



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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

June 28, 1991

MEMORANDUM

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

GLP Regulations Advisory No. 36

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 398-8333 (703) 308-8333.

Attachment

cc: C. Musgrove



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Dear

This is in response to your letter of January 15, 1991, requesting information on the EPA interpretation of current Good Laboratory Practice Standards (GLPs) with respect to retention of mutagenicity test specimens. You asked for a formal determination of whether your client's mutagenicity specimens need to be retained.

Specifically, your client, was archiving 782 petri dishes and 362 slides in conjunction with three mutagenicity tests. Final reports were submitted to EPA on July 27, 1988. You stated that the only response to the submission of the data to date has been the EPA acknowledgment that the data passed the formatting screen and had been assigned MRID numbers.

Please refer to the preamble of the final rule amending the GLPs (54 FR 34066, August 17, 1989, enclosed). A commentor had asked what the term "quality assurance verification" meant. EPA responded that specimens must be retained until the quality assurance unit assures that discarding the specimens does not negatively impact the integrity of the study. Therefore, once the testing facility quality assurance unit determines that the discarding of the specimens will not negatively impact the integrity of the study, the materials in question may be discarded. There is no need to await the final EPA approval of the report or EPA inspection, under current EPA GLP requirements.

If you have any questions on this response, please contact Virginia Lathrop of my staff at 703/308-8292.

Sincerely yours,

/s/ John J. Neylan III, Director,

Policy and Grants Division
Office of Compliance Monitoring

Enclosure

cc: David L. Dull
GLP File

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 160

[OPP-300165A; FRL-3518-2]

RIN 2070-AB68

Federal , Fungicide and Rodenticide Act (FIFRA); Good Laboratory Practice Standards

AGENCY: Environmental Protection Agency (EPA)

ACTION: Final rule.,

SUMMARY: EPA is issuing this final rule that expands the regulations to require compliance with Good Laboratory Practice (GLP) standards for testing conducted in the field and for such disciplines of testing as ecological effects, chemical fate, residue chemistry, and, as required to be submitted by 40 CFR 158.640, product performance (efficacy testing). EPA is amending these regulations to ensure the quality and integrity of all data submitted to EPA in conjunction with pesticide product registration, or other marketing and research permits. EPA is also amending the FIFRA GLP standards to incorporate many of the changes made by the Food and Drug Administration (FDA) to its GLP regulations (52 FR 33768, September 4, 1987; 21 CFR Part 58).

DATE: Effective: This rule becomes effective on October 16, 1989. Compliance: All studies conducted, initiated, or supported after the effective date of this rule shall be subject to these regulations.

FOR FURTHER INFORMATION CONTACT: Stephen Howie, Office of Compliance Monitoring (EN-342), Rm. E-707B, 401 M St., SW., Washington, DC 20460, Telephone: (202) 382-7825. **SUPPLEMENTARY INFORMATION** Following is an index to the remainder of this preamble:

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I. Introduction

EPA is amending the FIFRA GLP standards (40 CFR Part 160) to incorporate many of the changes made by the Food and Drug Administration to its GLP regulations.

A. Legal Authority

These standards are promulgated under the authority of sections 3, 4, 5, 6, 8, 18, 24(c), and 25(a) of FIFRA, 7 U.S.C. 138 et seq., as amended, sections 408, 409, and 701 of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 301 et seq., and the Reorganization Plan No. 3 of 1970.

B. Background

EPA originally published FIFRA GLP standards in the Federal Register of November 29, 1983 (48 FR 53946), which were codified as 40 CFR part 180. At the same time, EPA published GLP standards applicable to testing required under the Toxic Substances Control Act (TSCA, 48 FR 53922, 40 CFR part 792). These regulations were promulgated in Response to investigations by EPA and FDA during the mid-1970s which revealed that some studies submitted to the Agencies had not been conducted in accordance with acceptable laboratory practices. Some studies had been conducted so poorly that the resulting data could not be relied upon in EPA's regulatory decision-making process. For instance, some studies had been submitted which did not adhere to specified protocols, were conducted by under qualified personnel and supervisors, or were not adequately monitored by study sponsors. In some cases results were selectively reported, under reported, or fraudulently reported. In addition, it was discovered that some testing facilities displayed poor animal care procedures and inadequate record keeping techniques. The FIFRA GLP standards specify minimum practices and procedures which must be followed in order to ensure the quality and integrity of data submitted to EPA in support of a research or marketing permit for a pesticide product.

When EPA published its final FIFRA and TSCA GLP standards in the Federal Register of November 29, 1983, EPA sought to harmonize

the requirements and language with those regulations promulgated by the FDA in the Federal Register of December 22, 1978 (43 FR 60013), and codified as 21 CFR part 58. Differences between the two Agencies' current GLP regulations exist only to the extent necessary to reflect the Agencies' different statutory responsibilities under TSCA, FIFRA, and the Federal Food, Drug and Cosmetic Act (FFDCA). Similar to the FDA GLP regulations, the FIFRA and TSCA GLP standards delineate standards for studies designed to determine the health effects of a test substance; however, the TSCA GLP standards also contain provisions related to environmental testing (i.e., ecological effects and chemical fate).

Compliance with EPA's FIFRA and TSCA GLP standards has been monitored through a program of laboratory inspections and study audits coordinated between EPA and FDA. Under an Interagency Agreement originated in 1978, FDA carries out GLP inspections at laboratories which conduct health effects testing. EPA primarily performs GLP inspections for environmental laboratories and conducts data audits for health effects and environmental studies.

After a thorough review of its GLP regulations and compliance program, FDA concluded that some of the provisions of the GLP regulations needed to be clarified, amended, or deleted to reduce the regulatory burden on testing facilities. Accordingly, FDA revised its GLP REGULATIONS in the Federal Register of September 4, 1987 (52 FR 33768). These GLP revisions are intended to simplify the regulations without compromising study integrity.

EPA agrees with FDA that many provisions of the GLP regulations can be streamlined without compromising the goals of the GLP standards. Therefore, EPA is amending the FIFRA GLP standards to incorporate many of the changes made by FDA to its revised GLP regulations. In addition, EPA is expanding the scope of the FIFRA GLP standards to include the environmental testing provisions currently found in the TSCA GLP standards. EPA's revision to the FIFRA GLP standards also extends their scope to include product performance data (efficacy testing) as currently required to be submitted by 40 CFR 158.640. In summary, the FIFRA GLP standards will allow EPA to ensure the quality and integrity of all data submitted in support of pesticide product research or marketing permits. Elsewhere in this Federal Register, EPA is making similar changes to the TSCA GLP standards.

C. Consistency With FDA GLP Regulations .

It is EPA's policy to minimize the regulatory burden on the public which might arise from conflicting requirements promulgated under different regulatory authorities. In keeping with this policy, the final FIFRA 1983 GLP standards, 40 CFR part 160, followed the format and, with few ((34053)) exceptions, the wording of FDA's final GLP regulations, 21 CFR part 58. Differences between the EPA and FDA GLP regulations were based upon varying needs and responsibilities under each Agency's regulatory statutes. This revision to the FIFRA GLP standards follows this same policy by conforming to many of the changes FDA made to its GLP regulations, published in the Federal Register of September 4, 1987 (52 FR 33768). EPA has varied from FDA's revised GLP REGULATIONS only when

necessary due to EPA's statutory responsibilities. The most significant differences between the EPA and the FDA revised GLP regulations are the scope of the testing and test systems affected.

