SUBPART F
TEST AND CONTROL ARTICLES

58.105 TEST AND CONTROL ARTICLE CHARACTERIZATION
58.107 TEST AND CONTROL ARTICLE HANDLING
58.113 MIXTURES OF ARTICLES WITH CARRIERS

1. Are laboratories required to go beyond shelf storage of reserve samples of test article-carrier mixtures to whatever methods (e.g., cryogenic temperatures), regardless of cost that will maximize stability? Does the Agency expect stability studies to determine optimum storage conditions for each sample?

   No, heroic measures need not be taken. Storage conditions should be consistent with the knowledge of the stability of the mixture under conditions of use and reasonable so as not to permit accelerated decomposition.

2. What are the details of the Agency's reserve sample retention policy?

   With regard to reserve sample retention, the GLPs provide as follows:

   Reserve samples are to be retained from each batch of test and control article prepared in accord with section 58.105(a) for all nonclinical laboratory studies lasting more than 4 weeks. For the purposes of these sections, the 4-week period includes initial dosing to the final *in vivo* observations. Only sufficient sample need be retained to permit meaningful reanalysis. The samples need be retained either for the terms specified in section 58.195 or for the useful life of the sample (dependent on the stability or the quality of the sample) whichever is shorter. Storage conditions should be those commonly accepted as minimizing the deterioration of sample quality and need not require exhaustive study to determine those which maximize stability. All batches of test and control article mixtures are to be retained even if they are prepared daily.

3. For medical devices, how can stability be demonstrated any more effectively than by the continued functioning of a device within specifications during an *in vivo* nonclinical study?

   The stated procedure is acceptable.

4. The cost of chemical assay development and assay of dosage forms prior to conducting acute studies far exceeds the cost of doing the experiment. Will data confirming the weighing, mixing and administration of the test article be considered sufficient?

   No. The test article must be sufficiently characterized to ensure that the same article is used in any further studies.

5. Does FDA expect a firm to conduct long-term stability tests on test article-carrier mixtures, which are used within a day of preparation?

The firm must determine the stability of the mixtures over the period of their use. The GLPs require retention of samples of all batches of test article-carrier mixtures for studies that last longer than 4 weeks. The regulations do not require stability studies on such samples. Samples placed in storage may be analyzed periodically to determine their useful storage life.

6. Am I correct in assuming that the chemical testing done by the sponsor to characterize the test article is not covered by the GLPs when the test article is subsequently submitted to a contract laboratory as a blind sample for safety testing?

The GLPs do not cover the basic exploratory chemical tests done to derive the specifications of the test article. They do cover those chemical tests done on discrete batches of test article to determine identity, strength, purity and composition.

7. Does the phrase "mixtures of articles and carriers" also refer to solutions and suspensions, e.g., a solution of a test article in distilled water?

Yes.

8. For acute studies, is it necessary for the laboratory to analyze each batch of test article-carrier mixture prior to dosing the test system?

No. Uniformity of the mixture must be known and periodic batch analyses need to be done.

9. Will dialogues such as this and recent inspectional experience bring about substantive changes in the final regulations through FDA initiated proposed amendments? What changes are anticipated in the reserve sample retention requirements?

The Agency does not believe the initiative to change the GLPs rests with FDA. Petitions for change may be submitted to the Agency in accord with the 21 CFR 10.30. As was mentioned at the meeting, the Agency recognizes that the reserve sample retention requirements are extensive and expensive and a petition for change would be considered.

10. What guidelines can be used by a laboratory or sponsor in deciding how frequently concentration analyses should be made?

The Agency has not established guidelines with regard to the frequency of periodic reanalysis of test article-carrier mixtures. Enough batches should be analyzed to

assure that the test systems are being exposed to the quantities of test article in the specified protocol.

11. How long must one retain samples of feed used in nonclinical laboratory studies and should they be frozen?

    The sample retention period differs for the various regulated products and the periods are listed in section 58.195. Feed samples need not be frozen for storage.

