HOW GLP PROVISIONS INFLUENCE COSTS OF RODENTICIDE FIELD EVALUATIONS

RICHARD M. POCHÉ, Genesis Laboratories, P.O. Box 42, Richfield, Wisconsin 53076

ABSTRACT: Good Laboratory Practice (GLP) guidelines were implemented by the U.S. Environmental Protection Agency in August 1989. The purpose of the standards are to ensure the integrity of laboratory and field studies which are conducted in support of FIFRA permits and pesticide registrations. Since the advent of GLP requirements, the cost of conducting field trials has increased 40 to 200%, depending upon the type of study. The increased expenses associated with laboratory and field testing, coupled with reregistration expenses, and annual EPA and state registration maintenance fees, have placed a tremendous burden on smaller companies in the U.S.

Proc. 15th Vertebrate Pest Conf. (J. E. Borrecco & R. E. Marsh, Editors) Published at University of Calif., Davis. 1992

INTRODUCTION

The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Good Laboratory Practice (GLP) standards specify the minimum practices and procedures which must be followed to ensure the quality and integrity of data submitted to the EPA in support of a permit or product registration. These requirements are outlined in 40 CFR Part 160. The GLP regulations were initially promulgated on November 29, 1983 and were revised on August 17, 1989.

Any study completed to support a registration must be conducted under GLP. Compliance with these standards is monitored through a program of field and laboratory inspections and study audits coordinated between the EPA and the Food and Drug Administration.

The purpose of the GLP provisions are to ensure the quality and integrity of data submitted pursuant to sections 3, 4, 5, 8, 10 and 24(c) of FIFRA as amended. The requirements took effect on October 16, 1989.

Both laboratory and field studies are affected by the GLP standards. Prior to the GLP standards, sponsors of studies wishing to have research completed contracted a consultant or the services of a laboratory. Too often there was no formalized protocol and much of the experimental design was left up to the lab or consultant. Upon completion of the project a report was drafted and submitted to the EPA to support a registration or Experimental Use Permit application.

Years following the submission of such data, details were often lacking, such as the actual chemical concentration in the bait as verified by a reliable laboratory, qualifications of the study personnel, or availability of the original raw data. Information lacking in any number of the components of a field study could have affected the integrity of the study and may have cast doubt on the reliability of the results.

Within the last several years, all rodenticide compounds have been subjected to the reregistration process. Both original studies accepted by the EPA and additional requirements are subject to GLP provisions. As a result, the EPA is in the process of reviewing previously submitted product support data and new studies to determine if GLPs were adhered to. With many older studies, chances were the study did not meet the GLP standards and new studies were required.

Although there are numerous components within the GLP guidelines, I will attempt to highlight those most pertinent to rodenticide testing and assess the impact on the cost of testing during the 1990s as opposed to 15 to 20 years ago. To further understand why GLP provisions have impacted the cost of research, one must gain a better understanding of all that is contained within the guidelines.

The GLP provisions affect studies in a number of areas. The standards are summarized in the following sections of 40 CRF Part 160:

Subpart A: General Provisions
Subpart B: Organization and Personnel
Subpart C: Facilities
Subpart D: Equipment
Subpart E: Testing Facilities Operation
Subpart F: Test, Control, and Reference Substances
Subpart G: Protocol for and Conduct of Study
Subpart J: Records and Reports

Subpart A—General Provisions

A facility undertaking studies that are to be submitted for FIFRA or FDA product support, is required to have a GLP program and separate Quality Assurance Unit. The net result is the addition of more personnel. A small laboratory can exist with a single QA Officer/Manager or hire an outside QA consultant to conduct the required inspections and reviews to remain in compliance.

Anyone submitting an application for a research or marketing permit and providing data from a study shall include a true and correct statement of compliance signed by the applicant, the sponsor, and study director. One of the following statements has to be provided:

(a) A statement that the study was conducted in accordance with the GLP provisions;
(b) A statement describing in detail all differences between the practices used in the study and those required by the provisions; or
(c) A statement that the person was not a sponsor of the study, did not conduct the study, and does not know whether the study was conducted in accordance with GLP standards. The persons signing the GLP statement become liable in the event an EPA inspection of the data occurs. Failure to comply with the standards may result in the rejection of a study.