More specifically, EPA is requiring compliance with the FIFRA GLP standards for all studies submitted to EPA which are intended to support pesticide product research or marketing permits. Under the 1983 FIFRA GLP regulations EPA only required GLP compliance under FIFRA for health effects testing. However, unlike FDA, testing required by EPA in support of research or marketing permits may include ecological effects, environmental and chemical fate, and efficacy (as stipulated by 40 CFR 158.640 Product performance data requirements), as well as health effects testing. Therefore, in an effort to attain consistency in the quality and the integrity of all data submitted to the Agency, EPA has determined that it is necessary to expand the scope of the FIFRA GLP standards to require that all types of testing which are used to obtain data in support of research or marketing permits be conducted in accordance with the amended GLP standards that are required to be submitted under 40 CFR 158.640.

EPA's amended FIFRA GLP standards also vary from FDA's in their coverage of testing conducted in the field. To ensure the quality and integrity of all data submitted in support of research or marketing permits, EPA believes that GLP standards must apply whenever data collection occurs. Because many of the test data required by EPA under FIFRA are developed in the field, or more accurately in outdoor laboratories (i.e., ground water studies, air monitoring studies, degradation in soil, etc.), EPA is including field testing within the scope of the standards.

EPA's FIFRA GLP standards also differ from FDA's in the scope of the requirements provided for test system care facilities, test system supply facilities, and test system care. Because testing required by FDA is focused on health testing, in which animals are the central test system, it is appropriate for FDA's GLP regulations to focus on requirements for appropriate animal care facilities (21 CFR 58.43), adequate animal supply facilities (21 CFR 58.45), and proper animal care (21 CFR 58.90). However, the broad range of testing required by EPA may involve plants, soils, and microorganisms, as well as animals, for the primary test systems. To ensure the quality and integrity of all data submitted to EPA, §160.43 Animal care facilities, §160.45 Animal supply facilities, and §160.90 Animal care are being expanded to cover facilities, handling, and care of all test systems. Accordingly, EPA is retitling these sections as follows: §160.43 Test system care facilities, §160.45 Test system supply facilities, and §160.90 Animal and other test system care. Further, in most instances, EPA is replacing the term "animal," which is currently used in the FIFRA GLP standards, with the broader term "test system." Specifically, this change occurs in §§160.43, 160.45, 160.81, 160.90 and 160.120. These changes are further discussed in Unit II. of this preamble.

The remaining differences between the EPA and FDA GLP regulations are described in the preamble to this final rule and

the preamble to the FIFRA GLP standards, published in the Federal Register of November 29, 1983 (48 FR 53946). EPA has coordinated this final rule with FDA and has considered public Comments on the December 28, 1987 EPA proposal (52 FR 48920).

D. Publication of the Complete Rule

The entire FIFRA GLP rule (40 CFR part 160) is published in this notice to simplify interpretation and facilitate the use of this notice by the regulated community. The following lists the sections of 40 CFR part 160 that were changed from the 1983 rule:

Section affected	Changes
160.3	"Batch," "Control substance," "Study," and "Test system," revised; "Test substance or mixture," removed; "Carrier," "Experimental start date," "Experimental termination date," "Reference substance," "Study completion date," "Study initiation date," "Test substance," and "Vehicle,"
160.29	(d), (e), and (f) revised
160.31	(b) and (d) revised
160.35	(a), (b)(1), and (3) revised; (e) removed
160.41	Revised
160.43	Revised
160.45	Revised
160.47	Revised
160.49	Revised
160.53	Removed
160.61	Revised
160.63	(b), revised
160.81	(b)(1), (2), (3), (5), (6), and (12) and © revised
160.90	Revised
Subpart F	Heading revised
160.105	Revised
160.107	Heading and introductory text revised
160.113	Revised
160.120	(a) revised
160.130	(d) and (e) revised
160.135	Added
160.185	(a) (4) and (5), and © revised
160.190	(a) and (e) revised
160.195	© revised; (I) added

II. Summary of Comments and Responses

EPA received 43 Comment letters: 24 from manufacturers of pesticide products regulated by EPA, 8 from associations, 10 from testing or consulting laboratories, and 1 from another government agency. The majority of the Comments supported the proposed changes, although numerous suggestions were made for additional revisions to parts of the 1983 FIFRA GLP regulations not subject to this rulemaking or modifications to the proposed changes. Comments that raised important policy questions, suggested modification to the essence of the proposed regulation, or required an individual Response, are discussed below. Comments addressing changes to the GLP standards that were not proposed are not the subject of this rulemaking. However, all Comments made have been placed in the public record.

A. General Provisions

1. *Scope - Comment*: EPA should specify exactly what categories of studies (especially efficacy) are covered under the revised GLP regulations since they are discussed in the preamble and will not appear at 40 CFR part 160 when the final rule is published.

Response: EPA intends GLP standards to cover all types of studies required to be submitted and does not feel it necessary to list each type.

Please note that EPA is developing additional product performance regulations. EPA plans to consider the impact that GLP standards will have on these new product performance requirements to determine if the full scope of the GLP standards should apply to studies performed to fulfill these requirements. Unless the GLP rule is modified to specifically exclude certain parts of product performance regulations, the full GLP rule will apply ((34054)) to all existing and prospective product performance studies required under 40 CFR 158.640.

2. *Definitions - a. Batch*. The definition of "batch" is expanded to include reference substances. This was an omission in the proposed rule that is corrected in the final rule to maintain consistency with the use of the term in §160.105 (a).

b. *Carrier - I. Comment*: The word "systems" should replace the word "organisms" in the definition of "Carrier," to be consistent with the term "test system."

Response: EPA concurs with the suggestion. To be consistent with the definition of "test systems," the word is changed accordingly.

ii. *Comment*: EPA should revise the list in parentheses that follows the word "material" in the definition of "carrier" to make it all inclusive.

Response: EPA has decided to add the phrase "including but not limited to ***", to indicate that the list provides examples and is not meant to be all inclusive.

c. *Control substance - I. Comment*: Since "material" conveys a broader description than "substance" and is already used in

definitions for "carrier," "control substance," and "reference substance." "chemical substance" should be changed to "chemical material" in the definition of "control substance."

Response: EPA does not believe that a change in terminology is needed to broaden the definition since the term "material" is already included in the present definition. The term "substance" must also be retained to maintain consistency with TSCA and the TSCA GLP standards.

ii. *Comment:* EPA should delete the phrase "for no-effect levels" in the definition of control substance. The definition as written is too narrow and excludes analytical chemistry (e.g., chemical fate, residue chemistry) operations where the term "control" has a meaning distinctly different from biological effects.

Response: Since the purpose of the analytical control is to establish eventually that none of the materials administered to the test system interfere with identification of the test substance and its degradate(s) and metabolite(s), EPA agrees that the terminology is too limiting and is replacing the phrase "for no effect levels" with the phrase "for known chemical or biological measurements." The definition now reads: "Control substance means any chemical substance or mixture, or any other material other than a test substance, feed, or water, that is administered to the test system in the course of a study for the purpose of establishing a basis for comparison with the test substance for known chemical or biological measurements."

d. *Experimental start and termination dates* - *Comment:* These dates would be difficult to predict, especially for field studies, because they would be subject to natural or man-made conditions that cannot be controlled or anticipated. Since the dates would be subject to change, many protocol amendments would be required, thereby creating an undue administrative burden.

Response: The experimental start and termination dates specified in the protocol are merely proposed dates. Therefore if the actual experimental start or termination date is different from the proposed dates no protocol amendment shall be required.

e. *Reference substance* - *Comment:* If EPA intended the term "reference substance" to include analytical and calibration standards, then several other sections of the proposed rule which mention "reference substance," would also require the same types of records to be kept for analytical standards. This would constitute an excessive burden on management which would require maintaining various records that do not add any value to the study.

