STANDARD OPERATING PROCEDURE		
SOP NO.: GLP-C-02		Page No.: 1 of 25
Title: **AUDITS FOR DETERMINING COMPLIANCE OF STUDIES WITH GLP STANDARDS REQUIREMENTS**		
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1. PURPOSE

To provide guidance and a standard procedure for audits to determine the compliance status of non-health effects studies (primarily, but not limited to, chemical and environmental fate, and field studies) with respect to the Good Laboratory Practice (GLP) Standards regulations [FIFRA: 40 CFR Part 160; TSCA: 40 CFR Part 792].

2. SCOPE

Unless specifically requested otherwise, all TSCA studies and all FIFRA non-health effects studies conducted after October 16, 1989, for which audits are requested, shall also be reviewed for compliance with the GLP Standards regulations following the procedures outlined in this SOP FIFRA health effects studies are addressed in separate SOPs: DA-01, DA-02, and DA-03. The types of studies covered by this SOP are listed in Attachment 1.

3. OUTLINE OF PROCEDURES

The facility will be reviewed for compliance with the following GLP elements [40 CFR, Part 160 or 792], as appropriate:

Subpart B: Personnel
Management
Study Director
Quality Assurance Unit

Subpart C: Facilities

Subpart D: Equipment

Subpart E: Standard Operating Procedures
Test System Care

Subpart F: Test, Control, and Reference Substance characterization.
Test, Control, and Reference Substance Handling Mixtures of Substances with carriers.

Subpart G: Protocol Conduct of Study

Subpart J: Study Report Storage and Retrieval of Records and Data Retention of Records

4. REFERENCES

4.1 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Good Laboratory Practice Standards, 54 FR 34052, August 17, 1989 [40 CFR Part 160]

4.2 Toxic Substances Control Act (TSCA) Good Laboratory Practice Standards, 54 FR 34034, August 17. 1989 [40 CFR Part 792]

4.3 Good Laboratory Practice Standards Inspection Manual, EPA 723-B-93-001, September 1993 and EPA 723-K-96-001, May 1996

5. SPECIFIC PROCEDURES

An integral part of a study audit should include verification that the study was conducted in compliance with the appropriate and applicable FIFRA or TSCA Good Laboratory Practice Standards regulations. It is the responsibility of the inspector to ensure that this determination of compliance is made. He/she may delegate all or part of the GLP compliance determination to the study auditor(s) and/or may conduct all or part of the study compliance inspection personally. The auditor(s) should be informed of their specific responsibilities for the study GLP compliance determination prior to entry into the facility, preferably at a pre-inspection meeting.

The following outline should be used to ensure that all applicable portions of a study are reviewed for GLP Standards compliance. This is intended to provide guidance and cannot anticipate every potential problem area. The professional experience and knowledge of the inspector/auditor should serve as a primary resource in conducting an adequate compliance review.

5.1 ORGANIZATION AND PERSONNEL

5.1.1 Personnel [Sections 160.29/792.29]

During the audit of a study, it is necessary to verify that all personnel involved in the conduct of the study had the education, training, and experience to adequately perform their assigned functions, and that there were sufficient numbers of personnel for the timely and proper conduct of the study.

The evaluation of the qualifications of study personnel can be accomplished largely by interviewing study personnel in conjunction with the audit of data for the study. If the auditor feels that it is necessary, particularly if study personnel are not available for interview. He/she should also review curricula vitae (CVs), resumes, training records, or other documentation of education. background, and/or training.

Verification should be made by reviewing the responses to the following inquiries:

- Who were the personnel responsible for the conduct of the study?
- What was each person's responsibility?
- Are CVs and up-to-date training records available for ail study personnel, even those no longer employed by the facility?
- Are CVs and training records available for temporary personnel, field personnel, pesticide applicators. cooperators, and any other personnel employed on a contractual or irregular basis who were involved with the study?
- Does a review of some or all of the CVs and training records indicate that personnel were competent to perform their assigned functions?
- Were various aspects of the study (i.e., sample collection sample preparation, sample analysis, and other activities performed in a timely manner? Were there unexplained delays indicating insufficient numbers of personnel?
- Does the master schedule for the time period of the study indicate that the number of ongoing studies was appropriate to the total number of personnel at the facility at that time?
- If appropriate, were personnel properly trained in personal sanitation and health precautions, and use of protective clothing appropriate to the type of study conducted?
- If appropriate, was there a procedure in effect at the time of the study for reporting any health or medical conditions which might adversely affect the study?