Subpart B—Organization and Personnel

Persons engaged in the conduct of, or responsible for, the supervision of a study shall have the education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.

Testing facilities are required to maintain a current summary of the education, training, experience and a job descrip-

tion for each individual engaged in or supervising the conduct of a study. Additional training is often required by outside consultants or training seminars to meet this provision.

There should be a sufficient number of personnel in order to conduct the study according to the protocol and in a timely manner. Also, protective clothing and other equipment are required to ensure the safety of personnel. Personnel is divided into testing facility management, study director, study personnel and QA Unit. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation, and reporting of results, and represents the single point for study control. The study director assures: the protocol and any change is approved; all experimental data, including deviations are accurately recorded and verified; unexpected circumstances that may affect the quality and integrity of the study are noted when they occur and corrective action is taken and documented; test animals are as specified in the protocol; GLP regulations are followed; and raw data, documentation, protocols, specimens and final reports are transferred to the archives during or at the close of the study (Table 1).

A quality assurance unit shall be established and operate independently and is responsible for monitoring each study. The unit shall ensure that the facilities, equipment, personnel, methods, practices, records, and controls are in compliance with the regulations. The QA unit shall maintain a copy of a master schedule of all studies conducted at the facility, copies of all protocols, and inspect each study at intervals to ensure the integrity of the study, maintaining signed records of each inspection. The QA unit also review all drafts and final study reports and attests to the accuracy and adherence to the protocol and standard operating procedures (SOP).

Table 1. A list of some of the major responsibilities of the QA unit before, during, and following a field trial. The objective of the QA unit is to certify the study adheres to GLP's, the study protocol, and SOPs.

Assign project number
Review and comment on protocol
Preparation of information for site inspection
In-progress inspection
Protocol review/deviations
SOPs
Sufficiency of protocol and SOPs
Documentation
MSDS, equipment manuals, etc.
Personnel CV's training records, job descriptions
Equipment use, calibration records
Data records
Report of findings
Test plot layout
Equipment calibration
Test bait mixing, weighing, records
Data audits
Report audits
Draft
Final
Records
GLP statement
Archives

Subpart C—Facilities

A testing facility shall be of suitable size and construction to facilitate the proper conduct of a study. Labs contracted to do a bait analysis, as an example, must have a GLP program in place, otherwise the study will not be in compliance. Many labs have made substantial investments in building expansions, equipment, air conditioning, and personnel to remain both competitive and in compliance with 40 CFR Part 160.

Within a laboratory, there should be separate areas for receipt and storage of test, control and reference substances; animal quarantine and care rooms; and mixing of test control and reference substances with a carrier (e.g. formulated bait).

Space will be provided for archives, with limited access by authorized personnel only, for the storage and retrieval of all reports, raw data and specimens from complete studies.

Subpart D—Equipment

The equipment used in the study to generate, measure, and assess data and equipment used for facility environ-mental controls shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning and maintenance. Written SOPs are to be developed for all equipment used in a GLP study, ranging from analytical balances to burrow builders. Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations.

Subpart E—Testing Facilities Operation

Standard operating procedures shall be developed in writing for study methods. SOPs shall be developed for animal area preparation, test system care, receipt, identification; storage, handling, mixing, and method of sampling of test, control, and reference substance; test system observation; laboratory or other tests; handling of test animals found moribund or dead during study; necropsy of test animals; collection and identification of animals; data handling, storage, and retrieval; maintenance and calibration of equipment; and the packing, handling, and shipment of tissues. There are many more provisions under this subpart that apply to laboratory animal tests and chemistry studies.

Subpart F—Test, Control, and Reference Substances

The identity, strength, purity and composition or other characteristics which appropriately define the test substance will be determined for each batch used in the study and shall be documented before its use. Methods of analysis shall be documented by the sponsor or testing facility. The storage and stability of test substances, along with directions on the safe handling of the materials and any mixtures will be clearly defined.