Response: The definition of reference substance is intended to include analytical reference standards. Therefore, EPA has modified the definition of "reference substance," as follows: "Reference substance means any chemical substance or mixture analytical reference standard, or material, other than a test substance feed, or water, that is administered to, or used, in analyzing the test system in the course of a study for purposes of establishing a

basis for comparison with the test substance for known chemical or biological measurements." EPA believes this change eliminates any ambiguity in the definition.

EPA disagrees that inclusion of analytical reference standards in this part constitutes an excessive documentation burden or adds no value to the study. Documentation which supports defining analytical reference standards should not require excess paperwork since common laboratory practices already require assurance of the validity of standards in order to make certain that the measurements are accurate.

f. *Study - I.* Comment: "Basic exploratory studies" are excluded from GLP standards, but the results of such studies may be required to meet GLP standards, if included in support of research or marketing permits.

Response: EPA does not wish to discourage basic exploratory testing and does not explicitly require GLP standards for such tests even if the data are later submitted to EPA. However, if the data are to be used in sole support of a marketing permit such non-GLP studies may not be accepted. GLP standards are required when data is developed in the context of a study that is required to be submitted to EPA in support of a research or marketing permit. Where GLP standards were not followed in the case of a study performed with the original intent of exploratory testing, a GLP compliance statement should be included in the study report to indicate this.

ii. *Comment:* It is not clear what constitutes separate studies and what studies could be included under a single protocol. Specifically, is a test system located in several different geographic allocations a single study or would each location by means of its particular requirements need to be a separate study?

Response: The protocol defines what the study entails. Therefore, if the test system for a specific study is located in different geographical locations, the protocol will describe the study as being located at the different sites. EPA is adding the phrase "at one or more test sites" to the definition of "study" to clarify the intent that more than one field site may be included in one study.

iii. *Comment:* The proposed definition of study would imply that each determination such as stability, solubility, octanol water partition coefficient, volatility, persistence, and other data point determinations would be separate studies with concomitant requirements such as protocols and quality assurance unit (QAU) inspections.

Response: EPA intends that QAU inspections as listed in § 160.35 be conducted at intervals adequate to ensure the integrity of the study for each determination such as stability solubility, octanol water partition coefficient, volatility, persistence, and other data point determinations. However, if done as part of a larger study, then these determinations are covered under the larger study's protocol or standard operating procedure (SOP). If they are submitted to EPA as studies unto themselves, then they do require their own protocols.

iv. *Comment*: An experiment such as product chemistry which does not involve a test system cannot be considered a "study" and therefore would not be covered by GLP standards.

((34055)) *Response*: Studies designed to determine the physical or chemical characteristics of a test substance are included within the scope of these regulations. Therefore, EPA intends to include product chemistry experiments in the definition of "study-" This change is consistent with the definition of the term "study" as it now appears, and as it appears in the TSCA GLP standards at 40 CFR Part 792. In the case of product chemistry experiments, the test substance itself may be the test system.

v. *Comment*: The addition of the term "or in the environment" to the definition of "study" indicates that the change extends the proposed regulations to field studies. While it is necessary to ensure the validity of all data collected, the variety and special requirements of field research have not been addressed in the new rules.

Response: These regulations are intended to apply to all studies required to be submitted under FIFRA, including those conducted in the field. EPA recognizes that field studies vary and have special requirements, but believes that the development of protocols and SOPs by the testing facility provides adequate flexibility in this respect.

vi. *Comment*: Why are metabolism, product performance, environmental and chemical fate, persistence and residue listed in the definition of "study", but not toxicology data or data to assess hazards and product chemistry.

Response: The list is not meant to be limiting in any way. Data to assess toxicology, hazards and product chemistry are included under "effects" and "other characteristics" under the new definition of "study".

vii. *Comment*: "Prospectively" should not be deleted from the definition of study. If the essence of GLPs requires a carefully planned study and the proposed rule is very strict about documentation that must be completed prior to the experimental start date, how can the GLP standards also apply to studies that were generated without a protocol! or advance planning, such as epidemiology

Response: EPA disagrees with the Comment. The term prospectively is deleted because EPA wishes all studies, including epidemiological studies where past exposure to a study population is determined or estimated retrospectively, to be performed under GLP standards. EPA recognizes that in such studies data used may not have been generated in conformance with FIFRA GLP standards. However, it is EPA's position that the epidemiological study itself can be conducted and submitted to EPA in accordance with the GLP standards. Retrospective aspects of such studies that are not performed according to GLP standards, for example, test system treatment, should be identified in the compliance statement submitted with the study report.

In addition, the types of studies potentially not covered by these regulations were expanded in the definition of "study" to include experiments involving test methods.

g. *Study initiation and completion date - Comment:* EPA should delete the definition of "study initiation date" and "study completion date," since these terms were not defined in the 1983 GLP standards. The dates will be included in the protocol and final report and do not need further emphasis.

Response: EPA believes that it is necessary to define the terms to differentiate them from "experimental start and termination" dates. These terms indicate the dates on which specific milestones occur during a study. The definition is necessary to clarify EPA's requirements, and to ensure consistency with FDA's GLP regulations (52 FR 33780).

The phrase "close of the study" as used in g 160.33(f), and the phrase "study is completed" as used in §160.195(b)(3) both refer to the "study completion date." Therefore, as of the study completion date: (1) Under §160.33(f), the study director must ensure that all raw data, documentation, protocols, specimens, and final reports are transferred to the archives; (2) after this date under §160.185(c), corrections or additions to the final report must be in the form of an amendment by the study director under the procedures specified in that section; and (3) in the applicable situations described in § 195(b)(3) records must be maintained for a period of at least 2 years following the study completion date.

Furthermore, the phrase "study is initiated" as used in §180.31(a), and the phrase "study was initiated" as used in §160.35(b)(1) would refer to the "study initiation date." Therefore, as of the study initiation date: (1) Under §160.31(a), the testing facility management would designate a study director; (2) under §160.35(b)(1), the study would be entered on the master schedule sheet by the QAU; and (3) under §160.120(b), after this date all changes or revisions in the protocol would be documented, signed by the study director, and dated. EPA also expects that as of the study initiation date, under §160.31(e), the testing facility management would have ensured that personnel, resources, facilities, equipment, material, and methodologies are available as scheduled.

h. *Test system - Comment:* What constitutes the "test system" in tests of pre-emergent herbicides, soil pesticides, and product chemistry studies?

Response: The definition of "test system" includes the statement that it is "* * * any * * * chemical or physical matrix * * *", including subparts thereof that are treated with the test, control, or reference substance and also appropriate components of the system that are not treated. Therefore, test systems may include the soils that pesticides are applied to, and in the case of product chemistry, the test system may be the test substance itself.

EPA is including the term "reference," which was inadvertently omitted from the definition as it appeared in the proposed rule. In addition, EPA is replacing "e.g." in the parenthetical with "including but not limited to" in order to clarify that it is not our intent for the list to be all encompassing.

I. *Vehicle - Comment:* The definition of "vehicle" serves to clarify the GLP standards, but there has been no confusion based on

the current standards and this change is contrary to EPA's stated objective of being consistent with FDA's GLP regulations.

Response: EPA believes that clarification is needed. The EPA GLP standards cover a larger number of types of studies and the need for clarification of the meaning of potentially ambiguous terms is greater.

B. Organization and Personnel

1. *Testing Facility Management - Comment:* The specific requirement to document the replacement of the study director as raw data should be retained. The "master schedule" should not be considered "raw data" as was indicated in the preamble (52 FR 48923) to the proposed rule.

