| STANDARD OPERATING PROCEDURE | | |
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| Title: **CONDUCTING A FIELD STUDIES GLP COMPLIANCE INSPECTION** | | |
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## 1. PURPOSE

To provide guidance and a standard procedure for conducting a Good Laboratory Practice (GLP) Standards compliance inspection at field sites conducting studies to be submitted to the Agency in support of applications for research or marketing permit for pesticide products regulated by EPA [Sections 3, 4, 5, 18, and 24(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended], or pursuant to testing consent agreements and test rules [issued under Section 4 of the Toxic Substances Control Act (TSCA)].

## 2. SCOPE

This standard operating procedure (SOP) will be used when inspecting field sites conducting testing under FIFRA or TSCA. Field sites shall be defined as sites which do not fit the generally accepted concept of laboratories, and shall include the following: large and small scale agricultural plots, including greenhouse and growth chambers; nonagricultural sites such as forests, ponds and wetlands, grassland, and other uncultivated areas; and facilities used for the care and maintenance of wild or domestic livestock

## 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 CFR 34052, August 17, 1989 [40 CFR Part 160]

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

4.3 Good Laboratory Practice Standard Inspection Manual, EPA 723-B-93-001, September 1993

## 5. SPECIFIC PROCEDURES

Ordinarily, a GLP Standards compliance inspection will be scheduled for a field site under one of two circumstances: (1) in conjunction with a study audit if one or more completed studies which have been submitted to the Agency under the appropriate section(s) of TSCA or FIFRA, or (2) in the case where no completed study is being audited, but there is at least one ongoing GLP regulated study in progress at the facility, which can serve as a partial basis for the inspection.

The inspector must bear in mind that the facility GLP compliance review is quite separate from the study audit. The purpose of the GLP review is to determine the current state of compliance of the facility's operations with the GLP Standards regulations. In order to make this determination, the inspector will review policies and practices in effect at the facility, interview facility personnel, and evaluate the existing facilities, including buildings, equipment, storage and maintenance areas, and experimental plots, ponds, fields, etc.

Part of the basis for the compliance review will normally include the review of a specific ongoing study which is expected to be submitted to the Agency under the above-mentioned sections of FIFRA or TSCA. If a study has not been selected by LDIB targeting personnel prior to the inspection, the inspector should examine the facility master schedule and select a representative study. This should be done as early in the inspection process as is feasible, since the facility may need to contact the sponsor and obtain permission to release study data and records to the Agency inspector.

The following outline should be used to ensure that all applicable areas of the facility's operations 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 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 inspection, it is necessary to verify that all personnel involved in the conduct of regulatory studies under TSCA and/or FIFRA have the education, training, and experience to adequately perform their assigned functions, and that there are sufficient numbers of personnel for the timely and proper conduct of the ongoing studies.

The evaluation of the qualifications of facility personnel can be accomplished largely by interviewing study personnel in conjunction with the conduct of the inspection. The inspector should also review curricula vitae (CV), resumes, training records, and other documentation of education, background, and/or training.

Evaluation of the adequacy of facility personnel may be made by reviewing the responses to the following inquiries:

- Who are the personnel responsible for the conduct of regulatory studies?
- What is each person's responsibility?
- Are CVs and up-to-date training records available for all 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 are involved with regulatory studies?
- Does a review of some or all of the CVs and training records indicate that personnel are competent to perform their assigned functions?
- Are various aspects of the studies (i.e., sample collection, sample preparation, sample analysis, and other activities) performed in a timely manner? Are there

unexplained delays indicating insufficient numbers of personnel?

- Does the master schedule indicate that the number of ongoing studies is appropriate to the total number of personnel at the facility?

- If appropriate, have personnel been properly trained in personal sanitation and health precautions, and use of protective clothing appropriate to the type of study being conducted?

- If appropriate, are there procedures for reporting any health or medical conditions which might adversely affect the study?

5.1.2 Management [Sections 160.31/792.31]

The inspector should verify that facility management is fulfilling its responsibilities as defined by the GLP Standards regulations, including: designating a study director and replacing the study director, if necessary; assuring that there is a quality assurance unit; assuring that test, control, and reference substances are appropriately tested for identity, strength, purity, stability, and/or uniformity; assuring that personnel, resources, facilities, equipment, materials, and methodologies are available; assuring that personnel understand their functions; and assuring that deviations from the GLP Standards reported by the quality assurance unit are communicated to the study director and corrective actions are 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 as outlined above.

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

- Was a single study director designated to oversee the ongoing study?

- Was the study director replaced during the study and, if so, was this done promptly? Who designated the new study director?

