

JUN 1981

GOOD LABORATORY PRACTICE REGULATIONS

QUESTIONS AND ANSWERS

Since June 20, 1979, the agency has been asked many questions on the Good Laboratory Practice regulations (GLPs, 21 CFR 58). In accord with the agency procedures, responses have been prepared and copies of the associated correspondence have been filed in the Dockets Management Branch (HFA-305). The responses have also been provided to the bioresearch monitoring program managers and to the district offices in order to ensure consistency of interpretation and equity of program operation. Unfortunately, the numerous filed correspondence contain many, repeat questions that are not categorized to relate to the specific GLP subpart and section. On occasion, the answers appear somewhat cryptic. These disadvantages serve to limit the utility of the correspondences as advisories to our headquarters and field offices.

This document, therefore, consolidates all GLP questions answered by the agency during the past 2 years, clarifies the questions and answers as needed, and relates the questions and answers to the specific pertinent provisions of the GLPs. It represents a digest of some 30 letters, 160 memoranda of telephone conversations, 34 memoranda of meetings and 30 miscellaneous correspondences that have been issued by agency personnel. The document does not duplicate questions and answers that were dealt with in the August, 1979 Post Conference Report on the Good Laboratory Practice Regulations Management Briefings.

This document should be reviewed by field investigators prior to making GLP inspections and by headquarters personnel involved in the GLP program. Questions should be directed to:

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SUBPART A
GENERAL PROVISIONS

Section 58.1 Scope.

1. Do the GLPs apply to validation trials conducted to confirm the analytical methods used to determine the concentration of test article in animal tissues and drug dosage forms?

No.

2. Do the GLPs apply to the following studies on animal health products: overdosage studies in the target species, animal safety studies in the target species, tissue residue accumulation and depletion studies, and udder irritation studies?

Yes

3. Do the GLPs apply to safety studies on cosmetic products?

No. Such studies are not carried out in support of a marketing permit. However, the GLPs represent good quality control; a goal that all testing facilities should strive to attain.

4. Do safety studies done to determine the potential drug abuse characteristics of a test article have to be done under the GLPs?

Yes they do, but only when the studies are required to be submitted to the agency as part of an application for a research or marketing permit.

5. Do the GLPs apply to the organoleptic evaluation of processed foods?

No.

6. Do the GLPs apply to all of the analytical support work conducted to provide supplementary data to a safety study?

The GLPs apply to the chemical procedures used to characterize the test article, to determine the stability of the test article and its mixtures, and to determine the homogeneity and concentration of test article mixtures. Likewise, the GLPs apply to the chemical procedures used to analyze specimens (e.g. clinical chemistry, urinalysis). The GLPs do not apply to the work done to develop chemical methods of analysis or to establish the specifications of a test article.

7. Is it possible to obtain an exemption from specific provisions of the GLPs for special nonclinical laboratory studies?

Yes. The GLPs were written with the aim of being applicable to a broad variety of studies, test articles and test systems. Nonetheless, the agency realizes that not all of the GLP provisions apply to all studies and, indeed, for some special studies certain of the GLP provisions may compromise proper science. For this reason, laboratories may petition the agency for exemption for certain studies from some of the GLP provisions. The petition should contain sufficient facts to justify granting the exemption.

8. Are subcontractor laboratories that furnish a particular service such as ophthalmology exams, reading of animal ECGs, EEGs, EMGs, preparation of blocks and slides from tissues, statistical analysis and hematology covered by the GLPs?

Yes, to the extent that they contribute to a study that is subject to the GLPs.

Section 58.3 Definitions.

1. Are animal cage cards considered to be raw data?

Raw data is defined as "any laboratory worksheets, records, memorandum, notes that are the result of original observations and activities and are necessary for the reconstruction and evaluation of the report of that study." Cage cards are not raw data if they contain information like animal number, study number, study dates, and cage number (information that is not the result of original observations and that is not necessary for study reconstruction). However, if an original observation is put on the cage cards, then all cards must be saved as raw data.

2. Are photo copies of raw data which are dated and verified by signature of the copier considered to be "exact" copies of the raw data?

Yes.

3. Are records of quarantine, animal receipt, environmental monitoring, and instrument calibration considered to be raw data?

Yes.

4. A laboratory conducts animal studies to establish a baseline set of data for a different test species/strain. No test article is administered but the toxicology laboratory facilities and procedures will be used and the resulting data may eventually be submitted to the agency as part of a research or marketing permit. Are the studies considered to be nonclinical laboratory studies that are covered by the GLPs?