5.1.2 Management [Sections 160.3/792.3]

The auditor or inspector should verify that facility: management fulfilled its responsibilities, as defined by the GLP Standards, including: designating a study director and replacing the study director, if necessary; assuring that there was a quality assurance unit; assuring that test, control, and reference substances were appropriately tested for identity, strength, purity, stability, and/or uniformity; assuring that personnel, resources, facilities, equipment, materials, and methodologies were available; assuring that personnel understood their functions; and assuring that deviations from the GLP Standards reported by the quality assurance and were communicated to the study director and corrective action were taken and documented.

Study management need not be physically present at the facility. It can consist of a combination of sponsor and/or facility personnel, as long as it meets the GLP Standards requirements for study management outlined above.

Deficiencies in facility management will often be evidenced by deficiencies in other areas of GLP Standards compliance which may be determined by considering the following aspects of the study:

- Was a single study director designated to oversee the study?
- Was the study director replaced during the study and, if, was this done promptly? Who designated the new stud; director?
- Was a quality assurance unit in place at the time of the study?
- Were test, control, and reference substances documented as described by the GLP Standards?
- Did personnel, resources, facilities, equipment, etc. appear to be adequate for the proper conduct of the study?
- Were deviations in procedures properly documented and communicated to the study director?

5.1 3 Study Director [Sections 160.33/729.33]

The auditor/inspector should verify that a study director was designated for the study and that he/she adequately fulfilled the GLP Standards requirements, taking into consideration the following points:

- Was a single study director designated to oversee the study?
- Were the qualifications of the study director appropriate to enable him/her to maintain overall responsibility for the technical conduct of the study? Was he/she a sponsor representative or a facility representative? What, specifically were his/her responsibilities? Did he/she visit the laboratory of field sites prior to or during the conduct of the study?
- Did the study director approve (i.e., sign and date) the study protocol? The final report?
- Did the study director approve (i.e., sign and date) all deviations from the study protocol, and/or take appropriate corrective actions when necessary to assure the quality and integrity of the study? How was this documented? Did the study director approve all SOP deviations?
- Were all required data and records adequately archived at the close of the study? Were they promptly archived?

5.1.4 Quality Assurance Unit [Sections 160.35/792.35]

The testing facility is required to have a quality assurance unit (QAU) which is responsible for monitoring the study to assure management that the facilities, equipment, personnel methods, practices, records. and controls are in conformance with the GLP regulations. The QAU must be entirely separate from and independent of management and of the personnel engaged in conducting the study. The QAU must conduct inspections and maintain records appropriate to the study.

The inspector/auditor should verify that the QAU fulfilled its responsibilities with regard to the study being audited, but must not examine QAU records of QAU inspection findings and problems, or actions recommended and taken. The following areas, however, should be taken into consideration:

- Was a QAU, as defined by the GLP Standards, in existence at the time the study was conducted?

- Were periodic QA inspections conducted for the study? What phases were inspected? Were the number of inspections and choices of phases appropriate, and were they adequate to ensure the integrity of the study?

- Were any problems or deviations from the study protocol or standard operating procedures found by the QAU? If so, how were these brought to the attention of the study director and management? Were the study director and management notified in a timely manner, in the opinion of the inspector/auditor?

- Were written reports of study phase inspections submitted to the study director and management?

- Did the QAU review the final report? How was this documented?

- Did the final report include a signed and dated quality assurance statement? Did this statement specify the dates that phase inspections were made and the dates that findings were reported to management and the study director?

5.2 FACILITIES

The GLP Standards regulations require that facilities be adequate for the proper conduct of the study. The main concerns, from the standpoint of the study being audited, are that the location, size, construction, and design are such that there is no adverse effect on the study. This includes separation, isolation, and quarantine of the test systems as appropriate for the type of studies conducted at the facility. This also includes adequate storage areas, and areas for culturing, holding, or maintaining stocks of plants or animals used in the study. The facility must also have adequate areas for receiving and storing test, control, and reference substances, and for preparing and storing test, control, and reference substance mixtures. Separate laboratory space must be available as needed, and space must be provided for archives and for storage and retrieval of raw data and specimens generated during the study.