- Is a quality assurance unit in place?

- Is there a policy for documenting test, control, and reference substances, as described by the GLP Standards?

- Do personnel, resources, facilities, equipment, etc. appear to be adequate for the proper conduct of the study?

- Are any deviations in procedures properly documented and communicated to the study director?

5.1.3 Study Director [Sections 160.33/729.33]

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

- Was a single study director designated to oversee the ongoing study?

- Are the qualifications of the study director appropriate to enable him/her to maintain overall responsibility for the technical conduct of the study? What, specifically, are his/her responsibilities?

- Is he/she a sponsor representative, or a facility employee? If he/she is stationed at a site other than the test facility, has he/she visited the laboratory or field sites prior to and/or during the conduct of the study?

- Did the study director approve (i.e., sign and date) the protocol for the ongoing study?

- Did the study director approve (i.e., sign and date) any corrective action when necessary to assure the quality and integrity of the study? How was this documented? Did the study director approve any SOP deviations?

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 the personnel engaged in conducting the study. The QAU must conduct inspections and maintain records appropriate for the type of study.

The inspector should verify that the QAU is fulfilling its responsibilities with regard to the conduct of regulatory studies, but is not permitted to examine reports of QAU inspection findings

and problems, or actions recommended and taken. The following areas, however, should be taken into consideration:

- Is a QAU, as defined by the GLP Standards, in existence at the facility? Does it appear to have adequate staff and training to fulfill its responsibilities?

- Does the QAU have written SOPs or other documents describing the responsibilities and procedures applicable to the QAU, the records to be maintained by the QAU, and the method of indexing the records?

- Does the QAU have a master schedule of studies being conducted at the facility? Does it have a copy of the protocols for all ongoing studies?

- Are periodic QA inspections conducted and/or scheduled for the ongoing study? What phases were or are to be inspected? Are the number of inspections and choices of phases appropriate, and are 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?

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

## 5.2 FACILITIES

The GLP Standards regulations require that facilities be adequate for the proper conduct of the study. The main concerns are that the location, size, construction, 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. Space must be provided for archives, if necessary, and policies established for storage and retrieval of any raw data and specimens which are archived at the site.

The inspector should verify that the GLP Standards requirements for facilities are adequately met at the field facility. This can best be accomplished by visiting the facility areas which are being used for the conduct of the ongoing study, in order to make a direct assessment of the adequacy of the facilities. In addition, other areas used to conduct regulatory studies should also be evaluated during the inspection. To aid in this evaluation, the following aspects should be considered, as appropriate and applicable:

- Are buildings of appropriate size, design, and construction?

- Are field sites (outdoor) of appropriate size and location and, if applicable, of appropriate design and construction for the conduct of regulatory studies?

- Does the design of the facilities allow for separation of test systems, as appropriate? Does the design of the facilities allow for adequate isolation of individual projects?

- Are there areas for quarantine or isolation of animals? Is animal housing adequate for the conduct of regulatory studies?

- Are aquatic toxicology facilities adequate to separate projects and organisms, and to prevent cross contamination with chemicals used in other studies?

- What does the protocol for the ongoing study specify for environmental conditions to be used in the study? Are there appropriate and adequate instruments for measuring environmental conditions (temperature, humidity, rainfall, wind, photo period, etc.), as specified in the protocol? Is there appropriate and adequate regulation of environmental conditions as specified in the protocol? What records are available to document the environmental conditions and/or adequacy of environmental control?

- What is the source of water used in the study? Are water supplies appropriate and adequate? How are water conditions monitored? How is water quality assured? How is water stored? Does the water quality and composition meet the specifications of the study protocol?

- What is the source of soil used in the study? How is soil obtained and stored? How and by whom is soil composition determined? Was soil characterization determined under GLP Standards? Are the source and composition of soil the same as specified in the protocol?

- Are there adequate areas for storage of feed, nutrients, soil, bedding, supplies, and equipment? Are these separated from areas where the test system is located?

- Are facilities for holding, culturing, and maintaining algae and/or aquatic plants appropriate and adequate? Are facilities for aquatic animals appropriate, and do they meet the conditions, as specified in the protocol?

- Where and how are test, control, and reference substances received and stored? Are storage conditions adequate to prevent contamination? Are environmental conditions for storage areas monitored? Is security for storage areas adequate? Are storage areas kept locked? Who has responsibility for storage areas? Who has access to storage areas?

- Are there adequate facilities for mixing test, control, and reference substances with carrier? What precautions are taken to ensure that cross-contamination from mixing equipment does not occur?