12. What is the definition of carrier?

    Carrier is the material with which the test article is mixed for administration to the test system. It can be feed, water, solvents and excipients depending on dosage form and route of administration.

13. Once stability of a given concentration of a test article-carrier mixture is substantiated, is it necessary to establish a stability profile for each batch at that concentration?

    No. Stability need be determined only on a single batch of test article-carrier mixture; however, periodic reanalysis to determine concentration must be done.

14. In the course of a 14-C tissue residue study in the target animal, is it necessary to retain:

    a. a sample of the 14-C labeled drug,
    b. samples of the diet fed control and experimental animals,
    c. samples of urine and feces after completion of the analyses,
    d. samples of collected tissues after completion of the analyses,
    e. if they must be retained, for how long?
    f. is similar sample retention necessary when doing "cold" tissue residue studies in target animals?

    All samples listed in a - d and f above should be retained for the term listed in section 58.195.

15. If a battery of different tests on a substance is being conducted by different contractors, is it necessary to run replicate stability analyses from each and every contractor especially when long-term stability has been documented for the substance?

    No. Once stability has been determined in accord with good science, it is not necessary to continually replicate the stability determination.

SUBPART G
PROTOCOL FOR AND CONDUCT OF A NONCLINICAL LABORATORY STUDY

58.120 PROTOCOL
58.130 CONDUCT OF A NONCLINICAL LABORATORY STUDY

1. In as much as only wet tissues, blocks and slides are necessary to reconstruct the histopathologic aspects of a study by a third party, are written notes, tapes, etc. of the histopathologist's thought process in arriving at a final report legitimately considered "raw data" in the presence of a signed and dated final report? Does the Agency have the right to inspect the written notes from the pathologist?

   Raw data in this case, refers only to the signed and dated final report of the pathologist. Agency investigators may wish to examine the interim notes and reports in an attempt to reconstruct the study but not to second-guess the scientific process used to arrive at the final report. The GLPs do not require that these interim reports and notes be retained.

2. What is considered to be raw data in computer systems when the data is generated from dictated results?

   Transcribed dictation, which has been proofread and corrected for typographical -and transcription errors, is raw data.

3. Do the GLPs require that the protocol be amended to reflect the actual starting date of the study?

   Yes, this is a critical piece of information, which should be supplied by way of a formal protocol amendment.

4. It is said that raw data may be any verified exact copy of the original data. In a computerized data system where data is put directly on disc thence to tape, what documentation of the program performing this transfer is required to assure that the tape copy is exact?

   The standard operating procedures, which cover computer operations, should describe the computer program and the procedure used to assure the production of an exact tape copy.

5. If reformatting of data is done as part of the transfer described in question 4 above, is the new file not raw data even if all data is transferred intact although in a different organization?

   The Agency can not precisely answer this question without further details of the new data format.

6. Are initials and dates on data printouts (e.g., scintillation counters, gas chromatographs), when these printouts include standards, sufficient documentation for standardization?

   Yes.

7. Is there a time limit for submission of the final report of a nonclinical laboratory study after its conclusion?

   Generally no. On occasion, for marketed products, the Agency may establish time frames for study conduct. Of course alarming findings on marketed products should be reported as soon as possible.

8. Is it permissible to list changes in a final report on a page, which is appended, to the original final report?

   Yes.

9. Does "studies in progress on June 20, 1979" refer to the phase of dosing of the test system or the phase post-dosing but not yet reported?

   The quotation pertains to all studies for which the final report has not yet been completed. Included are all post-dosing phases.

10. The final report requires a list of participants. Should this include technicians as well as people who perform support functions?

    The final report should include the name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel involved in the study.

11. When an analysis protocol is developed for the first time by using standard scientific technique, who shall validate the protocol?

    The Agency does not *per se* validate protocols. Persons developing new protocols may submit them to the responsible bureau for review and comment prior to initiating a nonclinical laboratory study.

12. Why is the signature of the sponsor required on a protocol for routine acute testing when these procedures are published and sufficiently standardized by the industry? Would written standard operating procedures of the testing facility be sufficient to replace the protocol without the sponsor signature?