Response: EPA deleted the requirement that the replacement of a study director must be documented as "raw data" to conform to the revised FDA GLP regulations. This is because replacement of the study director must be reflected on the master schedule sheet, which is a study record that must be retained.

In addition, the term "reference," which was inadvertently omitted in the proposed rule, has been added to §160.31(d).

2. *Study Director - Comment:* Archiving the study records within a "reasonable period" after the study completion date, instead of at the close of the study as required by §160.33(f), would not impact on the integrity of the records.

((34056)) *Response:* EPA believes that the requirement that all raw data, documentation, protocols, specimens, and final reports be transferred to the archives at a definitive time, i.e. the study completion date, is necessary. This assures an intact audit trail for the study.

3. *Quality assurance unit - I. Comment:* A QAU that is entirely separate from and independent of the personnel engaged in the conduct of the study creates an unjustified financial burden on some facilities. In some cases it would be impossible to establish a completely independent QAU with qualified personnel.

Response: As stated in the proposed rule (52 FR 48920), EPA does not require the QAU to be a fixed, permanently staffed unit whose only functions are to monitor the quality of a study. EPA is only concerned that there be a distinct separation of duties between those personnel involved with the conduct or direction of a study and those personnel performing quality assurance on the same study. Therefore, §160.35(a) prohibits personnel from performing quality assurance activities on their own study. The regulations allow a study director for a particular study to serve as a part of the QAU or as the QAU for a different study. FDA noted (52 FR 33771) that it was aware that many small laboratories could not afford the operation of a permanently staffed QAU. EPA would like to point out that in those situations where there are different individuals performing the quality assurance functions for different studies, each individual is required to maintain that portion of the master schedule sheet which relates to the study

being monitored. For this reason EPA agrees with FDA's conclusion that the separation of functions on a study by-study basis, as permitted in the existing and revised regulations, would provide effective quality assurance. In view of the potential gain to management, to sponsors, and to EPA through the added assurance of well conducted studies, the increased costs are thereby justified. EPA believes that its intent is more clearly indicated by the changes now being made.

ii. *Comment*: EPA should delete the requirement to index the master schedule by test substance, and the QAU should only be required to index the master schedule to facilitate retrieval of the information monitored.

Response: EPA acknowledges that a test facility may have several studies in progress on each test substance that is listed on the master schedule sheet. However, EPA concludes that deleting the requirement to index by test substance would be inappropriate, since the master schedule sheet is the mechanism through which the QAU can assure management that the facilities are satisfactory and there are adequate numbers of competent personnel available to perform the scheduled tasks. Furthermore, §160.31(e) requires that management assure that study materials (e.g., test substances) are available as planned. Therefore, elimination of this requirement would hinder a major function of the master schedule sheet and hamper the conduct of a critical management role.

iii. *Comment*: Laboratory management should have the discretion to determine who enters the data into the master schedule, as long as the required information is listed.

Response: EPA believes that management retains such discretion since it is involved in determining the composition of the QAU and it provides an adequate number of such personnel (§ 160.31(c) and (e)). The QAU is distinguished by training that ensures that QAU functions are properly conducted. As stated above, study personnel may belong to the QAU as long as they are not performing the QAU functions associated with studies they are involved in.

iv. *Comment*: Do all studies conducted by an analytical laboratory have to be listed on a master schedule, or just those studies that will be, or likely be submitted to EPA?

Response: The GLP standards specifically exempt many product chemistry studies as described in §160.135. The master schedule need only list those analytical chemistry studies that will be or will likely be submitted to EPA.

v. *Comment*: The requirement for inspection of each study under §160.35(b)(3) regardless of duration is excessive for the quality assurance needed to address study integrity, especially where studies are performed by highly standardized procedures. The repetitive inspection of these types of studies would consume large amounts of time for both the study personnel and QAU staff. Auditing each study is not necessary to ensure the work is conducted in compliance with the regulations. Random sampling procedures should be allowed in selecting studies and phases of studies to inspect to decrease the work load and resource

requirements of the QAU.

Response: EPA does not believe that a random inspection program would be an appropriate method of evaluating a study. Generally, random sampling provides an adequate means of quality control where analysis involves repetition or identical procedures. However, any assumption that the conduct of one phase of one study would be representative of another would be invalidated by the differences among study personnel and the operations they conduct. Furthermore, this requirement is not intended for all routine studies. Section 160.35(b) is among the exclusions for chemical and physical characterization studies as listed in §160.135(b). In conformance with the revised FDA GLP regulations (52 FR 33780), EPA modified the requirements of §160.35(b)(3) to provide for inspections of a study on a schedule adequate to ensure the integrity of the study. The changes to this section will allow the QAU the necessary latitude to adjust its monitoring activities to meet the individual needs of each study. However, each study, no matter how short, must be inspected at least once while in progress. EPA expects that by allowing the QAU flexibility in designing a reasonable inspection schedule, the goal of ensuring the quality of the study can be best achieved.

vi. *Comment:* EPA indicates in the preamble to the proposed rule (§160.35(e), (52 FR 48923)) that all QAU records will now be routinely available to inspectors. Existing GLP standards treat certain QAU records as confidential, and explicitly state that the only QAU records to be reviewed by EPA auditors would be the master schedule (e.g., the inspection dates, study inspected, the phase or segment of the study inspected and the name of the individual performing the inspection). If QAU records for findings and corrective action are available on an auditor's request, QAUs would lose their effectiveness.

Response: EPA shares the concerns of the Commenters that access to all parts of a QAU inspection would weaken the inspection system, and recognizes the need to maintain a degree of confidentiality. Therefore, records of findings and problems, as well as records of corrective action recommended and taken, are exempt from routine EPA inspections, except under special circumstances as indicated in §160.15. However, EPA maintains that all other reports and records must be easily accessible and made available to EPA and FDA inspectors when requested as indicated in §160.35(c). ((34057))

C. Facilities

1. *General - I. Comment:* Outdoor testing facilities should not be under GLP standards since: (a) Outdoor test facilities will be conducting studies according to approved protocols; (b) ensuring suitability is highly subjective based on the diverse number of possible locations; © there is a concomitant lack of clear standards for determining suitability of locations. Procedures must be specified by EPA regarding the determination of suitability for locations, testing facilities. etc.

Despite best efforts, the choice could always be subject to criticism and even criminal liability based on a good faith

Compliance Statement indicating GLP standards had been followed. Most outdoor testing is done to mimic normal agricultural conditions which are specific for the test substance and use being proposed. Therefore, the determination of whether the size, construction or location of a facility is suitable for a study is a technical issue, and is not within the scope of the GLP regulation and would be considered in the experimental design of the protocol.

Response: In cases where an EPA approved protocol establishes test locations, that protocol would satisfy GLP requirements. EPA considers any site to be the testing facility wherever testing is undertaken to generate data required to be submitted to EPA. The conditions required by the protocol are not necessarily conducive to artificial manipulation in the field, or to other outdoor testing facilities. Therefore, ensuring the suitability of the location of these types of testing facilities is both a valid and necessary part of protocols approved by EPA.

ii. *Comment:* The design of the individual scientist could be dictated by §160.41 since a "testing facility" (definition from §160.3) means "a person who actually conducts a study * * *". The term "test site" should be defined to refer to the actual location of a given "study system. "Testing facility" could then be used as currently defined and refer to an individual (mobile development scientist or scientist working from a testing farm facility).

Response: The definition of "person" in this Part refers to the legal entity responsible for testing~ including organizational units. Consequently, it does not specifically indicate an individual scientist.