Generally, a nonclinical laboratory study involves a test article studied under laboratory conditions for the purpose of determining its safety. The cited example does not fit the definition so it would not be covered by the GLPs. Since the data from the baseline studies may be used to interpret the results of a nonclinical laboratory study, it is recommended, but not required, that the study be conducted in accord with GLPs in order to ensure valid baseline data.

5. The definition of "nonclinical laboratory study" excludes field trials in animals. What is a field trial in animals?

A field trial in animals is similar to a human clinical trial. It is conducted for the purpose of obtaining data on animal drug efficacy and it is excluded from coverage under the GLPs.

6. Necropsies are done by prosectors trained by and working under the supervision of a pathologist. The necropsy data are recorded by the prosector on data sheets, and when making the final report, the pathologist summarizes the data collected by the prosector as well as by him/herself. What constitutes the raw data in this example?

Both the prosector's data sheets as well as the signed and dated report of the pathologist would be considered raw data.

Is a computer print-out derived from data transferred to computer media from laboratory data sheets considered to be raw data?

No

8. Are the assay plates used in the 10t1/2 mammalian cell transformation assay considered to be specimens?

Yes.

9. If a firm uses paraprofessionals to screen tissue preparations, are the paraprofessionals' data sheets considered to be raw data?

Yes.

Section 58.10 Applicability to studies performed under grants and contracts.

1. Certain contracts specify that a series of nonclinical laboratory studies be done on a single test article. Do the GLPs permit the designation of different study directors for each study under the contract?

Yes.

2. Do the GLPs require that a sponsor approve the study director for a contracted study?

No. Testing facility management designates the study director.

3. A firm functions as a primary contractor for nonclinical laboratory studies. The actual studies are then subcontracted to nonclinical laboratories. Is the firm considered to be a "sponsor?"

The GLPs define "sponsor" as a person who initiates and supports a nonclinical laboratory study. Sponsorship in the cited example would be determined by the specific provisions of the contract.

4. Who is responsible for test article characterization - the sponsor or the contractor?

The GLPs do not assign the responsibility in this area. The matter is a subject of the specific contractual arrangement between the sponsor and the contractor.

5. Do contract laboratories have to show the sponsor's name on the Master Schedule Sheet or can this information be coded?

The information can be coded but the code must be revealed to the FDA investigator on request.

6. A sponsor desires to contract for a nonclinical laboratory study to be conducted in a foreign laboratory. Must the sponsor notify the foreign laboratory that compliance with the U.S. GLPs is required?

Yes.

7. Must a contractor include in the final report information on test article characterization and stability when such information has been collected by the sponsor?

No. The contractor should identify in its final report which information will be subsequently supplied by the sponsor.

8. Must a sponsor reveal toxicology data already collected on a test article to a contract laboratory?

No. If use of the test article involves a potential danger to laboratory personnel, the contract laboratory should be advised so that appropriate precautions can be taken.

Section 58.15 Inspection of a testing facility.

1. What is the usual procedure for the issuance of a form FD-483?

The FD-483 is the written notice of objectionable practices or deviations from the regulations that is prepared by the FDA investigator at the end of the inspection. The items listed on the form serve as the basis for the exit discussion with laboratory management at which time management can either agree or disagree with the items and can offer possible corrective actions to be taken. Management may also respond to the district office in writing after it has had sufficient time to properly study the FD-483.

2. Will a laboratory subsequently be notified of GLP deviations not listed on the FD-483?

This does happen. The FDA investigator prepares an establishment inspection report (EIR) which summarizes the observations made at the laboratory and which contains exhibits concerning the studies audited (Protocols, SOPS, CV's, etc.). The EIR is then reviewed by District personnel as well as headquarters personnel. This review may reveal additional GLP deviations that should be and are communicated to laboratory management.

3. What kinds of domestic toxicology laboratory inspections does FDA perform and how frequently are they done?

FDA performs four kinds of inspections related to the GLPs and nonclinical laboratory studies. These include: A GLP inspection - an inspection undertaken as a periodic, routine determination of a laboratory's compliance with the GLPs, it includes examination of an ongoing study as well as a completed study; A data audit - an inspection made to verify that the information contained in a final report submitted to FDA is accurate and reflected by the raw data; A directed inspection - any of a series of inspections conducted for various compelling reasons (questionable data in a final report, tips from informers, etc.); A followup inspection - an inspection made sometime after a GLP inspection which revealed objectionable practices and conditions. The purpose of the followup inspection is to assure that proper corrective actions have been taken. GLP inspections are scheduled once every two years whereas the other kinds of inspections are scheduled as needed.

4. Should GLP investigators comment on the scientific merits of a protocol or the scientific interpretation given in the final report?

No. Their function is strictly a noting of observations and verification. Scientific judgments are made by the respective headquarters review units that deal with the test article.

