CURRENT AND FUTURE EPA REQUIREMENTS CONCERNING GOOD LABORATORY PRACTICES RELATIVE TO VERTEBRATE PESTICIDES

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ABSTRACT: In this paper I present a discussion of current Environmental Protection Agency (EPA) policy on ensuring compliance with the Good Laboratory Practice (GLP) regulations as applied to health effects studies submitted to the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The EPA has recently proposed extending these regulations to essentially all studies submitted to the Office of Pesticide Programs (OPP) in support of a request for a new registration or in response to data requirements issued under Section 3(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The potential impact of these proposed regulations as they may apply to vertebrate pesticide efficacy testing is presented and discussed.

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REGULATORY BACKGROUND

Under the Federal Insecticide, Fungicide, and Rodenticide Act, known by the acronym, "FIFRA", all pesticides that are sold or distributed in commerce must be registered. Agreed. It follows that to obtain a registration the EPA must have available data that will allow an evaluation of both the risks and the benefits devolving from the use of the pesticide. The final requirements for registration of entire classes of agricultural chemicals were published in July of 1975. Between 1975 and 1981 the Agency issued a number of "Guidelines for Registering Pesticides in the United States". These guidelines, never converted into regulations and for good reason, provided to any registrant the standards for conducting acceptable tests along with guidance on the evaluation and reporting of data and even provided examples of acceptable protocols.

GENERAL DATA REQUIREMENTS UNDER FIFRA

Recognizing that trying to make the guidelines into regulations would be a relatively useless exercise the EPA did issue, in October of 1984, Part 158 of FIFRA which specifies the kinds of data that must be submitted to the EPA in support of a registration of a pesticide. Based on the proposed usage pattern, a registrant could now select those tests and those test guidelines which were both necessary and sufficient for fulfilling a registration application. In its proposed version of Section 158 on data requirements the EPA initially proposed to waive the product efficacy requirements for vertebrate control agents. Public comment suggested that this was not the way to go and in the final rule product performance requirements were inserted to cover two classes of pesticides, namely, pest microorganisms that pose a threat to public health and, secondly, vertebrate control agents intended for control of pests that directly or indirectly transmit disease to humans. The final set of data requirements for all classes of chemicals and all types of tests is shown in Table 1.

These range from product chemistry through a great variety of both very simple to very complex testing. Efficacy testing of vertebrate pesticides is a small requirement under 158.160, product performance. This is shown again in Table 2.

This is not to infer that these efficacy and performance tests are minor or simple, not at all. It is but one tree in a major forest of data requirements.

Table 1. Generalized data set which may be required for registration of a product under the Federal Insecticide, Fungicide and Rodenticide Act*

Section	Requirement
158.120	Product chemistry
158.125	Residue chemistry
158.130	Environmental fate
158.135	Toxicology
158.140	Reentry protection
158.142	Spray drift
158.145	Wildlife and aquatic organisms
158.150	Plant Protection
158.155	Nontarget insect
158.160	Product performance
158.165	Biochemical pesticides
158.170	Microbial pesticides

*Source: 40 CFR Part 1, Chapter 158

PRODUCT PERFORMANCE DATA REQUIREMENTS

Section 158.160 of FIFRA defines the types of data required for product performance. Data are required on the efficacy of vertebrate control agents and, specifically, the end-use products. As shown in Table 2, these products include avian toxicants, repellents and frightening agents, bat toxicants and repellents, commercial rodenticides, farm and rangeland rodenticides, rodent fumigants, inhibitors of ro-

Table 2. Generalized set of data which may be required for a vertebrate pesticide.

Section 158.160 Product performance data requirements	
Kind of data required	Comments
1. Avian toxicants	
2. Avian repellents	
3. Avian frightening agents	"Data requirements to
4. Bat toxicants and repellents	determine the efficacy of vertebrate control
5. Commercial rodenticides	agents are reserved
6. Rodenticides on farm and rangelands	at this time"
7. Rodent fumigants	
8. Rodent reproductive inhibitors	
9. Mammalian predacides	

dent reproduction and, finally, mammalian pesticides. Since the active ingredients of these end-use products are potential human toxicants, it follows that the standard first or second tier testing must also be performed to assess their safety in the event of human exposure. Accordingly, in parallel with the efficacy tests results the Agency also requires the standard health effects test results.