2. *Test system care facilities* - I. *Comment:* Instead of expanding the original document to fit all test systems, the old rules should be left as is, and a statement added to cover non-animal test systems.

Response: EPA disagrees with the *Comment* and believes that specific changes of the old rule are necessary to avoid ambiguity concerning the meaning of non-animal test systems.

ii. *Comment:* Section 160.43(a)(2) and (b), (e), (f), (8)~ and (h) should be deleted because EPA has already stated that these GLP requirements will be applicable to all types of testing. It is not necessary to add the four new paragraphs detailing specific requirements of environmental conditions for aquatic organisms and plants.

Response: EPA believes that some test systems, e.g. aquatic, are unique, and for the sake of clarity, they require special treatment in the regulations.

iii. *Comment:* Field studies should be exempted because isolation is not possible in these types of studies.

Response: EPA disagrees and believes that inclusion of field studies poses no unusual burden, since the separation is only required to be "as needed" to ensure "proper separation." If the procedures used are justifiable based on experimental design and documented, then this requirement is met. "Proper separation" in a field study may mean simply that only one crop is planted in the same subplot.

iv. *Comment*: The change in §160.43© is appropriate but the current wording does not require separate disease handling facilities in every case. The proposed change has merit in clarifying the options available to laboratories and the change promotes harmony between EPA and FDA GLP regulations.

Response: EPA agrees with the Comment. In §160.43(c), EPA is deleting the requirement that separate areas be provided in all cases for the diagnosis, treatment, and control of test system diseases. Instead, a change is made so that separate areas are provided "as appropriate." This change is consistent with the September 4, 1987, revised FDA GLP regulations and the revised TSCA GLP regulations.

EPA has made this change to allow laboratories the option of disposing of diseased test systems without also bearing the expense of maintaining separate areas in testing facilities for diagnosis, treatment, and control of disease. Additionally, EPA recognizes that the diagnosis and treatment requirements of §180.43© may not be appropriate when dealing with such test systems as soil, plants, or microorganisms. However, if the decision is made not to dispose of the test system, test system care facilities, as specified in §160.43(c), must be provided.

3. *Test system supply facilities* - I. *Comment*: The first sentence in §160.45(a) should be changed so that plants and plant materials are covered in this section.

Response: EPA believes that since plants and plant materials are covered in § 160.45(b), including them in §160.45(a) is unnecessary.

ii. *Comment*: Change § 160.45(b) by deleting it or expanding it to include tests not confined to the indoor laboratory or greenhouse.

Response: EPA agrees with the Comment and is expanding the wording of §160.45 to emphasize that this section is not intended to be confining. Therefore, §160.45(a) is changed to read "* * * areas where the test systems are located * * *," and §160.45(b) is changed to read "* * * (included but not limited to fields, greenhouses. * * *)."

iii. *Comment*: The addition of the two new paragraphs outlining plant and aquatic facilities to §160.45(b) is unnecessary. These considerations are addressed in §180.41 with the requirement that testing facilities be of suitable construction "to facilitate proper conduct of studies."

Response: EPA maintains that testing facilities as mentioned in §160.41 and test system supply facilities as mentioned in §160.45, are not the same and must be addressed separately.

iv. *Comment*: EPA should delete §160.45(b) introductory text, (b)(1), (b)(2), and © because this information was adequately covered in §160.45(a) and in §160.43, and the facilities they refer to will be addressed in study protocol.

Response: EPA maintains that §160.43 (test system care) is different from §160.45 (test system supply facilities) and must therefore be treated separately.

4. *Facilities for handling test, control, and reference substances*

I. *Comment*: These requirements would severely restrict the ability of efficacy investigators to test their product, since §160.47 would require separation of facilities for test animals and testing material. The real issue for efficacy testing is test substance accountability, which should be a vital part of the efficacy testing protocol, and appropriate records maintained to verify test substance accountability.

Response: EPA notes that similar concerns were raised by Commenters regarding the 1983 rule. The wording "as necessary" was included then to allow latitude in facility design and operation. ((34058)) EPA agrees that other measures, i.e. protocol, SOPs, and appropriate records, must be adequate to demonstrate the integrity of test, control, and reference substances during handling.

ii. *Comment*. Would it be necessary to provide separate sink facilities or separate rooms for mixing of the test, control, and reference substances or for adding water to tank sprayers?

Response: Separate areas are required for receipt, mixing and storage of test, control, and reference substances and their mixtures as necessary to prevent contamination or mixups. The same sink could be used for all work involving mixing provided that the procedures (SOPs) used are adequate to prevent contamination and mixups. Separate areas for receipt and storage and for mixing and storage of test, control, and reference substance as required in §160.47(a)(1), (2)., and (3) does not mandate the use of separate rooms. The areas could be in the same room provided there is adequate space and equipment to provide that contamination and mixup do not occur. This determination should be made on a case-by-case basis.

D. *Equipment*

Maintenance and calibration of equipment

I. *Comment*: The entire section, § 160.63(b) requires unnecessary documentation and/or is vague about what is required, especially for field portions of residue studies. Equipment used in these studies may only be used on an occasional basis, and routine inspection should only be "before use." Requiring calibration and maintenance logs for all equipment involved in generation a residue sample would be prohibitive, would often be forgotten or overlooked and would then be a cause for not meeting audits.

Response: The requirement states that equipment shall be adequately inspected, cleaned and maintained" and "adequately tested, calibrated and/or standardized." This requirement is not changed from the old rule. The laboratory has latitude in defining in its SOPs what is "adequate" unless given specific guidance otherwise (i.e. in test rules or testing guidelines). However, EPA recommends that calibration and maintenance records be available for all equipment used in field studies. This includes equipment used only rarely and rental equipment.

ii. *Comment.* It is better to designate in § 160.63(b) that repair and maintenance will be performed by "qualified personnel" than to require that a person be designated in the written SOP. The requirement for written SOPs in § 160.63(b) causes problems since at many laboratories the equipment used in conducting a study is shared by a number of individuals and the care and maintenance of the equipment is also shared. In the event of equipment failure, a number of laboratory personnel may be capable of repairing or correcting a problem, or in more serious equipment failures, a service representative of the manufacturer may be called. It is therefore difficult and very inefficient to designate specific people to perform each specific maintenance and repair operation.

Response: The definition of "person" as it appears in §160.3(h) is not limited to an individual scientist or technician but includes an organizational subunit. Consequently, the SOP that designates the "person responsible" will be designating a subunit of the testing facility, which could be one or several individuals. This view is consistent with FDA's (52 FR 33774) interpretation and definition of "person." Where duties are delegated in the SOPs, all contingencies may be addressed, including the contracting of service personnel.

iii. *Comment:* Certain pieces of equipment, such as tractors, land preparation and land measuring devices should be exempt from the calibration requirement, as should standard commercially available laboratory ware, such as graduated cylinders, beakers, flasks, etc. Only equipment directly related to application of the test substance, such as sprayers or granular applicators should be listed as requiring calibration. Therefore, §160.63© is not appropriate for field studies.

Response: EPA believes that calibration should be required for the application phase of field studies. However, the method of calibration, and hence the exact equipment to be calibrated, are not specified in GLP standards, as long as the methods and records ensure the quality and integrity of the study. Some equipment, such as graduated cylinders and volumetric Basks are pre-calibrated and do not need to be recalibrated. Equipment directly related to the application of the test substance may require calibration, but application rates may include other parameters. The methods used to measure all parameters inherent in the determination of application rates would have to be adequately calibrated in order to ensure the quality and integrity of the study.