5. Can a GLP EIR be reviewed by laboratory management prior to issuance?

No. The GLP EIR is an internal agency document which reflects the observations and findings of the FDA investigator. It can not be released to anyone outside the agency until agency action has been completed and the released copy is s purged of all trade secret information. Laboratories that disagree with portions of the EIR should write a 1 letter which contains the areas of disagreement to the local FDA District Office. The laboratories can ask that their letters accompany the EIR whenever it is requested under the Freedom of Information Act.

6. Can FDA investigators take photographs of objectionable practices and conditions?

It is the agency position that photographs can be taken as a part of the inspection and this position has been sustained by a District Court decision.

7. The GLP Compliance Program requires the FDA investigator to select an ongoing study in order to inspect current laboratory operations. What criteria are used to select the study?

The studies are selected in accord with agency priorities, i.e. the longest term study on the most significant product.

8. Does FDA inspect international nonclinical laboratories once every two years?

No. Overseas laboratories are scheduled for inspection on the basis of having submitted to FDA the results of significant studies on important products.

9. What background materials are used by agency investigators to prepare for a GLP inspection?

Prior to an "inspection, the following materials are usually reviewed:

- (a) The GLP regulations;
- (b) The Management Briefings Post-Conference Report;
- (c) Assorted memoranda and policy issuances;
- (d) The GLP Compliance Program;
- (e) The protocol of an ongoing study, if available;
- (f) The final report of a completed study, if available;
- (g) The inspection report of the most recent inspection.

10. How long does FDA allow a laboratory to effect corrective actions after an inspection has been made?

If the results of an inspection reveal that significant deviations from the GLPs exist, the laboratory will be sent a regulatory letter that lists the major deviations and that requests a response within 10 days. The response should describe those actions that the laboratory has taken or plans to take to effect correction. The response should also encompass items that were listed on the FD-483 and those that were discussed during the exit discussion with laboratory management. A specific time table should be given for accomplishing the planned actions. The reasonableness of the time table will be determined by FDA compliance staff, based on the needs of the particular situation.

For less significant deviations, the laboratory will be sent a Notice of Adverse Findings letter that also lists the deviations but that requests a response within 30 days. Again, the reasonableness of the response will be determined by FDA staff.

11. Does a laboratory's responsibility for corrective action listed on a FD-483 begin at the conclusion of an inspection or upon receipt of correspondence from the originating bureau in which corrective action is requested?

The FD-483 lists observations of violative conditions that have the capability to adversely affect nonclinical laboratory studies. Corrective actions should be instituted as soon as possible.

12. Does FDA preannounce all GLP inspections?

Laboratory management is informed of all routine GLP inspections prior to the inspection, but special compliance or investigative inspections need not be preannounced.

SUBPART B
ORGANIZATION AND PERSONNEL

Section 58.29 Personnel.

1. For what sequence in the supervisory chain should position descriptions be available?

Position descriptions should be available for each individual engaged in or supervising the conduct of the study.

2. Should current summaries of training and experience list attendance at scientific and technical meetings?

Yes. The agency considers such attendance as a valuable adjunct to the other kinds of training received by laboratory personnel.

3. If certain specialists (pathologists, statisticians, ophthalmologists, etc.) are contracted to conduct certain aspects of a study, need they be identified in the final report?

Yes.

4. Does the QAU have to be composed of technical personnel?

No. Management is, however, responsible for assuring that "personnel clearly understand the functions they are to perform" (Section 58.31(f)) and that each individual engaged in the study has the appropriate combination of education, training and experience (Section 58.29(a)).

Section 58.31 Testing Facility Management.

1. Can the study director be the chief executive of a nonclinical laboratory?

No. The GLPs require that there be a separation of function between the study director and the QAU director. In the example, the QAU director would be reporting to the study director.

Section 58.33 Study director.

1. The GLPs permit the designation of an "acting" or "deputy" study director to be responsible for a study when the study director is on leave. Should study records identify the designated "deputy" or "acting" study director?

Yes.

2. Is the study director responsible for adherence to the GLPs?

Yes.

Section 58.35 Quality Assurance Unit.

1. As a QAU person, I have no expertise in the field of pathology. How do I audit pathology findings?

The QAU is not expected to perform a scientific evaluation of a study nor to "second-guess" the scientific procedures that are used. QAU inspections are made to ensure that the GLPs, SOPs and protocols are being followed and that the data summarized in the final report accurately reflect the results of the study. A variety of procedures can be used to do this but certainly the procedures should include an examination and correlation of the raw data records.

2. Must the QAU keep copies of all protocols and amendments and SOPs and amendments?

The QAU must keep copies of all protocols as currently amended. The only SOPs that the QAU are required to keep are those concerned with the operations and procedures of the QAU.

