



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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

December 4, 1992

MEMORANDUM

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

GLP Regulations Advisory No. 55

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 (703) 308-8333.

Attachment

cc: M. Stahl
C. Musgrove



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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Dear

This is in reply to your letter of August 3, 1992, in which you requested clarification concerning the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Good Laboratory Practice Standards (GLPS). In your letter you raised three questions related to test, control, and reference substance characterization requirements. Your questions are presented and responded to separately below.

1. Samples of the dosage forms, administered to animals on GLP studies, are sent to analytical laboratories for determination of concentration and uniformity as required at 40 CFR 160.113(a)(1). Must these analyses be conducted under full GLP compliance (i.e., 40 CFR 160.135(a)) or under limited GLP compliance (i.e., 40 CFR 160.135(b))?

When mixtures of test substances in carriers must be analyzed in order to meet the requirements of 40 CFR 160.113(a)(1), such analyses must be performed under GLPS. However, this is because these analyses are being performed as part of a greater study which is under GLPS. The analyses themselves are not "studies" and hence the distinctions provided at 40 CFR 160.135 for physical and chemical characterization studies do not apply.

Since the analysis is part of a larger study, all of the GLP requirements relevant to that study apply to the analytical work. However, where those requirements are complied with by the "greater study" it may not be necessary to duplicate compliance in detail for each analysis.

2. On occasion, a large container (10 kg or more) of a particular compound is received in an individual container. For ease of handling, the bulk compound is transferred to smaller containers. Compound is then taken from these containers (designated one container at a time) to supply "working bottles" for individual studies. Must all of these "storage" containers be retained for the duration of the study or is it only necessary to retain the "working bottles" which are assigned to individual studies?

The regulations at 40 CFR 160.105(c) state that "storage containers shall be assigned to a particular test substance for the duration of the study." This requirement refers to all container(s) used during a study to store that test substance which is used in

the study. If an adequate, smaller test substance storage container is assigned before the study commences, and that container is where all of the test substance used in the study is stored throughout the study, the container retention requirements would apply to that container. It would be necessary to retain this container throughout the study but it would not be necessary to keep larger bulk containers from which material was transferred before the study began.

Note that if a larger container is used to refill the smaller container during the study, that larger container would be considered to be a test substance storage container for that study. Similarly, if test substance is drawn from the smaller container for use in additional studies, the smaller container would be required to meet retention requirements for all such studies (i.e., it must be retained until the last study is completed.) The requirements at 40 CFR 160.105(c) are not intended to apply to "working bottles" which are used only for transfer of test substance from a storage container for its direct use in the study. However, if such "working bottles" are in fact used for test substance storage they must comply with the requirements at 40 CFR 160.105(c). If there is any doubt concerning the status of such working bottles, presume that compliance is required. Note that this would not preclude refilling working bottles during the study from the primary storage container.

3. Must the analytical methods used to determine stability, concentration, and uniformity of mixtures or to characterize test, control, or reference substances be validated?

The GLPS require that certain analyses be performed for characterizing test, control, and reference substances and for characterizing mixtures. To the extent that such analyses must be required under a particular study, they must comply with all relevant GLP standards. While "method validation" is not a specific regulatory requirement under the GLPS, if there is insufficient documentation to support study characterization requirements, including inadequate documentation supporting the validity of the methods used, the characterization data may be considered invalid or incomplete.

If you have any questions concerning this response, please contact Steve Howie of my staff at (703) 308-8290.

Sincerely yours,

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