The inspector/auditor should verify that the GLP Standards requirements for facilities were adequately met for the study being audited. If possible and appropriate, particularly for recent studies, the inspector/auditor should visit the facility areas which were used during the conduct of the audited study, and should make a direct assessment of the adequacy of the facilities. If this is not possible, the personnel who conducted the study should be interviewed to assess

the adequacy of the facilities. Photographs blueprints, diagrams, and other documentation retained with study records may also be used for this assessment. To aid in this evaluation, the following aspects should be considered, as appropriate and applicable:

- Were buildings of appropriate size, design, and construction?
- Were field sites (outdoor) of appropriate size and location and if applicable, of appropriate design and construction for the conduct of this study?
- Did the design of the facilities allow for separation of test systems, as appropriate? Did the design of the facilities allow for adequate isolation of individual projects?
- Were there areas for quarantine or isolation of animals? Was animal housing adequate for the conduct of the study?
- Were aquatic toxicology facilities adequate to separate projects and organisms, and to prevent cross-contamination with chemicals used in other studies?
- What did the protocol specify for environmental conditions to be used in the study? Was there appropriate and adequate regulation of environmental conditions (temperature, humidity, photoperiod), as specified in the protocol? What records were available to document the adequacy of this control?
- What was the source of water used in the study? Were water supplies appropriate and adequate? How were water conditions monitored? How was water quality assured? How was water stored? Did the water quality and composition meet the specifications of the study protocol?
- What was the source of soil used in the study? How was soil obtained and stored? How and by whom was soil composition determined? Were the source and composition of soil the same as specified in the protocol?
- Were there adequate areas for storage of feed, nutrients, soil. bedding, supplies, and equipment? Were these separated from areas where the test system was located?
- Were facilities for holding, culturing, and maintaining algae and/or aquatic plants appropriate and adequate? Were facilities for aquatic animals appropriate, and did they meet the conditions, as specified in the protocol?

- Where and how were test, control, and reference substances received and stored? Were storage conditions adequate to prevent contamination? Were environmental conditions for storage areas monitored? Was security for storage areas adequate? Were storage areas kept locked? Who had responsibility for storage areas? Who had access to storage areas?

- Were facilities for mixing test, control, and reference substances with carrier adequate? What precautions were taken to ensure that cross-contamination from mixing equipment did not occur?

- Where were mixtures stored? Were storage conditions. especially temperature, monitored? What records were retained to confirm that storage conditions were adequate and met the requirements of the study protocol?

- Were laboratory areas available, as needed? Did laboratories appear to be adequate? Was there sufficient space for sample preparation? Were instruments maintained separate from wet chemistry areas?

- Were raw data and specimens readily available for audit? Were they stored in such a manner as to be in good condition? Where were the study data and specimens archived? If the data audit was performed using copies of raw data, where were the originals archived?

5.3 EQUIPMENT

The GLP Standards regulations require that any equipment used in the generation, measurement, or assessment of data, and equipment used for facility environmental control be of appropriate design and adequate capacity to function according to the protocol. Equipment used for the generation, measurement or assessment of data must be adequately tested, calibrated, and or standardized.

It is necessary for the inspector/auditor to verify that the equipment used for the audited study met the above requirements The reliability of equipment used to generate, measure, or assess quantitative data is critical to the integrity of the study raw data and any audit of raw data must include a review of facility procedures in effect at the time of the study for instrument maintenance and calibration. This includes all equipment used to apply the test substance to the test system, as well as laboratory analytical equipment. The auditor's review of equipment should include calibration of any of the following which are applicable. balances and volumetric devices used to prepare mixtures of e control, or reference substance with carrier; agriculture equipment

including sprayers, granular applicators, and aerial applicators; metering devices used in aquatic toxicity testing; analytical balances used in the laboratory; thermometers, hygrometers, pH meters, and other meters and gauges used to monitor environmental conditions and storage conditions which are specified in the study protocol; analytical instruments used to produce quantitative information; and any other measuring or analytical equipment.

The following areas should be addressed by the auditor/ inspector:

- What specific-equipment and instruments were used in the study to generate, measure, or assess data?
- Did the raw data include data for the calibration of all equipment and instruments used in the study?
- Did it appear that the calibration methods were adequate and appropriate? Were SOPs in effect at the time of the study which addressed instrument use, maintenance, and calibration?
- Did the equipment and instruments appear to have been properly maintained, tested, and/or standardized?

