SUBPART B
ORGANIZATION AND PERSONNEL

58.29 PERSONNEL
58.31 TESTING FACILITY MANAGEMENT
58.33 STUDY DIRECTOR
58.35 QUALITY ASSURANCE UNIT

1. Must an employee with a cold or the flu be removed from the study?

   This decision is left to management. If an employee's disease can adversely affect the test system or the study results, the employee should be removed from the study until the employee is well.

2. In view of the precautions being taken to adequately document diet preparation, the provision for quality assurance unit inspection of the procedure more than once on each study, what is the Agency's thinking on what is to be accomplished by retaining all samples for the period required?

   Maintaining a reserve sample is necessary to provide independent assurance that the test system was exposed to the test article as specified in the protocol. If the results of the study raise questions about the composition of the test article, the reserve sample analysis may provide answers to the questions. The Agency is willing to accept a petition from industry to consider changing the reserve sample retention provisions as discussed elsewhere.

3. Under what circumstances may QAU audit reports be inspected by FDA? Is there any requirement to maintain these reports or can they be discarded?

   QAU audit reports as a matter of administrative policy are exempt from routine FDA inspection. FDA's access to QAU audit reports would be through the Courts should the subject matter of those reports be litigated. Since there is no FDA requirement that these reports be maintained, the disposition of these reports is up to the firm's management. FDA advises that such records not be destroyed without the firm seeking advice from its legal counsel.

4. What are the quality assurance unit inspection requirements for acute and short-term studies?

   For studies lasting less than 4 weeks, each final report should be reviewed by the quality assurance unit for accuracy. With regard to the in process phases (dose preparation, dose administration, in vivo observation and measurement, necropsy, etc.), a random sampling approach could be used so that over a series of studies each critical phase has been monitored. The random sampling approach should be

statistically designed so that it is adequate for revealing GLP deviations. The approach and its justification should be made a part of the standard operating procedures of the quality assurance unit.

5. What constitutes proper quality assurance unit inspection of each phase of a nonclinical laboratory study?

   A variety of procedures are acceptable for performing a quality assurance unit inspection. The GLPs do not mandate specific procedures. The development of an acceptable procedure should not necessarily be limited to but should consider the following:

   (a) nonclinical laboratory studies lasting longer than 6 months should be inspected every 3 months; whereas, studies lasting less than 6 months should be inspected at suitable intervals,

   (b) each phase of the study should be inspected,

   (c) inspection reports are to be submitted to management and to the study director, and

   (d) the purpose of the inspections is to identify significant problems, which may affect study integrity, and to determine that no changes from approved protocols or standard operating procedures were made without proper authorization.

   The phases of a particular study will be determined by the nature of the study. For example, the phases of a typical feeding study include the following:

   1. protocol development and approval
   2. test article characterization
   3. test article stability determination
   4. test article-carrier mixture preparation
   5. test article-carrier mixture sampling
   6. test article-carrier mixture homogeneity determination
   7. test system quarantine
   8. test system allocation to housing
   9. test article carrier mixture distribution to test system
   10. periodic measurements
       - animal observations
       - food consumption
       - body weights
       - blood sampling -- hematology and clinical chemistry
   11. necropsy -- histopathology
   12. statistical analyses and report preparation

The type of inspection will depend on the nature of the phase. Each phase must be inspected at least once during the study; the times selected for inspection should be those most likely to reveal problems before the quality of the data generated could be adversely affected.

6. Could you take a typical subacute 14-day study and define the phases?

   Phases in a short term study (depending on the type) would include protocol preparation, dose preparation, animal allocation, test system dosage, animal observation, necropsy, data recording, data analysis and final report writing.

7. By what authority may the Agency examine master schedule sheets for studies, which may never be used in support of an application for a research or marketing permit?

   Studies that are not intended to be used to support an application for a research or marketing permit are not covered by the GLPs and need not appear on the master schedule sheet. If however, the studies are intended to be submitted, then they should be listed and can be inspected by the Agency under its authority to evaluate the results of studies designed to demonstrate product safety.

8. Are acute studies to be included on the master schedule sheet?

   Yes, if they fall within the scope of the GLPs.

9. In regard to the master schedule sheet, can the "current status of each study" be satisfied by listing the starting date and completion date of the study? Can the "status of the final report" be satisfied by listing the estimated or actual date of issuance of the final report?

   Although the GLPs do not specify entries for "current status of each study," dates alone would not be adequate. Suggested entries that are possible include "study proceeding according to protocol," "study proceeding according to protocol as amended on such-and-such date," "study terminated due to such-and-such," etc. Likewise, entries for the status of the final report might include "awaiting final hematology report," "data in statistical analysis," "first draft prepared," "draft under circulation for review and comment," etc.