One of the testing deficiencies found in the early Agency investigations of nonclinical studies was protocol changes that were made without informing the sponsor. The changes prejudiced the validity of the studies. Accordingly, the GLPs require that each study have a specific protocol, which is attested to by the sponsor.

13. The identity of the individual collecting data entered into a computer can be recorded via the use of a code known only to the individual but directly identifying the individual; similarly the identity of the individuals witnessing or reviewing the data can be recorded. Is this acceptable?

    Yes, this procedure is acceptable. The key to the code must be made available to Agency investigators. Do note, however, the final GLPs do not require that data entries need be witnessed by a second person.

14. Does the following proposal on data entry to computer files satisfy the GLP intent?

    Data is entered through keyboard commands and stored in a "temporary" computer file with accompanying date, time, and analyst codes. The analyst may be technician level personnel. At the conclusion of a set of observations, no more than one day's worth, the data in the "temporary file" is reviewed by a scientist (this person may or may not be the same person who entered the original data) and "corrected" for any typing or entry errors. When it is determined that the data are correct, the data are transferred to a "permanent" computer file. Only authorized personnel may make changes to the "permanent" file.

    No audit trail is kept for changes to "temporary" file. All changes to permanent file are recorded in a change file with appropriate data, personnel code, and comments regarding reason for change and original entry.

    No. This method would permit unauthorized tampering with the temporary file before the raw data are transferred to the permanent file.

15. When should a protocol amendment issue? Should it be as soon as possible or could a list of all deviations from a protocol be prepared at the end of the study?

    If the deviation from the protocol is intended to be permanent, the protocol should be amended as soon as possible. If the deviation is an error, it should be promptly corrected and noted in the raw data.

16. Section 58.120 describes a sixteen-part protocol and section 58.185 describes a fourteen part final report. Must all of these be included in protocols and reports for LD 50's and other short-term tests?

    Yes.

17. Is a protocol required for routine research and experimentation?

    Protocols are required for all studies covered by the GLPs.

18. If all raw data are not required in a final report, does this mean, for example, that weekly body weight or food intake averages can be in a report without the individual animal data?

    The data appearing in a final report depends on the type of study and the kind of regulated product. Specific advice can be obtained by contacting the Agency bureau, which has responsibility for the regulated product.

19. If a compound or formula is proprietary, must the final report describe its detailed composition or chemical structure?

    If the proprietary material is a commercially available article to be used as a control, the final report need only describe the trade or chemical name, the source and the manufacturer's batch number.

20. How does the requirement for "approval" of protocols apply to "in house" studies which are' conducted in the laboratories of the actual "sponsor?" Who approves? What is an "approved" protocol?

    The word "approved" was retained in the final order to emphasize that a sponsor should have a mechanism for evaluation and approval of initial protocols and all amendments. The specifics of the mechanism can vary but a formal mechanism should be in place.

21. Must the protocol contain both the name and the code number of the test article?

    No, either designation is acceptable.

22. Section 58.120 states that the protocol shall contain the records to be maintained. Is this intended as a detailed list of each data form to be generated?

    No, in this case generalized statements would be satisfactory.

23. How much raw data must be entered into notebooks when performing well-documented routine tests?

    Basically, the GLPs define raw data as the immediate results of original observations. All such immediate results must be entered.

24. What is meant by the statement in section 58.120(a)(12), which pertains to the method by which the degree of absorption of the test and control articles by the test system will be determined?

    The GLPs do not mandate that absorption studies need be done, or which kind of study is satisfactory. The GLPs do require, however, that the protocol describe the method used if one is necessary to achieve the study objectives.

25. Please clarify the issue of having to provide reasons for all corrections to data entries. It seems unreasonable to require reasons for "obvious" error corrections such as misspell ings, transposed numbers, and wrong year early in a calendar year.