5.4 TESTING FACILITIES OPERATION

5.4.1 Standard Operating Procedures [Sections 160.81/792.81]

The GLP Standard regulations require that the testing facility have written standard operating procedures, that all deviations in the study from the SOPs shall be authorized by the study director and documented in the raw data, and that significant changes in established SOPs shall be authorized in writing by management.

It is not necessary for the auditor to review all SOPs in effect at the time of the study. However, he/she should verify that written SOPs existed, should review one or two of the key SOPs and should be alert to any deviations from SOPs and ascertain that these changes were properly authorized, as described above. Review of raw data and notebooks, and interviews with study personnel may be used to assess compliance with this requirement.

The following specific areas should be addressed by the auditor:

- Were the SOPs that were in use at the time of the study available to the auditor if requested?
- If SOPs were reviewed by the inspector/auditor, were they of adequate scope and detail?

- Do the study records and data document any deviations from standard operating procedures? Were these deviations communicated promptly to the study director and management?

- Were significant changes in standard operating procedure made and, if so, were they authorized in writing by management?

- Did deviations from standard operating procedures occur which were not properly authorized?

- Were any deviations from standard operating procedures serious enough to affect the outcome of the study? Could study personnel provide an adequate rationale, or defend the scientific basis for any deviations from standard operating procedures?

5.4.2 Test System Care [Sections 160.90/792.90]

As defined by the revised GLP Standards regulations, the test system can be individual animals, groups of plants, animals or microorganisms of one or more species; fields, ponds, orchards, soil, water, or components thereof. The test system is the matrix to which the test control, or reference substance is administered for the study. The test system can also include untreated groups or components of the system.

The regulations define certain requirements for care of the test system to ensure that there is adequate care, a suitable health status, individual identification of animals where appropriate, appropriate separation from other test systems, and assurance that the study results not be affected by contaminants in feed. soil, water, or bedding.

Where appropriate, compliance should be determined by interviewing study personnel and visiting facility areas where the test system was housed and cared for. The auditor should verify that the GLP requirements were met, particularly by reviewing all of the following which are applicable:

- Did study personnel follow applicable SOPs for the housing. feeding, handling, and care of the test system? Were deviations from the SOPs properly authorized?

- Was the test system which was used in the study received from an outside source? What was the source of the test system? Was the test system adequately isolated upon receipt? How was the health status or other pertinent

qualities of the test system determined? Were all data and records on the origin, health and/or quality of the test system retained in study files?

- How long was the test system acclimatized prior to use in the study? Was the acclimatization period adequate?

- Did the study file contain documentation that the test system was free of disease at the initiation of the study? How often was the test system observed to determine the health and condition of the individuals? How were the records of these observations maintained? Who was responsible for monitoring the health of the test system) Did this individual have adequate experience and training to evaluate the health of the test system? What provisions were made for weekends or other periods when the primary monitor was not available? Was the method and frequency of monitoring considered by the auditor to be adequate?

- Did any disease occur during the conduct of the study? Was the disease detected in a timely manner? How was the disease diagnosed and treated? What drugs, pesticides, or chemicals were used to treat the disease? Were the diseased individuals isolated? Were documents retained to show diagnosis, authorization of treatment, description of treatment, and date of treatment?

- How was the test system housed or contained during the study? Was the housing adequate to separate species and studies? Were fields, ponds, or other sites adequately separated from each other? How did study personnel document that separation was adequate?

- Was the housing adequately cleaned and sanitized at appropriate intervals?

- If individual identification was necessary, how were individual test systems identified? Was the method of identification adequate to prevent mix up of individuals?

- Was there any documentation of feed, soil, or water contaminants which were known to be capable of interfering with the study? If so, were feed, soil, and/or water analyzed periodically for these contaminants? Were the analytical raw data maintained?

- Did the study data document the application of any pest control materials? What pest control materials were used.

and at what intervals In agricultural situations, did the study data document usual horticultural procedures such as application of fertilizer, irrigation, and tillage? Were these issues addressed in the protocol?

5.5 TEST, CONTROL, AND REFERENCE SUBSTANCES

5.5.1 Test Control, and Reference Substance Characterization [Sections 160.105/792.105]

The regulations require that the test, control, and reference substances be analyzed for identity, strength, purity, and composition, as appropriate for the type of study. Where applicable, the solubility and stability of these substances must also be determined, as well as stability under storage conditions at the test site. There are also requirements for retention of reserve samples from each batch of test, control. and reference substances, which are defined in Section 160.195.