HISTORY OF GOOD LABORATORY PRACTICE REGULATIONS

In their initial inception, the test requirements on the one hand and the test guidelines on the other presented minimal acceptable scientific standards for range and design of toxicity tests but did not address the conduct and management of these tests since it was assumed that scientists were honest and upright people. However, history caught up with data requirements in the mid-70s when the Food and Drug Administration uncovered fraud in the testing and reporting of some pesticide safety data. Eventually, and following Congressional hearings on the matter and demands for change, enforceable regulations on the management and conduct of health effects testing using laboratory animals became a fact of life in 1979. That was the year that the Food and Drug Administration, hard pressed by these revelations of scandals in some pesticide testing laboratories, by outright fraud and deceit on the part of a few scientists and managers, made final a set of regulations designed to make sure that testing was conducted properly and that raw data were retained. These regulations were known as the Good Laboratory Practice Standards or GLPs.

PRINCIPLES OF GOOD LABORATORY PRACTICES

The principles of GLPs are sufficiently simple. What the regulations require is that the test be clearly defined by a protocol agreeable to both the sponsor and the laboratory, that a qualified person be in charge of the test, that the test be conducted by qualified personnel following written standard operating procedures, that equipment used be properly calibrated and maintained, that the location of the test be appropriate, that data are properly gathered and recorded, that raw data are preserved for a future audit, and, finally, that some independent person assure management that all these principles are followed and that the final report accurately reflects and interprets all of the data. I do not think that these are unreasonable requests to make of any scientist. Some-eyears later, the end of 1983 to be exact, the Office of Pesticides and Toxic Substances of the Environmental Protection Agency issued its own set of GLP regulations. The Office of Pesticides and Toxic Substances is responsible for the application of two Acts, the Toxic Substances Control Act, or TSCA, which is the responsibility of the Office of Toxic Substances, and the Federal Insecticide, Fungicide and Rodenticide Act, or FIFRA, which is the responsibility of the Office of Pesticide Programs. While TSCA is a relatively recent creation, FIFRA has its origins in much earlier legislation. The control of vertebrate pesticides clearly falls under FIFRA.

Please note that we have been talking about the conduct of the tests and not their scientific validity. GLP compliance is not synonymous with quality. The quality of the test is set in the study design and interpretation, the compliance with the regulations is set in the conduct and management of the test.

EXCLUSIONS FROM THE GLP REGULATIONS

Until now, there was a dividing line between tests required to be conducted in compliance with the Good Laboratory Practice regulations, namely the health effects testing which are covered by the regulations, and all other types of testing, for which this requirement was not applied. The importance of these excluded tests should not be underestimated or understated since they include testing likely to lead to action for or against a given registered product. These tests include all tolerance-setting studies, all residue studies, all environmental fate studies, all fish and wildlife studies, all genetic toxicology studies, all worker protection and field reentry studies as well as all vertebrate pesticide studies.

ADDITIONAL LEGAL REQUIREMENTS FOR ALL REGISTRANTS

Just because these types of testing could be done without adherence to the GLP regulations did not mean that other basic legal requirements could be ignored. Section 6(a) of FIFRA requires that the registrant notify the EPA in the event that any data are developed or discovered showing the test compound to be hazardous to the environment or to people. Section 8(a) of FIFRA further requires that all raw data from a test be retained by the registrant for the lifetime of the registration. This means all raw data in its original form and all raw data must be retrievable.

Please note carefully what I just said: FIFRA places all responsibility for data and compliance on the registrant, not

on the performing laboratory. The contract between the registrant and the laboratory is of no legal interest to the EPA. If anything goes wrong, if the data are suspect, if the data are lost, it is the registrant that catches hell. What the registrant does with the performing laboratory is between those two worthies; the EPA does not enter that argument. The same holds true for compliance with the GLP regulations. While we can take action against the test laboratory for lack of compliance, and especially for repeated lack of compliance, the real penalty is on the registrant for he, be he an individual or a corporation or a State or a Federal agency or facility, loses the registration or receives a restricted use or loses a couple of years of market share. That's heavy stuff.

