of responsibility for the validity of all the data. The extent of compliance with the GLP Principles should be indicated with specific reference to the OECD Principles of GLP and Regulations with which compliance is being claimed. This claim of compliance will cover all phases of the study and should be consistent with the information presented in the Principal Investigator claims. Any sites not compliant with the OECD Principles of GLP should be indicated in the final report.

44. The GLP compliance statement signed by the Study Director should list any test site that is not GLP certified (not included in the GLP monitoring programme by the relevant regulatory authority).

The final report should identify the storage location(s) of the study plan, samples of test and reference items, specimens, raw data and the final report. Reports produced by Principal Investigators should provide information concerning the retention of materials for which they were responsible.

Amendments to the final report may only be produced by the Study Director. Where the necessary amendment relates to a phase conducted at any test site the Study Director should contact the Principal Investigator to agree appropriate corrective actions. These corrective actions must be fully documented.

If a Principal Investigator prepares a report, that report should where appropriate comply with the same requirements that apply to the final report.

STANDARD OPERATING PROCEDURES (SOPs)

The GLP Principles require that appropriate and technically valid SOPs are established and followed. The following examples are procedures specific to multi-site studies:

- Selection and monitoring of test sites;
- Appointment and replacement of Principal Investigators;
- Transfer of data, specimens and samples between sites;

- Verification or approval of foreign language translations of study plans or SOPs; and
- Storage, return or disposal of test and reference items being used at remote test sites.

The Principles of GLP require that SOPs should be immediately available to study personnel when they are conducting activities, regardless of where they are carrying out the work.

It is recommended that test site personnel should follow test site SOPs. When they are required to follow other procedures specified by the Study Director, for example SOPs provided by the test facility management, this requirement should be identified in the study plan. The Principal Investigator is responsible for ensuring that test site personnel are aware of the procedures to be followed and have access to the appropriate documentation.

45. The SOPs of other sites to be used are to be specified in the study plan or a separate agreement/document (it is not a GLP requirement to include this information in the study plan) – see also § 24 and 27. Additional SOPs should be prepared describing the management of multi-site studies, management of other sites' SOPs and training for SOPs provided by other sites.

If personnel at a test site are required to follow SOPs provided by the test facility management, it is necessary for test site management to give written acceptance.

46. See § 27.

When SOPs from a test facility have been issued for use at a test site, test facility management should ensure that any subsequent SOP revisions produced during the course of the study are also sent to the test site and the superseded versions are removed from use. The Principal Investigator should ensure that all test site personnel are aware of the revision and only have access to the current version.

47. See § 27.

It should be stressed that SOP versions which are superseded, but have been used at the site, should also be kept there, as required by GLP (indispensable for reconstruction of events during the study and to allow QA to check the final report, etc.).

When SOPs from a test facility are to be followed at test sites, it may be necessary for the SOPs to be translated into other languages. In this situation it is essential that any translations be thoroughly checked to ensure that the instructions and meaning of the different language versions remain identical. The original language should be defined in the translated SOPs.

48. See § 27.

The translation method and associated responsibilities should be set out in a SOP.

STORAGE AND RETENTION OF RECORDS AND MATERIALS

During the conduct of multi-site studies attention should be given to the temporary storage of materials. Such storage facilities should be secure and protect the integrity of their contents. When data are stored away from the test facility, assurance will be needed of the site's ability to readily retrieve data which may be needed for review.

49. A certified site ought to be able to assure the correct temporary storage of data; the Principal Investigator should guarantee GLP compliance also for this aspect. Procedures should be set out/agreed for non-certified sites or particular sites (in field studies).

Records and materials need to be stored in a manner that complies with GLP Principles. When test site storage facilities are not adequate to satisfy GLP requirements, records and materials should be transferred to a GLP-compliant archive.

50. A certified site ought to be able to assure correct data archiving; the Principal Investigator should guarantee GLP compliance also for this aspect.

Transfer of data/materials generated at non-certified sites to a GLP-compliant archive should be arranged.

Test site management should ensure that adequate records are available to demonstrate test site involvement in the study.

51. Where the data are sent to the Study Director, a SOP should be prepared specifying the minimum documentation to be retained at each site (master schedule, study plan, list of data/material generated at the site and sent to the Study Director, copy of results sent to the Study Director – final report/tables/..., QA data, GLP compliance statement, QA statement).

Obviously, QA documentation and documentation not specifically study-related should be retained (curricula vitae, training records, instrument maintenance files ...).

It is better to specify archiving times in the study plan or in a separate agreement/document (as well as in the report).