Subpart G—Protocol for and Conduct of Study

Each study shall have an approved written protocol that clearly indicates the objectives and methods for the conduct of a study. The details contained in the protocol are listed in Table 2. Although much of the data collected during a field study with rodenticides may vary, the information collected should be well organized for future reference. Tables 3 and 4 give recommendations for field notebook organization.

Table 2. The major elements of a protocol as required by the GLP provisions are essential to remain in compliance.

Title/Purpose
Test and Control Articles
Sponsor and Testing Facility
Starting and Completion Dates
Justification for Species
Test System (Animals)
Unique Identification
Study Design and Methods
Prebait/Diet
Route of Administration (ex. oral, inhalation)
Dose Level
Degree of Absorption
Tests and Analysis
Records to Maintain
Approval
Statistical Methods

Table 3. The following lists the information generally required to maintain a good field notebook.

Table of Contents
Study Header
Title
Purpose
Personnel (signatures, initials)
Bait, Formulations, Suppliers
Receiving and Shipping Records (baits and residue samples)
Equipment
Applicable SOPs
Procedures/Methods
Copy of Protocol
Comments/Deviations
Charts
Results
Conclusions
Cross-references
Signature/Initials
Date
Checked by

Table 4. A list of reminders in recording information in field notebooks.

Record information/data at the time
Write directly in the notebook
Write legibly
Use permanent black ink
Provide signature/initials
Changes to data
Don't obscure original
Draw one line through original
Record correct value
Give a reason or error-code
Sign/Initial
Date
Verified by

Table 5. Following is a list of records that are to be maintained during the course of a field study for which the final report is submitted to the EPA in support of a permit or Section 3 registration.

Protocol and amendments
SOPs
Personnel records
Animal records
Weather conditions
Bait source, lot numbers, dates used, certification
Application records, concentration
Bulk chemical receipt, storage and use records
Formulation records
Analytical reports
Disposal of samples
Shipment of bulk chemical to supplier post study
Field observations
Photographs
Correspondence
Field notes/notebook
Raw data sheets
Product samples
Tissue residues:
Analytical standards information
Lab notebook
Chromatograms or other hard copy proofs
SOPs
QA inspection records, reviews, comments
Reports: drafts and final

Subpart J—Records and Reports

A final report will be prepared for each study and shall include information contained in the protocol along with the results and discussion. A copy will be maintained by the sponsor and test facility.

All raw data, documentation, records, protocols, specimens, field and lab notebooks, QA inspection records and reports, study personnel records, and the final report resulting from the study are to be archived. Correspondence and other documents relating to interpretation and data evaluation, other than those documents contained in the final report, shall be retained. These shall be stored in archives in an orderly manner to facilitate retrieval of raw data, documentation, protocols, specimens, and interim and final reports (Tables 5 and 6).

Records will be retained for the following period of time (whichever is longest): (1) for at least 5 years following the date on which the study results were submitted to the EPA in support of an application for a research or marketing permit; (2) the period during which the sponsor holds any research or market permit for which the study was used as support; or (3) in other situations where the study did not result in the submission to support an application for a research or marketing permit, the study must be kept at least two years following the date on which the study is completed, terminated, or discontinued. Much storage space is generally required to maintain archives and should have limited access to authorized personnel only.

AREAS OF COST INCREASE

EPA

The reregistration of rodenticides within the last several years has resulted in additional new studies not previously required, generating new data for older reports that did not comply with GLP provisions. As a result, numerous docu-

Table 6. The raw data should be collected and retained in a manner to review the original observations and activities for evaluation and reconstruction of the field test situations. The following should be collected and retained in the archives:

Laboratory and field worksheets
Records
Memoranda
Notes
Exact copies
Photographs
Microfilm or microfiche copies
Computer printouts
Magnetic media
Dictated observations
Records from automated instruments
VCR tapes of study sites/field work
Tissue/bait shipping records

ments have been submitted to the EPA for review. A complete registration application package for a rodenticide may contain in excess of 200 lbs of bound reports, GLP studies, and other documents and forms. Although staff numbers have not increased significantly within the EPA as a result of the GLP provisions, the review time has increased. Although the EPA obtains finances from registrants for reviews and processing of registrations, annual maintenance fees, and fines resulting from GLP other environmental violations, the expenses of maintaining registrations is ultimately passed on to the consumer.