RECENT REVISIONS TO THE GLP REGULATIONS

In the past year the EPA decided to significantly modify the existing GLP regulations under both TSCA and FIFRA and took the necessary steps to expand the GLP regulations and include in the GLP requirements essentially all testing presented to the Office of Pesticides and Toxic Substances regardless of test classification. The purpose behind this decision was to ensure that all data submitted to the Agency, not just selected health effects data, met the highest standards of conduct and management. The expansion of EPA's regulations took the form of generic GLPs. By this I mean that the proposed regulations focus on principles and practices and not on specific types of testing. After all, the GLP regulations, from their inception, have been a set of management and documentation guidelines, not a set of cookbook procedures for specific tests.

By concentrating on a generic approach to these regulations, by concentrating on principles and practices, by concentrating on what is important in test design and management, it has been possible to write a set of regulations that both relate to and control existing test types, as well as anticipate new types of testing.

GENERIC GLPS

The generic approach is accomplished mainly by redefining certain key concepts. Animal toxicity testing can be done anywhere that you can build a controlled environment animal facility. Other types of testing need specific locales. Field testing specific to crops in southern California cannot be carried out in North Dakota. So, a laboratory became not a controlled environment facility with animal rooms, but the location of the test, be it a traditional laboratory, field, stream or forest. The test system is no longer a mouse, perhaps in the shape of a fish; it is that to which the test substance is applied. So, test system includes not only genetically pure rodents, but also fish, wildlife, plants, bacteria, soil, water, etc. There were many other changes but the redefinition of the test facility and the redefinition of the test system were crucial to the development of generic GLPs.

STATUS OF THE PROPOSED REGULATIONS

The proposed regulations were published for public comment at the end of December, 1987. There is a 90-day comment period, that is, to the end of March, 1988. The comments will then be worked on by the GLP Workgroup and the proposal modified as necessary before starting the process of final review and publication. If the regulations go final then they should be effective this summer. I will talk about compliance and enforcement later.

TESTING EXCLUDED FROM THE APPLICATION OF THE GLP REGULATIONS

Before I go into what these PROPOSED regulations may mean to the testing of vertebrate pesticides, let me clearly define those types of testing that are NOT included in the scope of these proposed regulations. I mentioned earlier that essentially all tests submitted to the Agency either voluntarily, such as for a new registration, as well as all tests required by the Agency to maintain an existing registration will be covered by the proposed regulations. There is also a clear description of what is NOT required by the Agency. The Agency does not require submission of research data, in other words, experiments carried out for the purpose of increasing knowledge and to be published in the scientific literature. The Agency does not require the submission of range-finding tests unless those tests are required as a precursor to a long-term test. The Agency does not require efficacy testing results, with two exceptions: disinfectant efficacy and rodenticide efficacy.

Of course there is the tricky question of what happens when a published article is picked up by a chemical producer and submitted as fulfilling a requirement in the registration procedure. In case you are wondering, there is an exemption for that type of test.

RELATIONSHIP OF GLPs TO VERTEBRATE PESTICIDE TESTING

Vertebrate pesticide testing is not a barrel of fun. How are these regulations going to affect such testing and the reports of such testing?

For a traditional toxicologist, the simplest case occurs when the efficacy testing is conducted in a controlled location. Put a bunch of vertebrate pests in a confined space, expose them to pesticide and see how many die, dance on their toes, turn green or whatever the end result is supposed to be. This is certainly not the way tests of the efficacy of vertebrate pesticides are conducted. Vertebrate pesticide testing is complicated, among other things, by the eating and social habits of free-ranging animals, by the difficulty of monitoring baited carrion in rangeland, and by the inability to count exposed animals and record accurately their behavior. What will be required of persons conducting and reporting tests on the efficacy of vertebrate pesticides? I already answered that question earlier and let me repeat it now. What the regulations require is that the test be clearly defined by a protocol agreeable to both the sponsor and the laboratory, that a qualified person be in charge of the test, that the test be conducted by appropriately trained personnel follow-

ing written standard operating procedures, that any equipment used be properly calibrated and maintained, that the location of the test be appropriate, that data are properly gathered and recorded, that raw data are preserved for a future audit, and, finally, that some independent person assure management that all these principles are followed and that the final report accurately reflects and interprets all of the data.