***On-line data.** Check a priori the compatibility of systems in use at the various sites, otherwise agree on archiving at the site(s) where they are produced.*

***Regulatory inspections at a site.** Where the material/data are no longer at the site inspected, there are various options the regulatory authority may follow, such as:*

- *Request to the local regulatory authority to inspect the site where the material/data are retained*
- *Request to transfer material/data to the site being inspected (confined to material/data generated by that site)*

ADDITIONAL POINT DISCUSSED

Non-GLP certified sponsor and contract archives

Introduction

GLP expressly requires (section II § 10.4) that if a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archive of the sponsor(s) of the study(s). However, there is no reference to the sponsor(s) having to be GLP-compliant and there is no reference to the existence of contract archives seen as separate structures from the test site.

Points discussed

1. Possibility of using non-GLP certified archives (not included in the national GLP compliance monitoring programme by the relevant regulatory authority) for long-term archiving of data from GLP terminated studies (e.g. contract archives or archives at non-GLP certified Sponsors). Obviously it should be ensured that these archives give guarantees as to security, i.e. are managed in accordance with the principles of GLP.

2. Possibility of including contract archives in the national GLP compliance monitoring programme, even if not directly involved in the conduct of studies, but only dealing with archiving.

Outcome of the discussion

1. It is a sponsor's responsibility to make sure that the material/data are correctly archived. They may be kept at a GLP archive (e.g. archived for x years at a GLP-certified test site) or at a non GLP archive (e.g. at a sponsor's non-GLP-certified site). In any case it is essential that the sponsor assures that archiving is done in accordance with GLP principles, in order to guarantee traceability of the material/data after a period of years.

2. The possibility to include contract archives in the national GLP compliance monitoring programme will be assessed by the regulatory authority if and when an application will be received. The issue therefore remains open.

The reference to GLP principles included in the test are from the Italian GLP document: Decreto 5 agosto 1999. Disposizioni relative all'ispezione e verifica della buona prassi di laboratorio in recepimento delle direttive 1999/11/CE and 1999/12/CE. Gazzetta Ufficiale n. 241, 13 ottobre 1999.

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THE LIGHTER SIDE

New Meetings Procedure

Do you keep falling asleep at meetings? What about those long and boring conference calls? Here's a way to change all of that!

Before (or during) your next meeting, seminar, or conference call prepare a bingo card by drawing a square. 5″ × 5″ is a good size. Divide it into columns – five across and five down. That will give you twenty-five one-inch blocks.

Write one of the following words/phrases in each block (or use other favourites):

Synergy, strategic fit, core competencies
best practices, bottom line, revisit
24/7, vision, out of the loop
benchmark, value-added, proactive
win-win, think outside the box, fast track
results-driven, empower(ment)
knowledge base, at the end of the day
touch base, mindset, client focus(ed)
single working practice, quality control(led)
harmonisation, global

Check off the appropriate block when you hear one of those words/phrases.

When you get five blocks horizontally, vertically, or diagonally, stand up and shout 'I agree wholeheartedly!'

The following are testimonials from satisfied players:

'I had been in the meeting for only five minutes when I won!'

'My attention span at meetings has improved dramatically!'

'What a gas! Meetings will never be the same for me after my first win.'

'The atmosphere was tense in the last meeting as fourteen of us waited for the fifth box!'

'The speaker was stunned as eight of us screamed "I agree wholeheartedly" for the third time in two hours!'

Comments from Travel Agents

• I had someone ask for an aisle seat so that their hair wouldn't get messed up by being near the window.

• A client called in inquiring about a package to Hawaii. After going over all the cost info, she asked, 'Would it be cheaper to fly to California and then take the train to Hawaii?'

• I got a call from a woman who wanted to go to Capetown. I started to explain the length of the flight and the passport information when she interrupted me with, 'I'm not trying to make you look stupid, but Capetown is in Massachusetts.' Without trying to make her look like the stupid one, I calmly explained, 'Capecod is in Massachusetts, Capetown is in Africa.' Her response – click.

• A man called, furious about a Florida package we did. I asked what was wrong with the vacation in Orlando. He said he was expecting an ocean-view room. I tried to explain that is not possible, since Orlando is in the middle of the state. He replied, 'Don't lie to me. I looked on the map and Florida is a very thin state.'

• I got a call from a man who asked, 'Is it possible to see England from Canada?' I said, 'No.' He said, 'But they look so close on the map.'

• Another man called and asked if he could rent a car in Dallas. When I pulled up the reservation I noticed he had a one-hour lay-over in Dallas. When I asked him why he wanted to rent a car he said, 'I heard Dallas was a big airport, and I need a car to drive between the gates to save time.'

• A nice lady just called. She needed to know how it was possible that her flight from Detroit left at 8.20 am and got into Chicago at 8.33 am. I tried to explain that Michigan was an hour ahead of Illinois, but she could not understand the concept of time zones. Finally I told her the plane went very fast, and she bought that!