    It must be remembered that "raw data" is basically the results of original observations. Thus, the wrong year is not raw data and can be easily corrected. Misspellings may or may not be raw data whereas in all probability numbers are raw data. The Agency believes that it is sometimes difficult for a second party, such as the personnel in your quality assurance unit, to distinguish "obvious" errors. Consequently, the Agency insists that all corrections to raw data entries be justified.

26. How and to what extent is the selection of the test system to be justified in the protocol?

    Usually, the test system is selected after consideration of the state-of-the-art of toxicology testing in the area of interest. The protocol need not contain extensive justification.

27. Are we expected to label all specimens (e.g. serum, blood, urine, tissue slides) with their exact nature?

    Yes. Such information is useful in preventing mix-ups.

28. Why does "test system, study, nature and date of collection" have to be located on a specimen container? Can such information be coded?

    Specimen refers to any material derived from a test system for examination or analysis. Consequently, blood, tissues, urine, feces, etc. are considered to be specimens whose containers must carry the required label information. Such information will help preclude mix-ups in the subsequent handling of the specimens. Accession numbers or code numbers can be used for samples of specimens, which are subjected to further analysis. For example, in histopathology the excised fixed tissue is a specimen, which must carry all the label information. However, the blocks and slides prepared from that tissue could be identified by accession numbers. Similarly, in tissue residue analysis, the excised tissue is a specimen; whereas, tissue samples, which are homogenized and otherwise prepared for further analysis, are not specimens and need not carry full labeling.

SUBPART J
RECORDS AND REPORTS

58.185 REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS
58.190 STORAGE AND RETRIEVAL OF RECORDS AND DATA
58.195 RETENTION OF RECORDS

1. What types of storage conditions are required for the storage of retained specimens?

   The Agency has not developed guidelines for storage conditions. The Agency does not expect heroic measures to be used, but conditions should be reasonable in light of the nature of the specimen. Storage conditions, which foster accelerated deterioration, should be avoided.

2. In section 58.185, it is stated that test and control article identification and characterization must appear in the final report signed by the study director. However, if the study director is affiliated with a contract laboratory, he/she has no need to know such details of a proprietary test article. Do you agree that such information can be appended to the final report by the sponsor rather than be provided by the study director?

   Yes.

3. Is the storage of archival material (tissues, slides, raw data) the responsibility of the testing laboratory or can this responsibility be assigned to the sponsor of the study?

   The GLPs permit these materials to be stored in the archives of either the testing laboratory or the sponsor. If they are stored in the sponsor's archives, the archives of the testing laboratory must identify the storage location.

4. If a sponsor agrees to characterize and store test articles submitted for study to a contractor, must the contractor also verify the characterization and provide storage for the test articles?

   No, but the contractor must identify the storage location.

5. What is the "completion date" of a nonclinical laboratory study?

   The completion date is the date that the study director signs the final report. Some discretion must be used however, since the protocol calls for a proposed "completion date." In this case, it would be adequate for the protocol to list a completion date for the in vivo phase and qualify it as such.

6. With respect to archival material, what is required to be listed as the date of the study?

   The study date would be the same as the completion date of the study.

7. Do all studies on a test article need to be submitted in support of an application for a research or marketing permit?

   All studies need be submitted, however, not all studies need be conducted in accord with the GLPs. The conforming amendments provide that a statement be included in the submission which identifies which studies have not been conducted in compliance with the GLPs and the extent of the non-compliance.

8. What should be included in the signed and dated reports of the individual scientists participating in the study?

   The final report prepared by the study director should have appended to it all reports written by other participating scientists. These reports should contain sufficient detail to enable the study director to write a final report, which reflects the results of the study.