The auditor must determine that the requirements of this section were met for the test substance and any control or reference substances used in the study. Often the auditor will find that the analysis, characterization, solubility, and stability determinations were not performed at the facility being inspected. In this case, the auditor must determine where the analyses were conducted and where the raw data are archived. The auditor may find that it is appropriate to request the sponsor to provide these data if they are not available at the testing facility.

The auditor must also determine the experimental duration (time between experimental start date and experimental completion date, as defined by the protocol or other study documentation). If this is greater than 4 weeks, then the auditor should verify that reserve samples from each batch of test, control, and reference substance have been retained for the required time period.

As a guide to determining compliance with this section of the regulation the auditor should address the following issues:

- What analyses were performed on the test, control, and reference substances? Who conducted them? Where are the data stored?
- Were the results of these analyses made available to study personnel? Were the results accurately reflected in the study report?
- Were all appropriate analyses performed?

- Where the test or control substance was applied to the test system as a solution, was the solubility of the substance in the carrier determined prior to the experimental start date? Was the substance adequately soluble over the full range of concentrations and under environmental conditions specified in the protocol and/or study report?

- Was the stability of the test, control, and reference substances determined? Who performed the analyses and where are the data archived? Was the stability determined prior to the experimental start date, or concomitantly? Did the protocol specify the procedure to be used for determining stability?

- Was the stability of the test, control, and reference substances under storage conditions at the test site known? Did the protocol specify storage conditions, especially upper and lower limits for temperature and humidity?

- Was the study duration more than 4 weeks? If so, were reserve samples from each batch of substance retained. Who was responsible for retaining the reserve samples) Where are they archived?

- If reserve samples were originally retained, but have since been discarded, was disposal made for one of the following acceptable reasons:

  - The substance was relatively fragile, and was discarded after it had degraded and no longer afforded evaluation

  - The pesticide was not registered and at least 5 years have passed since the date the study was submitted to the Agency.

5.5.2 Test, Control, and Reference Substance Handling [Sections 160.107/792.107]

GLP regulations require that procedures be established to ensure proper storage, distribution, and identification of substances. They also require that receipt and distribution of each batch is documented, including date and quantity of each batch distributed or returned.

The inspector/auditor should ensure that these requirements are met, by interviewing responsible personnel and/or examining SOPs and substance control logbooks. The following questions can be used as a guide in making the determination of compliance:

- How were the above referenced substances stored? Were storage procedures such as to minimize the potential for contamination or degradation of the substances? In field situations, were substances adequately protected fro m environmental factors such as heat, cold, rain, and dust? In field situations, were substances stored so as to prevent contamination from other agricultural chemicals and fuel oils? Were these storage procedures described by SOPs? How did the QAU and study personnel assure that storage conditions were adequate, especially in field situations?

- How were the substances transported to the testing site? What kind of containers were they shipped in (i.e., paper bags, metal drums or cans, glass bottles)? If they were received in bulk. were they repackaged? What precautions were taken to preclude contamination, deterioration, or damage during repackaging? Were the original containers retained until the study was completed? Could the facility document the disposal of empty containers?

- Could the auditor trace the accountability for test, control, and reference substances through documentation that was retained in study records showing receipt, distribution, and disposal?

- What records were available to show receipt of the test, control, and reference substances? Who received them, and when? How much was received? Where were they stored? What was the condition and physical description of the materials when received?

- Was there documentation in a logbook or other records to show distribution of the substances for use in the study being audited? Who obtained the substances? How much was distributed, and on how many occasions? What were the dates? Were the substances used in other studies? Was any of the material transferred to a laboratory or the sponsor for analysis? How much remained at the end of the study?

- What happened to any excess material? Was any of it still retained at the facility? If so, did it match the original physical description of the substance given in the protocol, report, and/or accountability logs? Was it properly labeled and identified with name, chemical abstracts service (CAS) number or code number, batch number, expiration date. If any, and storage conditions?

5.5.3 Mixtures of Substances with Carriers
[Sections 160.113/792.113]

When the test, control, or reference substance is mixed with a carrier prior to being applied to the test system, the mixture must be analyzed to demonstrate the uniformity and actual concentration of substance in the mixture. This analysis must be done in a timely manner, ideally before the mixture is used in the study. If the analysis was not conducted until after the mixture was administered to the test system, the inspector/auditor must exercise professional judgment in determining if the delay was reasonable, appropriate, and scientifically defensible. Additional stability data may be needed to defend long analytical turnaround times.