E. Testing Facilities Operation

1. *Standard operating procedures - I. Comment:* There are few standardized tests available to researchers related to novel microbial pesticides. An experimental use permit is required for the evaluation of certain microbials at an earlier stage of research than is required for chemical evaluations. Therefore, it would be very cumbersome to require written SOPs for microbial pesticides, since the methodology may be in a state of flux. It may only be possible to develop SOPs following the completion of a study. If methods of application and assessment need to be modified for each microbial developed, it would be best to affirm that

methods development could be performed in accordance with accepted scientific standards without having SOPs as described in §160.81. EPA is encouraged to take a flexible, case-by-case approach to establishing appropriate GLP standards for a given set of experiments concerning development of microbial pesticides. Allowances could be made for situations in which SOPs are inappropriate, such as in the early stages of field work. These allowances, made in advance of the work, could then be positively affirmed as good laboratory practice, rather than as tolerated, non-compliance with GLP standards. This would alleviate the uncertainty of performing experiments in a scientifically sound fashion, without knowing until the conclusion of the work whether the data would be acceptable to EPA.

Response: EPA agrees that there are special problems associated with the early stage of method development. Method development phases of an experiment are not under GLP standards as has been clarified in the definition of "study" in §160.3. SOPs are thus required for those operations in which all steps have been worked out. However, SOPs are needed to ensure the quality and integrity of all studies performed under GLP standards, for instance, after the method has been developed. There is flexibility in relation to SOPs insofar as changes can occur during the study as long as they are authorized by the study director (and management, if the changes are significant) and documented with raw data. Furthermore, methodology that is not generalized or established sufficiently to be included in SOPs can be defined in the study protocol.

ii. *Comment:* Although unchanged from the old rule, the second half of §160.81(a) should not apply in some cases. The justification for this is as follows: (a) Unforeseen circumstances cannot be authorized; (b) minor deviations do not need authorization by the study director; © people who conduct the studies are required to be appropriately trained and are able to ((34059))make decisions if necessary to deviate from the SOPs; (d) in field studies, deviations from SOPs will occur before the researcher is able to consult with the study director; (e) decisions about deviations from SOPs that are made by field personnel would be based on standard agricultural practices.

Response: EPA disagrees with the suggestion that some deviations do not require authorization by the study director. It is necessary for the study director to authorize deviations from SOPs to ensure that these deviations do not have an adverse impact on the study. SOPs should be written with sufficient flexibility to accommodate field studies by anticipating conditions under which appropriate actions must be taken without the need for authorization by the study director. Standard agricultural practices can be referenced in SOPs as long as this does not lead to ambiguity concerning the appropriate action to be taken in a given situation. If SOPs state the constraints on action and a decision is made within these limits, there is no deviation. This is in concert with FDA's GLP regulations (52 FR 33774) which require that the study director make certain that specified procedures are followed and that all modifications to the procedures in the approved study plan are documented and approved.

iii. *Comment*: Some of the examples of required SOPs provided in §160.81(b) are not applicable to all test systems or study types. For example, "test room preparation" would not be appropriate when conducting field residue studies, and "necropsy of test system or postmortem examination of test systems," would not apply to studies using a chemical or physical matrix as the test system (sterile water, soil, agricultural fields). Furthermore, §160.81© states that, "Each laboratory or other study area shall have immediately available manuals and SOPs relative to the laboratory or field procedures being performed."

Response: EPA agrees that the term "room" in §160.81(b)(1) is inappropriate to many studies and is changing the word to "area" in order to clarify that field studies are included. EPA believes that §160.81(b) should apply in all cases since the purpose of SOPs is to insure the quality and integrity of the data generated in the course of a study as stated in §160.81(a). However, procedures that are not necessary to be performed, such as necropsy in the case of field studies, do not require SOPs.

iv. *Comment*: The term "test systems" should not replace "animals" in §160.81(b)(6) and (7). Although this requirement is useful for preventing or slowing autolysis for toxicology studies, for other studies, such as metabolism, addressing the handling of moribund or dead test systems is not appropriate. In these types of studies, if a test system were moribund or dead, the testing guidelines require the part of the study that was impacted to be repeated. and this requirement is only applicable to animals.

Response: EPA disagrees with the Comment. This rule applies to plants as well as animals.

v. *Comment*: Published literature (e.g., ASTM methods) should be acceptable in §160.81© as an appropriate part of an SOP and not just as a supplement to a written SOP. The written SOP could incorporate the published literature by reference, without having to rewrite the entire procedure.

Response: EPA agrees that it would not be appropriate to rewrite published literature, hence the allowance for SOPs to use it as supplements. The SOPs are still needed to establish the relationship of the method to data collection procedures and needs in the laboratory. While the resulting SOP would still have to be written, it would in effect be abbreviated in that all of the methodology referenced would not need to be rewritten.

2. *Animal and other test system care* - I. *Comment*: Section 160.90(a) should be deleted since the subject is covered in §160.81(b).

Response: EPA recognizes that §160.81(b) requires testing facilities to establish SOPs for animal or other test system care. Section 160.90(a), however, expressly specifies that SOPs shall also cover test system housing, feeding and handling. This section is consistent with FDA's GLP regulations and is not an additional requirement.

ii. *Comment*: Section 160.90(b) should be simplified to provide that test systems be evaluated prior to use but not necessarily isolated. For some studies, such as plant metabolism, isolating the

plants or soil is not appropriate.

Response: EPA disagrees. Isolation is necessary to insure that a test system is free from disease or other conditions that may impact the study. Further, the inclusion of this is consistent with FDA's GLP regulations.

iii. *Comment:* The evaluation of certain test systems according to "acceptable * * * scientific practice" creates some difficulty, particularly for plants, microorganisms, soil and water, since such practices are not defined. "Acceptable" should be deleted regarding scientific practice and the requirement be only that a scientific basis be used in determining appropriateness for testing. In this way, testing facilities would not need to justify or prove their basis to be "acceptable" in ill-defined areas or those in flux.

Response: EPA agrees that the term "acceptable scientific practice" may not be definable when method developments are in flux. The term "acceptable" is retained, but the term "scientific practice" is changed to "scientific methods." This change preserves EPA's intent that rigorous scientific methodology be used without implying that rigid practices be adhered to where they may not appropriately exist.

iv. *Comment:* The requirement under §160.90© that the test area be disease free prior to study initiation is inappropriate for field studies since it would be impossible to declare areas totally disease free under field conditions. Also, one of the objectives of performing studies in the field is to conduct the studies under representative environmental conditions which includes encountered disease and insect pressures, making this part in direct conflict with the study objective.

Response: The requirement is for the test system to be "free of disease or condition that interfere with the purpose or conduct of the study." The current wording therefore provides sufficient latitude for field studies. Furthermore, - EPA does not intend compliance with this provision to require deviation from accepted agricultural practices. If disease and insect pressures are considered to be an integral part of a study, they clearly do not interfere with the purpose and conduct of that study. The test system would therefore not need to be free of them.

v. *Comment:* Section 160.90© should be deleted since the effect of corrective treatment cannot be accounted for in test results.

Response: EPA believes that while the effects of corrective actions taken to isolate and treat disease or signs of disease may complicate interpretation of test results, so might the effects of the disease itself. This requirement for field studies is not inconsistent with its inclusion for laboratory, i.e., toxicology studies.

vi. *Comment:* Markings which identify animals individually, rather than the group as required by g 160.90(d), are needed in many studies with warm-blooded vertebrates in pens, or in the field. For example, precocial young of avian species should be marked individually.