- Where are mixtures stored? Are storage conditions, especially temperature, monitored? What records are retained to confirm that storage conditions are adequate and meet the requirements of the study protocol?

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

- Are raw data and specimens, which had been generated to date for the ongoing study, readily available for review by the inspector? Were they stored in such a manner as to be in good condition? Where will the study data and specimens to be archived at the completion of the study?

- Are any data and/or records for regulatory studies permanently archived at the facility? If so, do the archives meet the requirements of the GLP Standards regulations?

## 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 to verify that the equipment used by the test facility meets the above requirements. The reliability of equipment used to generate, measure, or assess quantitative data is critical to the integrity of the raw data, and the inspection must include a review of facility procedures for instrument maintenance and calibration. This includes all equipment used to apply the test substance to the test system, and all instruments used to monitor environmental conditions, as well as laboratory analytical equipment. The inspector's review of equipment should include procedures for maintenance and calibration of any of the following which are applicable: balances and volumetric devices used to prepare mixtures of test, control, or reference substance with carrier; agricultural equipment including sprayers, granular applicators, and aerial applicators; metering devices used in aquatic toxicity testing; analytical balances used in the laboratory; thermometers, hygrometers, anemometers, pH meters, and other meters and gauges used to monitor environmental 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 inspector:

- What specific equipment and instruments are used at the facility to generate, measure, or assess data?
- Do the raw data for the ongoing study include data for the calibration of all equipment and instruments used so far in the study?
- Does it appear that the calibration methods are adequate and appropriate? Are SOPs in effect which addressed equipment and instrument use, maintenance, and calibration?
- Do 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 Standards regulations require that the testing facility have written standard operating procedures (SOPs), that all deviations 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 inspector to review all SOPs in effect at the facility. However, he/she should verify that written SOPs exist and are of adequate scope and detail, should review several of the key SOPs, and should be alert to any deviations from SOPs which may have occurred during the conduct of the ongoing study, 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 area should be addressed by the inspector:

- Are current and historical SOPs available to the inspector if requested?
- If SOPs were reviewed by the inspector, were they of adequate scope and authorized by management?
- 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 procedures 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 components where appropriate, appropriate separation from other test systems and

studies, adequate acclimatization of 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 is housed and cared for. The inspector should verify that the GLP requirements are met, particularly by reviewing all of the following which are applicable:

- Do 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 ongoing 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?

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

- Have any diseases occurred 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 is the test system housed or contained? Is the housing adequate to separate species and studies? Are fields, ponds, or other sites adequately separated from

each other? How did study personnel document that separation is adequate?

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

- If individual identification is necessary, how are individual test system components identified? Is the method of identification adequate to prevent mixup of individuals?

- Is there any documentation of feed, soil, or water contaminants which are known to be capable of interfering with the study? If so, are feed, soil, and/or water analyzed periodically for these contaminants? Have the analytical raw data been retained?

- Do the data for the ongoing study document the application of any pest control materials? What pest control materials were used, and at what intervals? In agricultural situations, do 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 [Section 160.105/792.105]

The regulations require that the test, control, and reference substance 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 for each batch of test, control. and reference substances, which are defined in Section 160.195.

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

copies of the raw data for further review. Such circumstances may include: (1) a request by LDIB that these data be reviewed; (2) unusual, conflicting, or irregular findings during the GLP review or the study audits?

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

As a guide to determining compliance with this section of the regulations, the inspector should use the ongoing study as a basis for addressing 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 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?

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

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

- Is the study duration more than 4 weeks? If so, were reserve samples from each batch of substance retained? Who is responsible for retaining the reserve samples? Where are they stored?

5.5.2 Test Control and Reference Substance Handling [Section 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 should ensure that these requirements are met, by interviewing responsible personnel and/or examining SOPs and substance control logbooks. The following questions, as related to the ongoing study, can be used as a guide in making the determination of compliance:

- How are the above referenced substances stored? Are storage procedures such as to minimize the potential for contamination or degradation of the substances? In field situations, are substances adequately protected from environmental factors such as heat, cold, rain, ground moisture, and dust? In field situations, are substances stored so as to prevent contamination from other agricultural chemicals and fuel oils? Are these storage procedures described by SOPs? How do the QAU and study personnel assure that storage conditions are 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? If substances were repackaged, or if the entire contents of any of the containers have been used, have the empty original containers been retained? Where are they stored?

- What records are available to show receipt of the test, control and reference substances? Who received them, and when? How much was received? Where are they stored? What was the condition and physical description of the materials when received? Does this match the current appearance of the test, control, and/or reference substances?