If the test, control, or reference substance is used as a solution, the solubility of the substance must be determined before the experimental start date. The actual concentration of the test, control, or reference substance in the solution must also be determined analytically, as described above.

The analysis of agricultural tank mixes (or "use dilutions presents special analytical problems and is discussed in a separate SOP (SOP No. GLP-DA-02).

The stability of the test, control, or reference substance in the mixture must also be determined. This can be performed either prior to the experimental start date, or concomitantly according to the protocol or SOPs.

The regulations require that any vehicle used to facilitate mixing of a test substance with a carrier must not interfere with the integrity of the test. Vehicles are considered to include any solvent used to initially dissolve the test substance, as well as oils, emulsifiers, stickers and spreaders, etc.

During the audit of the study, the inspector/auditor must verify that any mixtures or solutions of test, control, or reference substance with carrier were adequately analyzed for uniformity. stability, and concentration, both for reasons of scientific soundness and to comply with the GLP Standards regulations. The raw data and records generated during these analyses should be audited as part of the overall data audit. Study personnel should also be interviewed, as required, and the protocol and/or SOPs reviewed to ensure that the analyses were conducted, as specified by those documents. The following questions are provided as guidance in conducting this portion of the audit:

- What mixtures or solutions were prepared for administration of test, control, or reference substances?

- What did the study protocol or SOPs specify by way of analyses of these mixtures?

- Were analyses conducted to determine the uniformity of the mixture? Where more than one batch of mixture was prepared during the study, was an analysis for uniformity conducted prior to the use of the first batch of mixture? Was an analysis conducted on all batches, or with representative batches? Did the protocol address this? Did there to be any problems with uniformity of mixtures which might compromise the validity of study results?

- Were analyses conducted to determine the actual concentration of test, control, or reference substance in the carrier (either mixture or solution)? Were analyses conducted for each batch? Where the test substance was metered continuously into water, as in aquatic toxicity testing, how was the concentration in the water determined? How often were water samples analyzed? Was the analytical intern al adequate? How much variation in measured concentration was observed between batches? In the professional judgment of the inspector and or auditor auditor, was the variation reasonable?

- When relevant, was the solubility of the test, control, or reference substance in the carrier determined? Was the solubility adequately determined over the range of concentrations used in the study? Did solubility testing take into consideration variations in water temperature, pH hardness; or other conditions which might affect solubility. Was water which was used as a carrier in the study monitored to ensure that the water parameters were within the range used in the solubility testing?

- Was the stability of the test, control, or standard substance In the carrier determined? Was the timing of the stability testing adequate to call attention to any stability problems before there could be adverse effect on the study? How often were analyses conducted on samples being stored for stability determinations? Did the analytical results reflect adequate stability of mixtures for the duration of their use in the study?

- Where it was demonstrated that the test, control, or reference substance had limited stability in a mixture or solution, what precautions were taken to determine expiration dates and to discard outdated portions of the mixture or solution? Were the expiration dates defined in the study protocol, or in other study documentation? Were records kept to show that the unused

mixtures were discarded, as required? Who had the responsibility for discarding outdated mixtures?

- What vehicles, if any, were used to facilitate mixing of the test substance with carrier? What was the source, lot number, expiration date, etc. of each vehicle? How did study personnel assure that the vehicle did not interfere with the integrity of the test?

- Was appropriate analytical methodology and instrumentation used in conducting the above analyses? Were all analytical raw data and records available for audit? Did the analyses conform with requirements of SOPs and/or the study protocol?

5.6 PROTOCOL AND CONDUCT OF THE STUDY

5.6.1 Protocol [Sections 160.120/792.120]

All regulatory studies are now required to have an approved written protocol which clearly indicates the objectives and methods for the conduct of the study. There are minimum elements which must be included in all study protocols where applicable. The inspector/auditor should review the study protocol as part of the data audit and should ensure that it contains all required elements. The specific protocol elements are listed on Attachment 2, which may be copied and used by the inspector auditor as a check list for verifying that the study protocol complies with the GLP Standards requirements.

Any changes in or revisions of an approved protocol and the reasons for the changes must be documented, signed by the study director, dated, and maintained with the original and all copies of the protocol. The auditor should review any protocol amendments which are present with the original study protocol to ensure that they were properly executed, as required by the GLP Standards

When auditing the study data and records, the auditor should also be alert to any changes which may have been made which did not result in a proper protocol amendment.