Response: Specific criteria for marking of individuals to meet

study ((34060)) requirements should be addressed separately in the protocol of the study. The requirement in § 160.90(d) addresses the need that test systems be adequately identified to prevent confounding with other test systems. Identification of precocial birds, for example, may be outlined in the study protocol.

vii. *Comment:* The proposed multi species housing under §160.80(e)(1) is redundant to proposed §160.43(a)(1) and is inconsistent with EPA's desire to streamline GLP standards.

Response: EPA disagrees with the conclusion that these sections are redundant. While §160.43(a)(1) states that the facilities shall be sufficient to allow proper separation of species, §160.90(e)(1) refers specifically to test system care within the facilities.

viii. *Comment:* Field studies should be exempt from the periodic testing requirement of § 160.90(8). A bioassay or chemical analysis prior to study initiation should suffice to show that contaminants are not present at levels capable of interfering with the study. The need for prior analysis may even be obviated by documentation of the previous history of pesticide use in the soil according to Standard Evaluation Procedures to ensure that no interfering contaminants are present.

Response: The regulations as written do not require that periodic tests be performed during a study unless there are "contaminants known to be capable of interfering with the study and reasonably expected to be present at levels above those specified in the protocol." If there is no reasonable expectation that a problem exists periodic testing is not needed. An acceptable method to determine this, such as evaluation of the history of pesticide use, should be defined in the protocol or SOPs.

ix. *Comment:* The requirement in §160.90(j) for acclimatization of plants and animals should be deleted, since it is not defined and promotes confusion. Animal toxicology tests would be subject to isolation and separately to acclimatization. Organisms in environmental studies will have been isolated with their health status being evaluated per §160.90(b) and acclimatization would have already been performed as part of the process. This part should be amended to indicate that test organisms be acclimatized to all experimental conditions except the test substance.

Response: EPA believes that the term acclimatization has common meaning that is clear in the context of its usage in the regulation. Acclimatization implies accustoming to experimental, i.e., environmental, conditions other than the actual introduction of the effect (e.g., test substance) to be measured in the experiment. If acclimatization is achieved during the process of isolation, it should be so stated in the protocol and does not require additional technical effort.

In addition, the term "organisms" in §160.90(j) has been changed to "systems." This change is consistent with the intended expansion of GLP standards and was an inadvertent omission in the proposed rule.

F. Test and Control Substances

1. *Test, control, and reference substance characterization - I. Comment:* Requiring stability and solubility before testing would result in a costly burden to the efficacy testing sponsor. The solubility testing portion of this requirement would not cause significant problems, but requiring stability testing to be completed before study initiation could result in significant time and cost burdens.

Response: It is more costly to have to repeat a study because of inadequate solubility or stability in respect to experimental needs. EPA agrees, however, that requiring stability testing to be completed before the study may result in unnecessary delays and is allowing concurrent stability testing. Therefore, EPA has changed the requirement to allow stability testing concurrently with the study. Solubility, where this is relevant to a study, must still be known before the experimental start date. Please note that the 1983 GLP standards require determination of characteristics which will appropriately define the test or control article before study initiation. Thus solubility determination before a study, where it is relevant to the study and hence an appropriate characteristic, is not a new requirement.

ii. *Comment:* The term "purity" should be expanded to include radiochemical purity since further definition is needed to encompass metabolism/. environmental fate studies conducted with radioactive materials.

Response: Radiochemical purity is covered under "other characteristics which appropriately define the test, control, or reference substance." It is not necessary to specifically list this characteristic.

iii. *Comment:* What level of analysis constitutes "appropriate" characterization? Is quality control batch analysis sufficient? Is it necessary to fully characterize technical materials to 0.1 percent?

Response: The details of what "appropriately" defines the test substance is a guideline or protocol issue that cannot be specified in a generic document such as GW standards. The appropriate level of characterization is largely dependent on the nature of the study that the substance is to be used for.

iv. *Comment:* What needs to be characterized, the technical grade active ingredient or the end product?

Response: The test substance needs to be characterized. If the test substance is the end product, the end product needs to be characterized.

v. *Comment:* The characterization requirement is inappropriate since it conflicts with management responsibilities, is costly, and adds unnecessary delays to the development process. It removes a necessary option of planning by objectives that responsible business management must retain. Delays and rescheduling, which may result if inadequate work is permitted by management, are real consequences that must be accepted by management, and management must decide whether or not to risk beginning an experiment prior to doing characterization studies. Since the ultimate validity of a

study will require that such data be obtained before the study is completed and as long as the sponsor can demonstrate that a study was conducted with authentic material, it is irrelevant when the characterization is completed. This proposal is not in concert with FDA GLP regulations. Many times prospective products fail to reach the marketplace due to unusual or insurmountable problems. Therefore, eliminating the need for characterization of product will reduce the costs of products that fall out of developmental process.

Response: Characterization is necessary to ensure integrity of studies. It is also necessary for EPA to have characterization data available for inspectional purposes during ongoing studies, and thus to have this information complete at the beginning of the study. Without characterization, it is not possible to know whether test, control, or reference substances from different batches that are used in a single study are in fact identical. Adequate testing for characterization normally occurs during the synthesis or production of test, control, and reference substances, and thus should already be available before the test begins. Consequently, having characterization data available should not impose an additional burden in most cases. ((34061)) EPA does agree, however, that stability testing should be allowed to be performed concurrently, to prevent unreasonable delays. The sponsor will bear the burden of a repeated test in the case that concurrent stability testing suggests that the study is not valid. For that reason, EPA is revising §160.105(b) to allow for concomitant determination of stability.

vi. *Comment:* The last sentence of §160.105(a), relating to methods and fabrication, should be deleted since these may contain CBI.

Response: This is not a new requirement and has not posed any problems. Inspectors are cleared to handle CBI material: any sensitive information can be declared CBI and treated as such.

vii. *Comment:* Some EPA auditors are interpreting this section to require that the testing facility not only archive certification records concerning the purity or assay of an analytical standard (reference substance), but to also archive copies of the raw data and records generated during the certification process. The sponsor or chemical supplier should only be required to archive the raw data supporting the certification of an analytical standard. The testing facility need only archive a copy of the certification of the standard.

Response: EPA agrees with the *Comment*, and is modifying §150.105(a) to allow for specification of the availability of the documentation supporting the characterization if it is not available at the testing facility. The phrase "and such documentation availability shall be specified" is added to the end of the first sentence in §160.105(a), following the word "* * * experiment."

viii. *Comment:* Many of the tests coming under the scope of the proposed GLP standards are in themselves stability studies. Soil dissipation tests are stability determinations of herbicides, as

are tests of microbial genetic markers for measuring persistence of recombinantly derived organisms. The proposal places industry in the quandary of conducting stability studies prior to a stability study.

Response: The performance tests cited cannot be considered to be stability tests under the GLP standards. In the context described above, the persistence of the substance in the environment is a separately measured parameter. However, when performing such tests, it is still important to know the stability of the substance to ensure that the measured effect was due to the effect of the test system.

ix. *Comment:* Would it be acceptable to EPA if the stability knowledge is based on the extrapolation of the results of a short-term stability study under extreme conditions carried out before the experimental starting date?

Response: Such an accelerated study would not demonstrate stability under test conditions, and could not be part of the concurrent stability testing performed in conjunction with a larger study. It would be a separate study with its own protocol.

x. *Comment:* The proposed rule does not address whether quality control activities fall under the GLP standards.

Response: Not all quality control activities are GLP issues. Quality control work that is integral to the laboratory performing the study would be under GLP standards, but not that performed during manufacturing. Studies as defined in this part are subject to GLP standards only when required to be submitted to fulfill data requirements.

xi. *Comment:* The part related to "storage container assignment for the duration of a study" in §160.105© would be unrealistic for field studies, especially where storage containers may be large tanks, or delivery systems which are possibly not even owned by the sponsor or testing facility.