3. Does the QAU have to monitor compliance with regulations promulgated by other government agencies?

The GLPs do not require this.

4. Can an individual who is involved in a nonclinical laboratory study perform QAU functions for portions of the study that the individual is not involved with?

No. However, the individual can perform QAU functions for a study that he/she is not involved with.

5. Does the QAU review amendments to the final report?

Yes.

6. What studies are required to be listed on the master schedule sheet?

The master schedule sheet should list all nonclinical laboratory studies conducted on FDA regulated products and intended to support an application for a research or marketing permit.

7. May the QAU in its periodic reports to management and the study director recommend actions to solve existing problems?

Yes.

8. If raw data are transcribed and sent to the sponsor for (a) preparing the data in computer format or (b) performing a statistical analysis, what are the responsibilities of the QAU?

For (a) the QAU should assure that the computer formatted data accurately reflect the raw data. For (b) the statistical analyses would comprise a report from a participating scientist, therefore it should be checked by QAU and appended to the final report.

9. Can the QAU also be responsible for maintaining the laboratory archives?

Yes.

10. Can a QAU be constituted as a single person?

Yes, provided that the workload is not excessive and other duties do not prevent the person from doing an adequate job. It would be prudent to designate an alternate in case of disability/vacations/ etc.

11. Who is responsible for defining study phases and designating critical study phases and can these be covered in the SOP?

The GLPs do not isolate this responsibility. Logically, the task should be done by the study director and the participating scientists working in concert with the QAU and laboratory management. It can be covered by an SOP.

SUBPART C FACILITIES

Section 58.41 General.

No questions were asked on the subject.

Section 58.43 Animal Care Facilities.

1. Do the GLPs require clean/dirty separation for the animal care areas?

No. They do require adequate separation of species and studies.

2. Do the GLPs require that separate animal rooms be used to house test systems and conduct different studies?

No. The GLPs require separate areas adequate to assure proper separation of test systems, isolation of individual projects, animal quarantine and routine or specialized housing of animals, as necessary to achieve the study objectives.

3. Do the GLPs require that access to animal rooms be limited only to authorized individuals?

No. However, undue stresses and potentially adverse influences on the test system should be minimized.

Section 58.45 Animal Supply Facilities.

No questions were asked on the subject.

Section 58.47 Facilities for Handling Test and Control Articles.

1. Do test and control articles have to be maintained in locked storage units?

No, but accurate records of test and control article accountability must be maintained.

Section 58.49 Laboratory operation areas.

No questions were asked on the subject.

Section 58.51 Specimen and data storage facilities.

1. What do the GLPs require with regard to facilities for the archives?

Space should be provided for archives limited to access by authorized personnel. Storage conditions should minimize deterioration of documents and specimens.

Section 58.53 Administrative and personnel facilities.

No questions were asked on the subject.

SUBPART D
EQUIPMENT

Section 58.61 Equipment design.

No questions were asked on the subject.

Section 58.63 Maintenance and calibration of equipment.

1. Has FDA established guidelines for the frequency of calibration of equipment (balances) used in nonclinical laboratory studies?

The agency has not established guidelines for the frequency of calibration of balances used in nonclinical laboratory studies. This would be a large undertaking in part due to the wide variety of equipment that is available and to the differing workloads that would be imposed on the equipment. It is suggested that you work with the equipment manufacturers and your study directors to arrive at a suitable calibration schedule. The key point is that the calibration should be frequent enough to assure data validity. The maintenance and calibration schedules should be part of the SOPS for each instrument.

2. When an equipment manufacturer performs the routine equipment maintenance, do the equipment manufacturer's maintenance procedures have to be described in the facilities' SOPS?

No. The facilities' SOPS would have to state that maintenance was being performed by the equipment manufacturer according to their own procedures.

SUBPART E
TESTING FACILITIES OPERATION

Section 58.81 Standard Operating Procedures.

1. What amount of detail should be included in the standard operating procedures (SOPS)?

The GLPs do not specify the amount of detail to be included in the SOPS. The SOPS are intended to minimize the introduction of systematic error into a study by ensuring that all personnel will be familiar with and use the same procedures. The adequacy of the SOPS is a key responsibility of management. A guideline of adequacy that could be used is to determine whether the SOPS are understood and can be followed by trained laboratory personnel.

2. Can the study director authorize changes in the SOPS?

No. Approval of the SOPS and changes thereto is a function of laboratory management.

3. How many copies of the complete laboratory SOPS are needed?

Each work station should have access to the SOPS applicable to the work performed at the station. A complete set of the SOPS, including authorized amendments, should be maintained in the archives.

