UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

August 3, 1993

MEMORANDUM

SUBJECT: Interpretation of the Good Laboratory Practice (GLP) Regulation

GLP Regulations Advisory No. 65

FROM: David L. Dull, Director
Laboratory Data Integrity Assurance Division

TO: GLP Inspectors

Please find attached an interpretation of the GLP regulations as issued by the Policy & Grants Division of the Office of Compliance Monitoring. This interpretation is official policy in the GLP program and should be followed by all GLP inspectors.

For further information, please contact Francisca E. Liem at FTS-398-8265 or (703) 308-8265.

Attachment

cc: M. Stahl
C. Musgrove

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

OFFICE OF
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Dear

This is in response to your letters Or March 18 and April 1, 1993, in which you requested assistance in dealing with a problem that you believe exists in the Federal Fungicide, and Rodenticide Act (FIFRA) Good Laboratory Practice Standards (GLPs).

In your March 18 letter you stated that GLP standards regarding characterization of test substances and mixtures (40 C.E. ' 160.105 and 160.1131 are routinely not complied with during acute toxicology studies. As examples, you cited two types of acute studies which cost, respectively, $5,000-5,500 and $1,300. You claimed that analytical chemistry could cost over $60,000, with 67% of this money spent on test article mixtures and positive controls.

You felt that these cost issues affect compliance with GLPs. Further, you state that registrants “do not routinely” analyze positive controls or mixtures for acute studies, and that although “everyone knows they are deviating” from compliance it is not always noted on the compliance statement. You asked whether EPA would consider amending GLPs to address the problems with respect to acute studies, and indicated that you would be willing to meet with me to discuss the issues in more detail. Although you did not say what changes you would propose to make to the rule, such change would presumably relieve acute studies of some of the characterization requirements.

Your April 1 letter vas written as a follow up to your March 18 letter. In your April L letter you stated that you had further consulted with a chemistry contracting laboratory and with Steve Howie, of my staff. You stated that you believed that part of the problems was that use of EPA product chemistry guidelines to provide characterization data for toxicology studies Sou stated that a possible solution Would be to allow pared down versions of these guidelines for the purposes of characterization under 40 CFR 160.105 and 160.113.

Also in your April l letter you inquired about a difference between the characterization requirements of the FDA's regulations at 21 CFR 58.105(a) and the FIFRA GLPS at 40 CFR 160.105(a). The FDA GLPS provide that marketed products which are used as control articles may be characterized “by their labeling”. The EPA regulations contain no such clause.

The GLP requirements of 40 CFR 160.105 and 160.113 differ significantly from the requirements for testing product chemistry data requirements at 40 CFR 158.150-158.190 and the product chemistry testing provisions as found in the series 63 guidelines. For example the GLP provisions at 40 CFR 160.105(a) require that certain parameters be characterized to appropriately define each batch of the test control and reference substances The testing necessary to appropriately define substances may differ depending on the substance and the nature of the study for which it is being used. In most cases it should be possible to appropriately define test control and reference substances with considerably less testing than is normally done to meet product chemistry guidelines Your opinion that a pared down version of product chemistry testing guidelines could provide acceptable data is therefore correct. However, please note that since the characterization needs may differ between substances and studies a pared down procedure which is adequate in one circumstance may not be adequate in another. Each situation must be evaluated on the basis of its own merit to determine the level of testing needed to adequately characterize the substance and mixture.

We are concerned about the instances of noncompliance with the regulations which you claim are occurring. If as you state persons do not routinely analyze the positive controls or mixture which they use in their studies they are in noncompliance with the regulations and subject to potential study rejection as stated at 40 CFR 160 lt(a). Those who fail to correctly record the compliance status on the submitted statement of compliance or noncompliance are subject to enforcement actions as stated at 40 CFR 160.17(b).

Finally, please note that the difference between FDA's GLP regulations at 21 CFR 58.105(a) and EPA's GLP regulations at 40 CFR 160.105(a), with respect to the use of label information to characterize certain control articles, has to do with different data requirements between the two Agencies. Tests involving the use as controls of products marketed by competitors are commonly required by FDA but not by EPA.

If you have any questions concerning this response, please contact Steve Howe of my staff at (703) 308-829.

Sincerely yours,

/s/John J. Neylan III, Director,
Policy and Grants Division
Office of Compliance Monitoring(EN-342)

cc: David L. Dull
GLP File