UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

April 8, 1995

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Guidelines for Study Rejection Based on GLP Considerations

From: Dan Barolo, Director /s/
Office of Pesticide Programs

To: All Division Directors
Office of Pesticide Programs

The Good Laboratory Practice (GLP) Lab Audit Round Table was asked by former Assistant Administrator Linda Fisher to develop, based upon ongoing case review, a list of GLP violations most likely to lead to study rejection. This was initiated in response to a recommendation from an Audit Report No. E1EPF2-11-0041, *Implementation of the Good Laboratory Practices Program* conducted by the Office of Inspector General (IG).

The IG's report recommended: "Expedite the development of standards for accepting/rejecting laboratory studies based on violations of GLP regulations." Further, in a subsequent memo to Linda Fisher, OPPTS AA, the IG stated: "OCM and OPP officials agree that the standards are needed to determine if a GLP violations is, or is not, a data integrity problem." and "We believe the standards would give a greater assurance to Agency management that concerns which develop during a data audit are appropriately evaluated during the review process. Developing and implementing these standards would also increase the uniformity and consistency of the review process. We believe the development of standards to accept or reject data studies due to GLP violations should be given high priority."

The Round Table has now completed this task. Attached for your use is a list of the Guidelines for Study Rejection Based on GLP Considerations. I believe these guidelines in addition to satisfying the IG's recommendation will provide OPP with useful guidance for our study evaluations.

Another useful purpose of this list could be bor use by OECA, Office of Compliance in their review GLP inspections for violations which could threaten the integrity of a study submitted under FIFRA. Any inspection with at least one Category I violation should be submitted to OPP for automatic regulatory review. Inspections with Category II or Category III violations should be screed by the Round Table. Other inspections without any violations on this list would not need OPP reviews

cc: David Dull, OECA (2225A)

Guidelines for Study Rejection Based on GLP Considerations

(Complied February 4, 1995)

The following items from the Good Laboratory Practice (GLP) regulations should be taken into consideration when assessing the acceptability of a FIFRA study. The items are grouped into three categories.

Category I

These items for consideration would lead to study rejection in almost all cases due to the seriousness of the violation(s) and the inability of the Agency to rely on the validity of the data.

1. Refusal to permit inspection [40 CFR 160.15];

2. Evidence data are falsified [40 CFR 160.33(b); 160.35(b)(6); 160.185(a)(9); 18 U.S.C. 100];

3. Evidence that the Final Report falsely reflects the raw data to the extent that conclusions in the submitted study could possibly be invalid [FIFRA Section 12(a)(2)(Q) and 40 CFR 160.185];

4. Evidence that there was no quality assurance during the conduct of a study conducted after October 16, 1989 [40 CFR 160.35];

5. Failure of the Quality Assurance Unit to conduct study specific inspections or maintain records of studies conducted after October 16, 1989 [40 CFR 160.35];

6. Evidence that a study was conducted without a sponsor approved written protocol [40 CFR 160.120];

7. Evidence that test control or reference substance characterization data are falsified or confused with other test material; or evidence that substances may have been contaminated or adulterated and subsequently used in the conduct of a study [40 CFR 160.107; 40 CFR 160.47; 40 CFR 160.105, 40 CFR 160.113];

8. Failure to record and archive critical raw data, including study specimens/tissues; inability to reconstruct a study due to the absence of raw data that the Agency has required and/or relied upon to make a regulatory decision [40 CFR 160.130; 40 CFR 160.195];

9. Use of unhealthy test animals or failure to maintain test animal care facilities to the extent that conclusion in the submitted study are likely to be unreliable [40 CFR 160.43; 40 CFR 160.90(c)]

Category II

This category includes items which would allow the individual disciplines to question the scientific conclusion made in the study. However, the registrants may be able to submit additional data which demonstrates that the violations do not affect the outcome of the study should not be rejected.

10. Failure to characterize or appropriately define the test, control, or reference substances [40 CFR 160.105]

11. Failure to engage qualified or properly supervised individuals in the conduct of a study [40 CFR 160.29(a); 40 CFR 160.33]

12. Failure to adequately inspect, clean, maintain, test, calibrate and/or standardize equipment and/or maintain proper records of these activities [40 CFR 160.63.(a);

13. Failure to provide appropriate animal identification of the test system in a toxicity study allowing potential confusion as to test group designation [40 CFR 160.90 (d)];

14. Failure to use test systems tat are free of any disease condition that might interfere with the conduct or interpretation of the study [40 CFR 160.90(c)];

15. Evidence that the testing conditions deviated grossly from the sponsor approved protocol to the extent that conclusions in the submitted study are likely to be unreliable [40 CFR 160.43; 40 CFR 160.120, 40 CFR 130];

16. Evidence that the sponsor approved protocol was significantly inadequate or that a study contains gross, unauthorized/undocumented deviation from the sponsor approved protocol [40 CFR 160.120 and 40 CFR 160.130];

Category III

GLP items concerning the study and facility management are included in this category. These violations indications indicate lack of control over the study (and testing facility) by the sponsor. While serious in nature, OPP may still be able to accept the study if sufficient raw data exist to reconstruct the study to ensure the validity of the data and the conclusions. These violation should warrant careful monitoring of any future studies submitted by the registrant and/or testing facility

17. Gross failure to maintain Standard Operating Procedures; failure to follow laboratory SOPs without documentation in the raw data and/or written authorization from the Study Director [40 CFR 160.81; 40 CFR 185(a)(14)]

18. Failure to submit with the final study report a statement specifying the dates of the Quality Assurance inspections and the findings reported to management and the Study Director [40 CFR 160.35(b)(7)];

19. The Study Report does not include a description, or the description is inadequate of the methods used [40 CFR 160.185 (a)(6)], the test system used [40 CFR 160.185(a)(7)], the dosage information [40 CFR 160.185.(a)(8), transformation, calculations or operations performed on the data [40 CFR 160.185(a)(11)], or statement by the quality assurance unit as described in 160.35(b)(7) [40 CFR 160.185(a)(14)]; Study report not signed and dated by the Study Director [40 CFR 160.185(b)];

20. Failure to notify verbally and in writing the person performing a study under contract of the applicability and legal demands of the GLPs [40 CFR 160.10];

21. Failure to keep personnel records, such as summary of training, experience and a job description for each individual engaged in or supervising the conduct of a study, so that an adequate determination of the qualifications of the employee can not be made [40 CFR 160.29];

22. Falsification of personnel records [18 U.S.C. 1001];

23. Failure to designate a Study Director, that is, one person in charge of the overall study [40 CFR 160.31].