Normally, the inspector/auditor may verify compliance with the regulations by answering the following questions:

- Did the study have an approved written protocol containing all the pertinent required elements? Was the protocol signed and dated by the study director and dated by the sponsor?

- Were all changes in and revisions to the protocol identified in properly executed protocol amendments?

- Were protocol amendments prepared and approved by the study director in a timely manner?

With field studies especially, the protocol issue may be considerably more complicated. If the study was conducted at multiple sites, and particularly if these sites were subcontracted by the sponsor, the study protocol may have been written as two or more quasi independent segments. These may have been identified using terms such as "field protocol" or "analytical protocol," and study personnel at the site may think of-them as separate protocols. In addition, each segment may have been written by personnel at the applicable subcontractor sites. If the inspector/auditor is auditing a portion of a multi-site study at one of the sites, the entire protocol may not be available for review, and study personnel at the site may have had access only to the portion of the protocol covering the study functions conducted at their site In such a case, the inspector/auditor may need to contact the sponsor to obtain a copy of the complete protocol.

This situation raises the potential for a number of deficiencies in the protocol and deviations from GLP Standard protocol requirements. The inspector/auditor should ascertain the following:

- Did the study director coordinate the writing of the protocol so that a single, coherent document was produced which complied with the spirit as well as the letter of the regulations? Did both the sponsor and the study director approve (i.e., sign and date) a single, complete protocol? Where was the original. complete, approved protocol kept?

- Did the complete document meet all the GLP Standard protocol requirements? Did the protocol contain a description of the design of the entire study from start to completion, and describe the responsibilities of each study site? Did the protocol properly identify the proposed experimental start and termination dates, or were these identified as experimental start and termination dates for the portions conducted at each site? Was analytical methodology included as part of the protocol?

- Were all approved (i.e., signed and dated by the study director) protocol amendments maintained with the original protocol?

5.6.2 Conduct of the Study [Sections 160.130/792.130]

The regulations specify that the study shall be conducted as described by the protocol and the test systems shall be monitored in conformity with the protocol. They also describe how data. except those that are generated by automated systems, shall be recorded, and sets

minimum requirements for automated data entries. For a detailed procedure to be used for auditing computer generated data, refer to SOP No. GLP-DA-03.

The inspector/auditor is responsible for verifying that the study was conducted, in a manner that complies with the GLP Standards regulations. Although some of these issues should already have been addressed during the review of other areas of GLP Standards compliance, the auditor should ensure that he/she has answered the following questions:

- Was the conduct of the study in accordance with the protocol and its approved amendments?

- Was the test system monitored, as described in the protocol?

Additionally, the auditor should verify that data generation conformed with the GLP Standards. In particular:

- Were data recorded promptly, and directly onto appropriate forms or into study notebooks, and were all data recorded in indelible ink? Were data entries legible?

- Were data entries dated and signed or initialed by the person entering the data? Were all data notebook pages, data forms. or individual entries (as appropriate) adequately identified by study title or number, test substance, specimen type, treatment level, field site, and/or any other information necessary to uniquely identify the data?

- How were data corrections and changes made? Were the original entries still legible? Were reasons for changes indicated? Were changes dated and signed at the time of entry?

- If data corrections and changes were made incorrectly (whiteouts, original entry otherwise illegible, changes not initialed or dated), how common were incorrect changes? Were there relatively few instances or did they appear throughout the data? Was more than one person responsible for incorrect data changes? Did the QAU address this matter during its internal inspections?

- Were instrument printouts (chromatogram, spectra, tables of data points from liquid scintillation counters, autoradiogram. thin-layer scanners, etc.) identified with project number, study name, sample number, treatment level, identification off instrument, date, instrument operator, and any other information necessary to uniquely identify the analytical data?

5.7 RECORDS AND REPORTS

5.7.1 Reporting of Study Results [Sections 160.185/792.185]

The regulations consider a study to be complete once the study report is signed and dated by the study director. The regulations specify that the study report must contain certain information; these specific study report elements are listed in Attachment 3. which may be copied and used as a checklist for verifying compliance of the study final report with this requirement. The regulations also describe the procedure by which the final report may be amended (i.e., the study director must make the amendment, and must identify the part of the report being added to or corrected and the reasons for the additions or corrections). The amendment must also be signed and dated by the person responsible for the additions or corrections. The regulations also require that a copy of the final report with amendments must be maintained by both the sponsor and the test facility.