The major problems that we have found in test facilities or in field stations almost always relate to lack of Standard Operating Procedures or SOPs, to the non-existence of a Quality Assurance Unit and to the improper recording and retention of raw data. The latter is a violation of FIFRA while the others are potential violations of the GLP regulations.

PRACTICAL APPLICATION OF THE GLP REGULATIONS

What will this mean in practical terms? It means that your test protocols will have to be worked out very carefully in advance and as many contingencies as possible included. For tests done under non-controlled conditions it means especially that all deviations from the approved protocol and problems with the test will have to be documented for future evaluation. All test variables, or at least all that you can plan for or predict, will have to be recorded in advance and the data properly gathered. It means field notebooks and pre-printed forms to make sure that field personnel do not forget to make observations and record facts. It may mean menu-driven portable computers in the field to make sure that all protocol variables are recorded.

Eventually, these efficacy tests may well be audited and the testing facilities inspected for compliance. It is possible that in the first year of checking for compliance that few enforcement actions will be taken as this is a significant change for the regulated community. Our job will be to visit, to inspect, to advise. Of course, if a violation of FIFRA is found that's a matter for immediate concern but that is also another story. Most FIFRA violations in this area concern the loss of raw data and that is a concern of FIFRA not of the GLP regulations.

LABORATORY INSPECTIONS AND STUDY SELECTIONS

It is possible that your laboratory will receive a GLP compliance inspection sometime after the proposed regulations become final.

Laboratories receive GLP compliance inspections and studies receive validation audits. The audit of a study often includes aspects of GLP compliance, aspects such as proper documentation, inventory of all raw data, and so on.

There are several reasons for selecting a study for audit and for selecting a facility for inspection. The most benign is that the facility comes up on our random listing of test facilities that should be inspected during the next nine to twelve months. We are able to develop a list of all studies that were conducted at that facility and submitted to the EPA in support of a registration.

OVERVIEW OF THE CONDUCT OF A COMPLIANCE INSPECTION

In an inspection we will want to see the facilities, talk with personnel, go over SOPs, see how the Quality Assurance Unit operates, check calibration and maintenance records, see how data are recorded and secured, test chain of custody procedures and so on.

In a data audit we will want you to retrieve all raw data from the study, assure ourselves that all raw data were reported and go through the raw data to validate the results of the final report.

Such an inspection or audit is relatively low-keyed and is intended to be that way. I have stressed non-confrontational and that is deliberate. No one starts out with the point of view that a test is fatally flawed, that a researcher imagines his data or that a facility should be closed down. We have consistently seen our job as one of enforcing compliance, to the extent possible, through education, cooperation and suggestion. These tests are important to both society and to the economy. It is essential that they be conducted properly and be capable of being validated. The proposed Good Laboratory Practice regulations make enforceable that which had been left out seven years ago.

PRACTICAL AID IN COMPLYING WITH THE GLP REGULATIONS

If you should need help, then help is available to you from many sources. The EPA will provide such help and advice as is possible. We have specialists in many fields who are conversant with the regulations. The Society of Quality Assurance is an excellent source of information and advice. There are many private contractors who can be employed on contract to help you develop your own quality assurance and compliance programs.

SUMMARY AND CONCLUSIONS

The Good Laboratory Practice regulations came into being as a result of uncovering fraud in the pesticide testing industry. The regulations are a series of management and procedural principles which, if followed, assure both the test laboratory, the test sponsor and the EPA that the test was done properly and that the results can be validated. Vertebrate pesticide efficacy testing, along with several other types of pesticide testing, all formerly excluded from GLP coverage, will likely be included in the expanded GLP regulations recently proposed by the EPA. The regulations are logical and easily followed by test management and test personnel.

If past experience can help to predict the future, the tests conducted in compliance with the proposed GLP regulations will ultimately cost less, be better managed and have less chance of failure or yielding equivocal results.

I wish you well in this the Thirteenth Vertebrate Pest Conference and thank you for inviting me. I will be here for most of the conference and will be pleased to answer your individual or group questions in whatever forum is convenient for you.