10. In our laboratory, critical operations for all studies are carried out by the same individuals using essentially similar procedures. Would it be adequate for the quality assurance unit to inspect a set of representative operations for GLP and standard operating procedure compliance that would incorporate a good cross-section of studies?

    No, but refer to the answer under question 4 above.

11. In reference to the quality assurance unit review of the final report, you have indicated that not all numbers have to be traced. Do you have in mind a standard, which describes an acceptable level of accuracy, e.g., 90%, 99%, 99.9%, 99.99%?

    The quality assurance unit review is to ensure that the final report accurately reflects the raw data. Inasmuch as final reports of certain long-term studies can encompass several hundred thousand observations, it would be a prodigious exercise for the quality assurance unit to verify and trace all raw data. Further, the Agency did not mean to require that the quality assurance unit review would include a check of the accuracy of the calculations used to arrive at the final report. This activity would be redundant since the contributing scientists would have already done so in preparing their reports. Rather, the review was expected to be of sufficient depth to reveal inaccuracies in the final report. Consequently, the Agency envisioned the development of a statistically based system, whereby; a random sample of the results in the final report is traced. The procedure should be made a part of the standard operating procedures.

    The Agency has not established an acceptable level of accuracy of the trace.

12. Is the master schedule sheet intended to be prospective or historical? If it is historical, what is the required retention period?

    The master schedule sheet is intended to include a listing of all nonclinical laboratory studies currently in progress as well as those which have been conducted during the terms specified in section 58.195 of the GLPs.

13. Does the master schedule sheet have to list studies on compounds for which no data has yet been submitted to the Agency?

    Yes. The GLPs cover all nonclinical laboratory studies of Agency regulated products that support or are intended to support applications for research or marketing permits.

14. The GLPs state that the quality assurance unit should assure that the final report reflects the study results. Is it required that every final report be reviewed by the quality assurance unit?

    Yes. This procedure helps to ensure the accuracy of the final report.

15. Does the quality assurance unit review of each final study report have to be reported to management?

    Yes. The quality assurance unit must make periodic reports to management and the study director on each study. These reports should include the results of the final report review.

16. At our facility the quality assurance unit reports directly to the executive vice president of the company and not to the vice president of research and development. Is it necessary for us to formulate a separate quality assurance unit within the research and development department?

    The GLPs require that the quality assurance unit director and the study director cannot be the same person. The quality assurance unit must report to a level of management that has the authority to effect the corrective action as indicated by the quality assurance unit inspection reports. How this is accomplished organizationally is a management prerogative.

17. Is it acceptable for the quality assurance unit to report to the management person who is also responsible for drug safety evaluation?

    This is acceptable provided that the management person is not the study director for the studies being inspected by the quality assurance unit.

18. Is it permissible to have a pharmacologist in the research division serve as the director of the quality assurance unit?

    The GLPs state that a person may not perform both quality assurance functions and study direction and conduct functions for the same study. Thus, a pharmacologist in a research division could serve as the director of the quality assurance unit as long as he or she did not otherwise participate in the studies under review by the quality assurance unit.

19. How is the requirement for a quality assurance unit to be interpreted when the testing facility is itself a quality assurance unit?

    By definition, a testing facility could not be a quality assurance unit. A quality assurance unit, which conducts nonclinical laboratory studies, should make separate provision for the performance of the GLP quality assurance functions.

20. Is a member of the statistical department of a testing facility entitled to be a member of the quality assurance unit?

    This decision rests with facility management but such a choice is acceptable.

21. Company A is conducting a study. Company B performs animal work for Company A to the extent of implanting test material, recovering test materials and tissues, and returning these to Company A for analysis and conclusions. Which company is designated as the testing facility, which company designates the study director, and which company does the study director work for?

In the cited example, Company A would be the study sponsor while Company B would be a contract laboratory performing a portion of a nonclinical laboratory study. Both companies would be considered testing facilities, but, since the GLPs require a single study director for each study, Company A would designate the study director. Company B would, no doubt, designate a participating scientist in charge of the animal work and would have the responsibility of submitting a participating scientist's report to Company A for inclusion into the final report.

22. Is it acceptable to have two study directors for a single study at the same time?

    No. The regulations require a single point of study control, which has been vested in the study director.

23. Do the GLPs permit the designation of a "deputy" or "acting" study director to be in charge of a nonclinical laboratory study when the study director is out of town, on vacation, etc.?

    Yes.

24. Must the study director personally verify all observations made during a nonclinical laboratory study?

    No. The study director must assure that study procedures are adequate to ensure the collection of valid data.

25. A study is only as good as the people who perform it and most importantly as the person who directs it. What does the Agency do to assess the training and experience of toxicologists?