- Is there documentation in the form of a logbook or other records to show distribution of the substances for use in the ongoing study? 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 remains?

- **!** Are the remaining substances 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 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.

Using records and data from the ongoing study, the inspector should verify that any mixtures or solutions of test, control, or reference substance with carrier were adequately analyzed for uniformity, stability, and concentration. 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 a 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 we of the first batch of mixture? Was an analysis conducted on each batch, or were representative batches analyzed? Did the protocol address this? Did there appear to be any problems with uniformity of mixtures which might compromise the validity of study result?

- 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 interval adequate? How much variation in measured concentration was observed between batches? In the professional judgment of the inspector, 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 reference 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 establish 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?

- Where appropriate analytical methodology and instrumentation used in conducting the above analyses? Were all analytical raw data and records available for audit? If not, where were they stored? Did the analyses conform to 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 should review the study protocol for the ongoing study as part of the GLP Standards review, and should ensure that it contains all required elements.

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 inspector 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 reviewing the data and records for the ongoing study, the inspector should also be alert to any changes which may have been made which did not result in a proper protocol amendment.

Normally, the inspector may verify compliance with the regulations by answering the following questions, as they relate to the ongoing study:

- Is it possible to determine if the study director coordinated the writing of the protocol so that a single, coherent document was produced which complies 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?

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

- Are 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 reviewing computer generated data, refer to SOP No. GLP-DA-03.

The inspector should verify that the ongoing study was conducted in a manner that complies with the GLP Standards regulations. If possible, this should include the observation of one or more study procedures in progress at the time of the inspection.

Although some of these issues should already have been addressed during the review of other areas of GLP Standards compliance, the inspector should ensure that he/she has answered the following questions:

- Was the conduct of the study, particularly the procedures which were observed by the inspector, in accordance with the protocol and its approved amendments?

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

Additionally, the inspector 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 mate incorrectly (whiteouts, original entry otherwise illegible, changes not initialed or dated), how common were incorrect changes? Were there relatively few instances or tit 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, autoradiograms, thin-layer scanners, etc.) identified with project number, study name, sample number, treatment level, identification of 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]

Compliance with this portion of the GLP Standards will not normally be determined during a GLP Standards review at a field site. The inspector can determine, however, how study data and results are conveyed to the study director, and who has the responsibility for preparing any written reports to the study director which are prepared for the portions of studies conducted at the field site? If any portion of reports for completed studies are prepared at the inspected site, the inspector should review report preparation procedures and, if possible, should review a

typical study report. The inspector should determine that all pertinent required elements are included in the report, and especially that the report includes a quality assurance statement [40 CFR, Section 160.35(b)(7)], and statement of compliance or noncompliance (40 CFR, Section 160.12) for portions of the study conducted at the site.

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. This includes logbooks for maintenance and calibration of equipment and instruments; logbooks for accountability of test control, and reference substances, and for specimens and samples; records of environmental and storage conditions; historical SOPs and CVs; historical master schedules; and other more general records which are not study specific.

Many field sites do not retain study specific records and data once a study has been completed, but will return these records to the sponsor for archiving. However, facility records and data are normally archived at the facility.

During the GLP compliance inspection, the inspector should determine the facility procedure for permanent archiving of records. If the procedures require the establishment of archiving facilities and procedures on-site, these should be reviewed for adequacy. Where applicable, the following may be considered:

- Were raw data, records, etc. readily available when requested?
- Where were data and records for the ongoing study stored? They need not be archived as long as the study is in progress, but should be stored in such a way as to preserve them.
- Were other records and documents, such as maintenance logs and receipt logs, archived at the facility? Who had access to the archives? Who was the archivist? Were SOPs available to describe archiving procedures?
- Were archived data in good condition and legible? Were archives set up such that the data retrieval was expedient?

5.8 REPORTING GLP INSPECTION FINDINGS

The GLP inspection report prepared by the inspector, which gives the findings from the inspection, should outline the specific areas which were reviewed as part of the GLP compliance review, and whether or not deficiencies were fount. The inspector should particularly identify any GLP deficiencies which, in his/her opinion, are serious enough to affect the integrity and/or reliability of data generated at the facility. All deficiencies, inconsistencies or irregularities must be properly documented. and the doc~mentation must be included with the inspection report as exhibits (see SOP No. GLP-S-02, Evidence Gathering and Documentation). The report should be prepared according to established procedures and formats (see SOP No. GLP-S-03, Format for Inspection Reports).

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

/s/_____ 06/01/99
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/s/_____ 06/07/99
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