4. Who approves the SOPS of the Quality Assurance Unit?

Laboratory Management.

5. To what extent are computer programs to be documented as SOPS?

The GLPs do not specify the contents of individual SOPS, but the SOP that deals with computerized data acquisition should include the purpose of the program, the specifications, the procedures, the end products, the language, the interactions with other programs, procedures for assuring authorized data entry and access, procedures for making and authorizing changes to the program, the source listing of the program and perhaps even a flow chart. The laboratory's computer specialists should determine what other characteristics need to be described in the SOP.

Section 58.83 Reagents and solutions,

1. What are the GLP requirements for labeling of reagents purchased directly from manufacturers?

All reagents used in a nonclinical laboratory have to be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Purchased reagents usually carry all these items except for the expiration date, so the 1 laboratory should label the reagent containers with an expiration date. The expiration date selected should be in line with laboratory experience and need not require specific stability testing.

2. How extensive should the procedures be for confirming the quality of incoming reagents used in nonclinical laboratory studies?

Laboratory management should make this decision but the SOPS should document the actual procedures used.

3. Do the procedures used for preparing the S9 activator fraction (liver microsomal fraction from rats challenged with a toxin) have to be performed in accord with the GLPs?

No. The GLPs consider the S9 activator fraction to be a reagent. Therefore, it must be labeled properly, stored properly, tested prior to use in accord with adequate SOPs, and, it can not be used if its potency is below established specifications.

4. Do the GLPs require the use of product accountability procedures for reagents and chemicals used in a nonclinical laboratory study?

No.

Section 58.90 Animal care.

1. Can diseased animals received from a supplier be diagnosed, treated, certified "well" and then entered into a nonclinical laboratory study?

The GLPs provide for this procedure by including provisions directed towards animal quarantine and isolation. The question of whether such animals can be entered into a study, however, is a scientific one that should be answered by the veterinarian-in-charge and the study director and other scientists involved in the study.

2. Do the GLPs prohibit the use of primates for multiple nonclinical laboratory studies?

No. Again, the question is a scientific one and the potential impact of multiple use on study interpretation should be carefully assessed.

3. Is a photocopy of an animal purchase order which has been signed and dated by the individual receiving the shipment sufficient proof of animal receipt?

Yes, but actual shipping tickets are also acceptable

4. Does FDA have guidelines for animal bedding?

No, but the GLPs prohibit the use of bedding which can interfere with the objectives of the study.

5. Does FDA permit the sterilization of animal feed with ethylene oxide.

No.

6. For certain test systems (timed-pregnant rodents), it is not possible to use long quarantine periods. Do the GLPs specify quarantine periods for each test system?

No. The quarantine period can be established by the veterinarian in charge of animal care and should be of sufficient length to permit evaluation of health status.

7. How are feed and water contaminants to be dealt with?

The protocol should include a positive statement as to the need for conducting feed analysis for contaminants. If analysis is necessary, the identities and specifications for the contaminants should be listed. The need for analysis as well as the specifications should be determined by the study scientists. Water contaminants can be handled similarly.

8. How is the adequacy of bedding materials to be handled?

This can be handled as are the analyses for possible contaminants in feed and water. The study director and associated scientists should consider the bedding and its possible impact on the study. The results of this consideration should appear in the protocol.

9. What do the GLPs require in regard to assuring the genetic quality of animals used in a nonclinical laboratory study?

This is a scientific issue that is not specifically addressed by the GLPs. Suitability of the test system for use in a study is a protocol matter and any required testing procedure should be arrived at by the study scientists.

10. Do the GLPs require specific procedures for the microbiological monitoring of animals used in nonclinical laboratory studies?

The procedures used should be in accord with acceptable veterinary medical practice.

11. The Japanese are preparing animal care guidelines which are similar but not identical to the U.S. guidelines prepared by NIH. Would these be acceptable?

Japanese guidelines that are similar, but no less stringent, in the important particulars with the NIH guidelines would be acceptable to FDA.

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12. What is the frequency of feed contaminant analysis?

If contaminant analyses are required by the protocol, then the GLPs require periodic analysis of the feed to ensure that the contaminant level is at or below that judged to be acceptable. Statistical procedures should be used to determine the frequency of analysis since this is dependent on the specific chemical characteristics of the interfering contaminant.

13. It is necessary to use "official" methods of analysis to determine the levels of interfering contaminants?

No. The methods should be appropriate for the analysis and FDA reserves the right to examine the raw data supporting the analytical results.

14. Do the GLPs require production facilities to be dedicated to the manufacture of specific animal feeds used in nonclinical laboratory studies?

No.