    The assessment of the training and experience of personnel is a routine part of the GLP Compliance Program. Agency investigators collect summaries of training and experience for individuals participating in the study. These summaries are evaluated by the headquarters scientific review staff.

26. In view of the shortage of board certified pathologists, is it permissible to permit either non-veterinarians or non-board certified veterinary pathologists to conduct necropsies? Is certification required for a pathologist to participate in a nonclinical laboratory study?

    The Agency recognizes the serious shortage of trained and certified pathologists as well as toxicologists. The GLPs require that personnel possess the appropriate combination of education, training and experience needed to do their jobs. Therefore, it is permissible to have non-veterinarians conduct necropsies provided their training and experience are adequate. The GLPs do not require board certification for either pathologists or toxicologists.

27. What does the agency consider to be the minimal acceptable educational requirements for someone appointed as "study director? "

    Due to the wide range of nonclinical laboratory studies and the numerous combinations of education, training and experience, which would be acceptable, the Agency did not specify minimal educational requirements for nonclinical laboratory study participants. The GLPs specify that the study director should have the appropriate mixture of education, training and experience to permit the performance of the assigned functions.

28. Will I, as the director rector of a contract pathology laboratory, be required to have a quality assurance unit and to store slides, blocks, wet tissues, etc. in the archives?

    The GLPs require that the quality assurance functions be performed. In your case, either you or the sponsor must have a quality assurance unit. Again, either you, the sponsor, or a separate commercial facility will have to store slides, blocks, wet tissues, etc., and the archives will have to specify the storage location.

SUBPART C
FACILITIES

58.41 GENERAL
58.43 ANIMAL CARE FACILITIES
58.45. ANIMAL SUPPLY FACILITIES
58.47 FACILITIES FOR HANDLING TEST AND CONTROL ARTICLES
58.49 LABORATORY OPERATION AREAS
58.51 SPECIMEN AND DATA STORAGE FACILITIES
58.53 ADMINISTRATIVE AND PERSONNEL FACILITIES

1. Would there be any criticism of a laboratory where animals of the same species, used concurrently in 6-8 short-term eye or dermal irritation studies, were housed in the same room, assuming there is sufficient spatial separation?

   No. This procedure would be acceptable provided that precautions were taken to prevent animal and experimental mix-ups and cross-contamination.

2. What is the relationship between the FDA and the USDA inspection of animal facilities?

   The USDA inspection is directed towards ensuring the humane care of animals used in research whereas the FDA inspection is directed towards ensuring the quality of data obtained from safety experiments that involve animals.

3. We feel that storage of test article - diet mixtures in animal rooms in well-labeled, vermin proof containers will lead to fewer errors than storage in a central common area. Is this permissible in light of section 58.47(b)?

   Yes. Section 58.47(b) requires separate areas for test article diet mixtures, which need not be a separate common area or a separate room. In the cited example, each animal room could have a separate area devoted to feed storage.

4. Is it necessary to provide space for the isolation of diseased animals if they are immediately removed from the study and sacrificed?

   No. The intent of the regulations is to ensure that diseased animals are handled in a manner that will not adversely impact on the nonclinical laboratory study.

5. Is it acceptable for a nonclinical laboratory to quarantine all newly arrived animals for the required period and then begin the study in the same area?

   Yes.

SUBPART D
EQUIPMENT

58.61 EQUIPMENT DESIGN
58.63 MAINTENANCE AND CALIBRATION OF EQUIPMENT

1. Regarding GLP required standard operating procedures for preventive maintenance, is it expected that detailed instructions be prepared for each piece of laboratory equipment? Can the standard operating procedures refer to an equipment manual for detailed instructions as appropriate?

   Specific standard operating procedures are required for each piece of equipment. These procedures can incorporate verbatim the instructions contained in the equipment manuals.

2. In order to calibrate a scale used to weigh large farm animals is it necessary to use a set of standard weights similar to those used for laboratory animal scales only much, much heavier?

   In this case, calibration and maintenance of a periodic nature can be performed by a manufacturer's representative and the records should reflect these operations. Additionally, calibration can be accomplished through use of secondary standards.

SUBPART E
TESTING FACILITIES OPERATION

58.81 STANDARD OPERATING PROCEDURES
58.83 REAGENTS AND SOLUTIONS
58.90 ANIMAL CARE

1. Is there a published tolerance regarding the amount of copper in water on the basis of species?

   The Agency is not aware of any.

2. With regard to section 58.90(c), does "separate" mean a separate air supply as well as space?

   Yes, insofar as it is required to ensure effective isolation of the disease.