SUBPART K
DISQUALIFICATION OF TESTING FACILITIES

58.200 PURPOSES
58.202 GROUNDS FOR DISQUALIFICATION
58.204 NOTICE OF AND OPPORTUNITY FOR HEARING ON PROPOSED DISQUALIFICATION
58.206 FINAL ORDER ON DISQUALIFICATION
58.210 ACTIONS UPON DISQUALIFICATION
58.213 PUBLIC DISCLOSURE OF INFORMATION REGARDING DISQUALIFICATION
58.215 ALTERNATIVE OR ADDITIONAL ACTIONS TO DISQUALIFICATION
58.217 SUSPENSION OR TERMINATION OF A TESTING FACILITY BY A SPONSOR
58.219 REINSTATEMENT OF A DISQUALIFIED TESTING FACILITY

ENFORCEMENT STRATEGY

1. What can FDA do to force a laboratory to take corrective actions to achieve compliance with the GLPs? Are warnings given to the laboratory?

   FDA has a number of regulatory sanctions, which can be brought to bear on a violative firm in order to, bring about compliance with the law. These include rejection of studies, withdrawal of approval of marketed products if such products are supported by defective studies, prosecution and, after June 20, 1979, disqualification of the laboratory. FDA's present GLP enforcement policy is to provide adequate warning and to afford a reasonable opportunity to take corrective action.

   Disqualifying a laboratory on the basis of failing to comply with one or more provisions of the GLPs raises the question of whether all violations are considered-equally, are weighted, or are evaluated scientifically to consider the impact on the outcome of the study.

   A laboratory will not be considered for disqualification unless all of the following criteria are met:

   a. failure to comply with one or more provisions of the GLPs;
   b. the noncompliance adversely affected the validity of the studies;
   c. other lesser regulatory actions (warnings, rejection of individual studies) have not or will not be adequate to achieve compliance with the GLPs.

   The violations of the various provisions of the GLPs are evaluated to assess their impact on the validity of the studies. It is impossible to assign weights to the various

provisions of the GLPs. Noncompliance with the various provisions must be evaluated in the context of the entire laboratory operation and the kinds of studies being performed. Thus, a violation of a specific provision may be critical for one laboratory doing long-term studies and not for another laboratory engaged in short term studies.

3. If a laboratory is disqualified, how long does the disqualification last? Under what conditions does reinstatement occur?

   The disqualification will last until the laboratory submits in writing to the Commissioner, reasons for reinstatement including a detailed description of the corrective actions it has taken to assure that the violations which led to disqualification will not recur. Reinstatement will depend upon one or more inspections which show that the laboratory is in compliance with GLPs.

4. Paragraph 231 of the preamble to the GLPs states: "The order of disqualification creates a rebuttable presumption that all studies previously conducted by the facility are unacceptable. Paragraph 226 states: "Studies conducted at facilities that are in substantial compliance will be presumed to be valid." Can we presume that studies conducted during a period when a lab is found to be substantially in compliance will be accepted by FDA as valid even if the laboratory is disqualified at a later date?

   Yes, unless FDA develops information to the contrary.

5. If a contract laboratory is disqualified because of a study performed for one sponsor, what effect does this have on other studies performed for other sponsors? What about studies underway at the time of disqualification?

   FDA will not disqualify a laboratory on the basis of one invalid study. Disqualification is viewed as a most serious regulatory sanction by FDA and will only be imposed when the facts demonstrate that the laboratory is incapable of producing valid scientific data and will not take adequate corrective measures. In the event a laboratory is disqualified, all studies performed by the laboratory, including those in progress are presumed to be unacceptable unless the sponsors of those studies can establish, to the satisfaction of FDA, that the studies were not affected by the circumstances that led to the disqualification.

6. What steps must be taken by FDA prior to removal of a product from the market because of a rejected study which was pivotal to the assessment of safety?

   If rejection of a study results in insufficient scientific data being available to support a decision on safety for a marketed product, FDA will initiate formal proceedings to withdraw the marketing approval of that product. These proceedings, for drugs, begin with a notice published in the FEDERAL REGISTER of FDA's proposal to withdraw approval setting forth the basis for the proposed action and affording

affected parties an opportunity for a public hearing on the matter. If a hearing is requested, affected parties will have the opportunity to present additional facts at the hearing for the Agency to consider The Commissioner's decision to withdraw or to continue the approval is based on the facts brought out at the hearing.