15. Is a separate room required for animal necropsy?

No. The GLPs require separate areas and/or rooms as necessary to prevent any activity from having an adverse effect on the study. If the necropsy is done in an animal room, precautions should be taken to minimize disturbances that may interfere with the study.

SUBPART F
TEST AND CONTROL ARTICLES

Section 58.105 Test and control article characterization

1. Is it necessary to retain samples of feed from nonclinical laboratory studies in which the feed serves as the control article?

Yes. It is not necessary, however, to retain reserve samples of feed from studies that involve test article administration by routes other than feed.

2. What expiration date is placed on the label of test articles whose stability is being assessed concurrently with the conduct of the study?

In this situation, the stability of the test article is unknown, but periodic analysis data exist. The label should contain a statement such as "see protocol" or "see periodic analysis results" so that test article users will know that current analytical data should be examined prior to continued use of the test article.

3. If analysis of the reserve samples is required by the Study Director or the QAU, is it permitted?

Yes, but sufficient reserve sample should be retained so that the sample is not exhausted.

4. Are physical and chemical tests conducted on test articles required to be done under the GLPs?

According to section 58.105, such tests conducted to characterize the specific batch of test article used in the nonclinical laboratory study are covered.

Section 58.107 Test and control article handling.

1. With regard to safety studies in n large animals (cattle, horses, etc.), must test article accountability be maintained and can the animals be used for food purposes?

Test article accountability must be maintained. For guidance on whether the treated animals can be used for food, you should contact the appropriate individuals in the Bureau of Veterinary Medicine.

Section 58.113 Mixtures of articles with carriers.

1. Do the GLPs require tests for homogeneity, concentration, and stability on mixtures of control articles used as positive controls?

Yes

2. Do test or control article concentration assays have to be performed on each batch of test or control article carrier mixture?

No. The GLPs require only periodic analysis of test or control article carrier mixtures.

3. What is the purpose of periodic analysis requirement for test or control article mixtures?

This requirement provides additional assurance that the test system is being exposed to protocol-specified quantities of test article. Whereas, in most instances proper assurance is obtained through adequate uniformity-of-mixing studies, adequate SOPs, and trained personnel, occasionally the mixing equipment can malfunction or other uncontrollable events can occur which lead to improper dosages. These events can be recognized through periodic analysis.

4. For acute studies, does the test article carrier mixture have to be analyzed (single dose studies)?

Yes, but the analysis need not be done prior to the study provided the mixture is stable in storage.

5. For liquid dosing studies where the test article mixture is made by dilution of the highest dose, which dose should be analyzed?

The lowest dose would be appropriate since it would confirm the efficacy of the dilution process, however the GLPs do not prohibit the analysis of any of the other doses.

6. Do homogeneity studies need to be done on solutions and suspensions of test articles used in acute nonclinical laboratory studies?

The answers to these questions are yes for suspensions of test articles and no for true solutions of test articles.

7. The analysis of test article mixtures that are used in acute studies is problematic. Usually at the stage of product development, the analytical method is not fully developed. Also, getting the analytical department to schedule the analysis is difficult. Stability is not a problem since fresh solutions are used. In view of the fact that acute studies are not pivotal in gaining approval of a research or marketing permit, is it necessary to analyze test article mixtures?

Yes. Although acute studies may be of lesser importance in assessing the safety of human drugs, they are important for animal drugs, biological products and certain food additives. For this reason, there must be some assurance that the test system was dosed with protocol specified quantities of test article. The GLPs do not require that, " the analysis be done prior to the use of the test article mixture provided that the mixture is stable on storage.

SUBPART G
PROTOCOL FOR THE CONDUCT OF A NONCLINICAL LABORATORY STUDY

Section .58.120 Protocol.

1. What are the proposed starting and completion dates for a nonclinical laboratory study?

There is a good deal of confusion on these dates and proper interpretation impacts on several GLP areas. Accordingly, the following clarification is offered: At the time of protocol development, the study director is to propose to management the approximate time frame of the study. Section 58.120(a) (4), therefore, requires that the protocol contain the proposed starting and completion date of the study. These dates are somewhat discretionary provided that they are identified in the protocol. Suitable identification can be the date of first dosing of the test system to the date of last dosing, the date of allocation of the test system to the experimental units to the date of necropsy of the last animal on test, the date of receipt of the test system to the date of final histopathological examination, or any combination of these or any other logical starting and completion dates. After this, the protocol is signed by the study director and forwarded for approval to management. Management approves, if indicated, signs and dates and at this point the study becomes a regulated study and must be entered on the Master Schedule Sheet. The study is carried on the Master Schedule Sheet until the study director submits a signed and dated final report. Thus, for Master Schedule Sheet purposes, the starting date of the study is the date of protocol approval by management and the completion date of the study is the date of signature of the final report by the study director. Neither of the foregoing timeframes need be used to define the study terms described in section 58.35(b)(3) and section 58.105(d). For these sections, the traditional terms found in the toxicology literature may be used.