3. There are many common reagents used in safety studies (e.g. glucose, sodium chloride, etc.). Do the GLPs intend that these reagents be labeled with storage conditions and expiration dates?

   Yes. It is of utmost importance that outdated and deteriorated reagents not be used in the study.

4. What are the environmental requirements for large animal (cattle/horses) safety studies?

   Guidance on this matter can be obtained by contacting the appropriate preclearance division within the Bureau of Veterinary Medicine.

5. How long do animal care records (cage cards, vendor information, etc.) need to be retained?

   These records should be retained in the archives for the terms specified in section 58.195.

6. Does approximate age of the test system need to be listed on the cage cards?

   No.

7. Why can't textbooks and manufacturer's literature be used as standard operating procedures?

   Textbooks and manufacturer's literature are not necessarily complete and it is highly unlikely that such materials could be used without modifications to more precisely fit

a laboratory's needs. These materials may be used, however, as supplements to and references for standard operating procedures.

8. In the absence of the "Guide for the Care of Laboratory Animals," what reference will FDA use in inspection of facilities for determining appropriate cage sizes, animal environment, animal facilities, veterinary care, and animal care practices?

   References to the guide and regulations promulgated by other agencies have been deleted from the final order on the GLPs. Nonetheless, these materials do provide guidance on the current state-of-the-art for animal care and they are helpful both to the laboratory and to the Agency in determining the adequacy of animal care practices.

9. Are expiration dates required on purchased chemicals and reagents present in the laboratory?

   Yes, expiration dates are required on such chemicals and reagents when they are used in a nonclinical laboratory study.

10. Are expiration dates required on prepared solutions made from purchased chemicals and reagents?

    Yes.

11. Are stability data required to substantiate the expiration dates of reagents and solutions?

    Not necessarily. It is sufficient to use scientific judgement coupled with literature documentation, manufacturer's literature or laboratory experience.

12. With respect to evaluating the effectiveness of reagents and solutions throughout their shelf life, what requirements are there on the certification of efficacy of the test reagents used to evaluate the effectiveness of the GLP reagents and solutions?

    Standard operating procedures for the analyses should provide such efficacy tests for reagents and solutions as the scientific literature, the manufacturer's literature, and the laboratory experience indicate are necessary.

13. What does the Agency expect in the area of analysis of feed and drinking water for known interfering contaminants?

    The GLPs require analysis for and control of contaminants known to be capable of interfering with the nonclinical laboratory study and which are reasonably expected to be present in the feed and water. Certain contaminants may affect study outcome by masking the effects of the test article, as was the case in recent toxicological studies

of pentachlorophenol and diethylstilbestrol. In these studies the feeds used as carriers of the test article were found to contain varying quantities of pentachlorophenol and estrogenic activity. These contaminants invalidated the studies by producing erratic results. The use of positive and negative controls in these studies was insufficient to compensate for the variability in the concentration of the contaminants.

To implement this provision of the GLPs, the study director and associated scientists should consider each study in the light of its length, the expected toxicological endpoints and pharmacological activity of the test article, the test system, the route of administration, and other relevant factors to determine what contaminants could reasonably be expected to interfere. These considerations coupled with scientific literature, experience and anticipated levels of contamination should be used to determine which contaminants should be controlled and analyzed.

It is unlikely that a blanket analysis conducted either by feed manufacturers or water authorities would be sufficient. These analyses would either provide data on contaminants which would not be expected to interfere or neglect to provide data for certain interfering contaminants.

For acute studies in which the test article dosage is sufficiently high, in most instances, to overcome any effects from feed or water contaminants, the analytical requirement would be minimized.

14. Study directors are frequently unfamiliar with certain aspects of their studies (e.g. chemical analyses, histopathology, etc.). Is it appropriate for the study director to authorize all deviations from standard operating procedures?

    Yes. As the focal point for study direction and conduct, the study director must be made aware of and react positively to any deviation from a standard operating procedure. Where necessary, a study director should consult with other scientists to determine the impact of a deviation on the study.

15. Is it required that the quality assurance unit test the reagents used in a nonclinical laboratory study?

    Whatever testing is required by section 58.83 of the GLPs for reagents and solutions may be accomplished by those organizational units that normally conduct such testing. It need not be done by the quality assurance unit.

16. May reagent grade chemicals be used in a study on the basis of label analysis declaration?

    Yes, provided that the reagent is labeled with an expiration date.

17. If animals do not have some form of unique identification actually attached to the animal, is identification using only cage cards appropriate? If the test system is housed in individual cages, which are uniquely identified, must each and every animal be identified?

    Section 58.90(d) requires that animals which are to be removed from their home cages or which are to be observed over a long period of time have appropriate identification. Therefore, identification using only cage cards is not sufficient in most cases and each animal should be identified.