The auditor should verify that the final report contains all the required elements, that it was signed and dated by the study director, and that any amendments meet the requirements of the GLP Standards.

5.7.2 Storage and Retrieval of Records and Data [Sections 160.190/792.190]

All raw data, documentation, records, protocols, specimens, and final reports generated as a result of the study must be retained. as well as correspondence and other documents relating to interpretation and evaluation of the data.

Since all this information is required in order to conduct a data audit and review of the study for GLP Standards compliance, the auditor can generally answer the following questions during the course of the audit:

- Were raw data, records, etc. readily available when needed? Were any of these documents archived other than at the audited facility? If so, were copies made available for the audit? If the audit was conducted using copies of documents, where were the originals archived?

NOTE: Both the FIFRA and TSCA GLP Standards permit the retention of records as either original records or as true copies. However, under 40 CFR, Part 169, FIFRA Books and Records, specifically, Section 169.2(k), original records containing research data relating to registered pesticides, including all underlying raw data, must be retained as long as the registration is valid and the producer is in business.

- Were the data in good condition and legible? Were archives set up such that the data retrieval was expedient?

/s/_____ 06/01/99
Reviewed by: Robert Cypher Date
Compliance Officer/Toxicologist

/S/_____ 06/01/99
Approved by: Francisca E. Liem Date
Chief, Laboratory Data Integrity Branch

/s/_____ 06/09/99
Approved by: Rick Colbert Date
Director, AgED
U.S. Environmental Protection Agency
Office of Enforcement and Compliance Assurance
Office of Compliance

ATTACHMENT 1

Office of Prevention, Pesticides and Toxic Substances
Harmonized Test Guidelines

Series	Guidelines Title
835	Fate, Transport and Transformation
840	Spray Drift
850	Ecological Effects
860	Residue Chemistry
875	Occupational and Residential Exposure Applicator
885	Microbial Pesticides

ATTACHMENT 2

Required Protocol Elements

1. A descriptive title.

2. A statement of the purpose of the study.

3. The identity of the test, control, and reference substances by name. CAS number, or code number.

4. The name and address of the sponsor.

5. The name and address of the testing facility or facilities at which the study is to be conducted.

6. The proposed experimental start date (the first date the test substance is applied to the test system) and termination date (the last date on which data are collected directly from the study).

7. Justification for selection of the test system.

8. Where applicable, the number, body weight range, sex, source ()f supply, species, strain, substrain, and age of the test system.

9. The procedure for identification of the test system.

10. The description of the experimental design, including methods for the control of bias.

11. Where applicable, a description/identification of the diet used in the study as well as solvents, emulsifiers and/or other materials used to solubilize or suspend the test, control, or reference substances before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

12. The route of administration and the reason for its choice.

13. Each exposure level expressed in appropriate units, and the method and frequency of administration.

14. The type and frequency of tests, analyses, and measurements to be made.

15. The records to be maintained.

ATTACHMENT 3

Required Study Report Elements

1. Name and address of the facility performing the study.

2. The date the study was initiated and the date it was completed (i.e., study report was signed), terminated, or discontinued.

3. The objectives and procedures as stated in the approved protocol, including any changes in the original protocol.

4. Statistical methods employed for analyzing the data.

5. The identity of test, control, and reference substances by name, chemical abstract service number or code number, strength, purity, and composition, or other appropriate characteristics.

6. Stability and, when relevant, solubility of the test, control, and reference substances under the conditions of administration.

7. A description of the method used.

8. A description of the test system. Where applicable, the final report shall include the number of animals used, sex, body weight range. source of supply, species, strain and substrain, age, and procedures used for identification.

9. A description of the dosage, dosage regimen, route of administration and duration.

10. A description of all circumstances that may have affected the quality or integrity of the data.

11. The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel involved with the study.

12. A description of transformation, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.

13. The signed and dated reports of each of the individual scientists or other professionals involved in the study, including each person who, at the request or direction of the testing facility or sponsor, conducted an analysis or evaluation of data or specimens from the study after data generation was completed.

ATTACHMENT 3

(Continued)

14. The locations where all specimens, raw data, and the final report are to be stored.

15. The QA statement prepared and signed by the QAU.

16. The dated signature of the study director.

17. The compliance statement signed and dated by the sponsor, applicant, and the Study Director