2. Must an analytical method be totally contained in the protocol?

No. The protocol must state the type and frequency of tests to be made. Type can be connoted by reference to literature citations or the SOPs as applicable.

3. Does each nonclinical laboratory study require a sponsor-approved specific protocol?

Yes. However, the laboratory that conducts the study can also qualify as the sponsor of the study.

4. Do unforeseen circumstances which occur during a study and which necessitate minor operational changes have to be reported as protocol amendments.

Unforeseen circumstances which have only a one time effect (different date of sample collection, animal weighings) need to be reported only in the raw data and the final report. However, such circumstances which result in a systematic change, e.g. in the SOPS or in the protocol, should also be made by a protocol amendment. The protocol amendment need not be made in advance but should be made as rapidly as possible.

5. Pathologists at a firm would like to take tissues from animals in a nonclinical study which would be used to conduct exploratory research studies. The tissues would not be part of the nonclinical laboratory study design and the results would not necessarily pertain to the study objectives. What would the GLPs require in this case?

The protocol should state that tissues are to be taken from the experimental animals and that the tissues would be used for exploratory research purposes. If any effects were observed in the exploratory research studies which would influence the interpretation of the results of the nonclinical laboratory study, these effects must be report in the final report.

6. Does the protocol have to list the SOPs used in a specific study?

The protocol must list the type and frequency of tests, analyses, and measurements to be made in the study. Where these are covered by SOPS, they should be listed in the protocol.

Do the GLPs require that absorption studies be done on each test article?

No. The GLPs require that, if absorption studies are needed to achieve the scientific objectives of the study plan, the protocol should describe the methods to be used to determine absorption. Whether or not absorption studies are required is a scientific issue to be decided by the study scientists.

8. Who assesses protocol validity (No. of animals, test article dosage, test system, etc.)?

This is done by the study scientists using the scientific literature, published guidelines, advice from regulatory agencies, and prior experimental work.

Section 58.130 Conduct of a nonclinical laboratory study.

1. Does raw data collected in nonclinical laboratory studies have to be cosigned by a second individual.

No.

2. What are the GLP requirements that are applicable to computerized data - acquisition systems?

An acceptable system must satisfy the following criteria

- (1) Only authorized individuals can make data entries,
- (2) data entries may not be deleted, but changes may be made in the form of dated amendments which provide the reason for data change,
- (3) the data base must be made as tamperproof as possible
- (4) the SOPS should describe the procedures used for ensuring the validity of the data, and
- (5) either the magnetic media or hard-copy printouts are considered to be raw data.

3. In Japan, employees do not sign raw data records but rather they use an official seal which is unique to the employee. Is this an acceptable procedure?

Yes.

4. Do tissue slides have to carry the complete sample labeling information stated in the GLPs?

No, accession numbers are permitted providing that these numbers can be translated into the information required under Section 58.130(c).

5. Is a positive notation (a statement of what was done in the raw data) required for routine laboratory operations such as:

- (a) identifying animals,
- (b) shaving or abrading rabbits,
- (c) specific dosing procedures, and
- (d) fasting of animals?

Yes.

6. Do the GLPs require the entry of raw data into bound notebooks?

No.

7. Is it acceptable to manually transcribe raw data into notebooks if it is verified accurate by signature and date?

Technically the GLPs do not preclude such an approach. It is not a preferred procedure, however, since the chance of transcription errors would exist. Accordingly, such an approach should be used only when necessary and in this event the raw data should also be retained.

SUBPART J RECORDS AND REPORTS

Section 58.185 Reporting of nonclinical laboratory study results.

1. Do contributing scientist's reports have to be prepared and appended to final reports or can the contributing scientist's report be included in the final report prepared by the study director and signed by each contributing scientist?

The signed reports of contributing scientists should be appended to the final report.

2. Does Section 58.115(a) describe the format for submission of a final report?

The cited section describes the information that has to be submitted in a final report but the specific format is left up to the laboratory.

3. Do all circumstances that may have affected the quality of the data have to be described in the final report?

Yes.

4. Who approves the final report of a nonclinical laboratory study?

The GLPs do not address the issue of approval of the final report. According to the GLPs, the final report is official when it is signed and dated by the study director. If persons reviewing the final report request changes, then such changes must be made by way of a formal amendment.

5. Can the chemistry information required by Section 58.185(a)(4) be located elsewhere in the application for a research or marketing permit?

Yes. The final report should, however, reference the location of the chemistry information.