Government Laboratories

The Denver Wildlife Research Center (U.S. Department of Agriculture, Denver Wildlife Research Center), has experienced significant increases in the amount of time and effort required to conduct research studies (Fagerstone et al. 1990). Coupled with an increase in staff to handle the details of GLP provisions, the reregistration of chemicals has required that the chemistry staff be increased from 3 to 15 individuals. The addition of a QA unit, drafting of SOPs, and staffing of QA scientists have added to the cost of testing rodenticides. The authors cite many of the GLP regulations discussed previously as they contribute to the added expense of conducting rodenticide research today.

According to G. Mitchell (pers. comm.), Quality Assurance Officer of DWRC,. the impact of GLPs has increased the cost of FIFRA related studies by 40%. This figure does not take into account the expansion of the laboratory, a project costing several million dollars.

Chemical Industry

Over the last ten years, U.S. companies have added or expanded internal laboratory capabilities to perform many studies with their own staff. Since the GLP provisions took effect in 1989, the cost of studies for efficacy both in the lab and field has increased significantly. Simple efficacy studies have increased by 25 to 100%, while studies requiring both efficacy and residue work, have augmented about 150%.

Although some companies were equipped with their own laboratories, QA units had to be added. This has meant an increase in personnel (salaries and benefits), and the involvement of more people in a typical study. In the past, the chief investigator worked directly with the sponsor of a study. Now, management, the study director, study personnel, and QA staff are essential to the completion of a study.

Companies with chemistry departments were required to upgrade their operation by drafting numerous SOP's and implementing new programs such as hazardous waste management plans, laboratory hygiene plans, and chemical tracking systems. This has required much time, paper work, and a substantial financial investment, in one case increasing the cost of testing by 200%.

Universities

Several universities traditionally used for rodenticide testing in the U.S. over the past 20 years have encountered financial difficulty in attaining GLP compliance. As a result these will probably not be available for laboratory or field related product support GLP testing. The expenses of increased staff requirements for a QA Unit, building modifications, and/or updated equipment have essentially halted all GLP studies. It is possible, however, for these labs to remain active in field testing, should they choose the option of contracting the quality assurance components of the studies with QA consultants or other laboratories.

Private Laboratories/Consultants

As with chemical companies, government labs, and universities, private laboratories and consultants have been obligated to adhere with the GLP regulations. Most of the areas impacted in the private labs are similar: increased personnel requirements and training, animal maintenance program, record keeping, archives, and a system of retrieving data, represent a fraction of the details that have to be organized and maintained.

With field studies, the QA Unit is required to inspect studies in the field for their reliability and adherence to the protocol, the sufficiency of SOP's, ensure accurate record keeping, equipment calibration, monitoring of bait usage, personnel, deviations from original study design, discern discrepancies and report them immediately to management and the study director. Although this seems routine, there is much time spent in the review of documents, field verification, drafting of reports, follow-up, and archiving. As a result, the expense of traditional field trials, such as efficacy, has increased by 60 to 100%.

CONCLUSIONS

Although the GLPs have resulted in the improvement of study quality and reliability, the impact has been economically significant. As a result, many smaller companies have been unable to maintain registrations and have ceased operations since the expense of new testing has become cost prohibitive.

LITERATURE CITED

FAGERSTONE, K.A., R.W. BULLARD, and C.A. RAMEY. 1990. Politics and economics of maintaining pesticide registrations. Proc. Fourteenth Vertebr. Pest Conf. 14:8-11. Univ. California, Davis.

FEDERAL REGISTER. 1989. Environmental Protection Agency, 40 CFR Part 160, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA): Good Laboratory Practice Standards. Vol. 54, No. 158.