6. Does everyone who participated in a study have to be identified in the final report?

No. The final report need identify only the name of the study director, the names of other participating scientists, and the names of all supervisory personnel.

7. Does the phase of the study which has been inspected need to be identified in the QAU statement in the final report?

No.

8. How are protocol deviations which are discovered after the completion of the study to be handled?

The deviations should be described in n the final report and in the study records.

9. How does the agency view interim reports of nonclinical laboratory studies?

Interim reports are to be treated the same as final reports, i.e. they are to be reviewed by the QAU so that the summarized data accurately reflects the raw data.

Section 58.190 Storage and retrieval of records and data.

1. Certain raw data records are not study specific (pest control, instrument calibration). Must these be filed in the archives in each study file?

No: These can be filed in a retrievable fashion such as chronological in the archive.

2. Where should the QAU records be retained?

At the completion of .a study, QAU records and inspection reports should be retained in the archives.

3. At the termination of a nonclinical laboratory study, can a contractor send all of the raw data, study records, and specimens to the sponsor of the study?

The regulations do not specifically address this issue. Section 58.195(g) requires contract laboratories that go out of business to transfer all raw data and records to the sponsor. Likewise, Section 58.190(b) permits raw data and study records to be stored elsewhere (other than the contract laboratory location) provided that the contract laboratory's archives have reference to the other locations and provided that the final study report identifies the other locations as directed by Section 58.195(a)(13).

Consequently, it is permissible for the sponsor to retain all raw data and records from the date of termination of the nonclinical laboratory study. Common sense dictates, however, that the contract laboratory keep copies of the material that has been forwarded to the sponsor.

4. Can a study director or a pathologist be responsible for storing and retaining specimens and raw data?

Yes, the GLPs permit multiple archival locations provided that these locations are identified in the central archives and that they provide adequate storage conditions and authorized access features.

Section 58.195 Retention of records.

1. With regard to blood and urine specimens which are analyzed for both labile and stable constituents, is it necessary to retain the specimen until the most stable constituent deteriorates?

All specimens should be retained for the term required by the regulations or for as long as their quality permits meaningful reevaluation, whichever is shorter.

2. For a GLP regulated metabolism study, whole tissues are homogenized and aliquots thereof are used for analysis. Is it necessary to retain all of the remaining homogenate as a reserve sample?

No, it is only necessary to retain a representative sample large enough to repeat the original measurements.

3. If animals used in acute studies are subjected to necropsy, is it necessary to retain the organs as study specimens.

Yes.

CONFORMING AMENDMENTS

1. Do acute studies not done in conformity with the GLPs have to be identified in the conforming amendment statement?

Yes

2. How extensive should the conforming amendment statement be for preliminary exploratory studies that are exempt from GLP coverage?

The statement should be brief and indicate the GLP exempt status of the study.

3. For contracted nonclinical laboratory studies, who is responsible for preparing the GLP compliance statement required by the conforming amendments?

The preparation of the conforming amendment statement is the responsibility of the product sponsor and the statement should be submitted as part of the application for a research or marketing permit. The contractor, however, should identify for the sponsor those non GLP practices which were used in each nonclinical laboratory study so that a proper conforming amendment statement can be prepared.

4. Who signs the conforming amendment statement?

This can be the same individual in the firm who signs the official application for a research or marketing permit.

5. Is a specific conforming amendment statement as required by Part 314(f)(7) to be prepared for each nonclinical laboratory study?

Yes. GLP deviations have to be identified for all nonclinical laboratory studies. This can be done by preparing a single comprehensive statement which includes all safety studies in the respective official filing. The conforming amendment statement in the official filing should be located in proximity to the animal safety studies section.

GENERAL

1. Have any nonclinical laboratories been disqualified since June 20, 1979?

No.

2. Does FDA reject nonclinical laboratory studies that have not been conducted in full compliance with the GLPs?

Not necessarily. The GLP Compliance Program provides guidance on the issue. For FDA to reject a study, it is necessary to find that there were deviations from the GLPs and that these deviations were of such a nature as to compromise the quality and integrity of the study covered by the agency inspection.

3. Must copies of the SOPS be submitted along with an application for a research or marketing permit?

No.

4. What should be done about nonclinical laboratory studies that are stopped prior to completion?

The agency recognizes that a variety of circumstances (disease outbreak, power failures, etc.) can lead to the premature termination of a nonclinical laboratory study. In these cases, a short final report should be prepared that describes the reasons for study termination.

5. Has the agency established permissible limits for environmental controls (temperature, humidity and lighting) for the animal facilities?

No, these are scientific matters that should be described in the protocol and/or the SOPS. Of course, accurate records should be maintained.