Response: The delivery systems and tanks that are part of delivery systems are not "storage containers." Test, control, and reference substance will, however, be stored before use in some container that is unique to that substance during the test. This may be the container that it comes in or that is assigned to it by the testing facility.

xii. *Comment:* Liquids from large containers are often placed into smaller containers for use during the study. Consolidation of the test substance into smaller containers as the supply is depleted should be allowed. These containers need not be retained after they are empty, since their retention does not enhance the quality or integrity of the data collected.

Response: EPA disagrees with the suggestion. The retention of containers is necessary to ensure the integrity of the study. This includes empty containers, which must be kept to verify the disposition of the test, control, and reference substance. Disposal of containers adversely affects accountability. This provision of the rule is not changed from the 1983 rule, but was commented on by the public because it may affect types of studies, such as field studies, that will now fall under the provisions of the rule as a result of these amendments.

xiii. *Comment*: How are "studies of more than 4 weeks duration" specified in §160.105(d) defined? They should be defined as studies having an "in-life phase" of more than 4 weeks.

Response: The term "4 weeks duration" is meant to apply to the experimental start and experimental termination dates. The suggestion of using the term "in-life phase" is not accepted since this introduces new terminology that is not adequately defined. The term "4 weeks experimental duration" replaces "4 weeks duration" in §160.105(d) to clarify that the study initiation and study completion dates are not implied.

xiv. *Comment*: Section 160.105 (b) and (e) do not provide necessary discretion to testing personnel to determine what data are needed to characterize stability for a substance, and how the determination is made. The phrase "under test conditions" needs additional clarification, since a variety of temperature, humidity, moisture, and other test conditions may be encountered across the United States. Routine product chemistry testing for emulsion stability, hydrolysis, photostability, etc., should satisfy this requirement.

Response: The terminology "under test conditions" is ambiguous and may be misinterpreted, so EPA has decided to delete "under test conditions" from §160.105(e) and replace it with "under storage conditions at the test site." This may be adequately addressed by routine product chemistry testing as long as storage of the substance at the test site is in known, acceptable conditions.

xv. *Comment*: Section 160.105(e) should be deleted since it was redundant with §160.113(a)(2).

Response: EPA disagrees that these sections are redundant. Section 160.105(e) refers to the test, control, and reference substance, while §160.113 refers to mixtures.

xvi. *Comment*: Knowledge of stability makes sense for long-term, but not short term studies because if stability is suspect then doses are made up each day and given or sprayed immediately. Adequate knowledge of stability may exist from chemical information about the test substance.

Response: If a substance is known to be stable for a few days, then its stability is known in terms of the test requirements. If the stability is not known, it must be determined, even for short-term studies. Storage stability needs to be known even if the material is used "immediately". If enough information is known about the material to support its stability from other testing, its stability is known and the requirement is met. However, ((34062)) theoretical stability is not considered to be adequate. The method used to compensate for poor stability, such as daily mixing or immediate application, is addressed in guidelines rather than in GLP standards.

2. *Test, control, and reference substance handling - Comment*: If the test, control, or reference substance is inherently unstable, it may not be possible to "preclude deterioration." -Therefore, the regulation should allow for periodic evaluation of the purity of the test substance during a study to assure its integrity and replace it when shown to be warranted.

Response: The intent is to prevent deterioration due to handling. Periodic testing is allowed under §160.105(b) as changed in the final rule.

3. *Mixtures of substances with carriers - I. Comment:* Does §160.113 require determination of uniformity, stability, and solubility during field residue studies? If so, does it require analyses for each tank preparation? This requirement would impose a large burden on testing facilities performing these types of studies.

Response: The purpose of this section is to assure that the methodology used to prepare the mixture is valid. Once the methodology has been proven for a particular mixture, it need not be reconfirmed each time that mixture is prepared. For field residue trials, there will be data submitted to EPA that support the uniformity, stability, and solubility of a substance in the carrier when prepared by appropriate methodology, i.e. according to the proposed use or label. In such cases it may not be necessary to test each batch that is prepared for field application. However, field residue trials do remain subject to the requirements of this section. Where available data are inadequate to support uniformity, stability, and solubility in a particular case, then it is necessary for the data to be generated under this section. Also, there may be protocol stipulations applicable to a particular study that require tank mixture analyses in addition to any provisions of this section.

ii. *Comment:* The range of environmental conditions encountered in field trials are great and would require extensive evaluations of stability and solubility under numerous environmental conditions. This amount of data could not be evaluated prior to study initiation.

Response: Section §160.113(a)(2) states that the determination(s) shall be "* * *" under the environmental conditions specified in the protocol and as required by the conditions of the test." All possible environmental conditions do not have to be anticipated and tested unless required in the protocol.

iii. *Comment:* Short-term toxicity and field residue studies should be exempted from this section since supplementary analyses are performed for other studies with the same test substance. The analytical cost could equal or exceed the cost of the remainder of the short-term study.

Response: The GLP standards do not require characterization for each study. The characterization is required for each test, control, and reference substance. The same substance may need to be characterized only once, even if used on multiple studies.

iv. *Comment:* The requirement for stability and solubility should allow flexibility for the sponsor to make the determination either before, during, or after the study. When to determine the stability is a business decision based on knowledge of the risk of having to repeat a study, if the stability data negatively impacts the integrity of the study.

Response: EPA understands that requiring stability testing to

be completed prior to a study may introduce unreasonable delays. In harmony with the modification of §160.105(b) to allow concurrent stability testing of test, control, and reference substances, §160.113(a)(2) is changed to allow stability testing of mixtures to be performed concomitantly with the study. This allows the necessary flexibility and is also consistent with FDA's GLP regulations.

v. *Comment*: In the very early stages of a compound's development there is a need for basic acute toxicity tests. However, there are no analytical methods and calibrated reference standards available to test the stability of the test substances in the carrier according to GLP standards. An estimate of the stability of the compound in an inert carrier like starch oil, or polyethylene glycol is possible and should be sufficient as a preliminary approach. The stability test will be carried out as early as the analytical methods are available.

Response: If a carrier is used, the mixture with the carrier must go through the same test, i.e. stability, solubility, etc. Instability of the mixture in a specific carrier is important since it may affect the apparent effects of the test substance.

vi. *Comment*: The assurances called for in §160.113© are not well defined. How would the addition of the vehicle used to facilitate mixing of the test substance with the carrier to the control system affect this requirement? If the vehicle is identically mixed in control, is there a need to show noninterference?

Response: Any vehicle used to facilitate mixing must be shown not to interfere with the study. This includes a vehicle control to determine interaction effect.

vii. *Comment*: If a test substance is applied to a soil, is the soil a carrier or test system?

Response: This section does not generally consider "soil" to be a carrier; it is considered to be part of the test system.

G. Protocol for and Conduct of a Study

1. *Protocol - General* - I. *Comment*: The proposed regulations do not offer sufficient latitude for the generation of protocols. The regulations state that a protocol must exist prior to study conduct, yet it would be almost impossible to specify the exact analyses that would be performed on biological samples collected in the field until the samples were collected.

Response: The protocol requirement is not too restrictive to allow for situations where the exact analysis performed may not be known in advance. The type or nature of analysis still needs to be specified in the protocol. The protocol should state what samples are intended to be collected, how they are to be collected, and how they are intended to be analyzed. If there is a need for latitude, (for instance it is not known specifically how many samples will result from a particular study) that should be anticipated and stated in the protocol.

ii. *Comment*: Section 160.120(a)(5), (7), (10), and (11) should not apply to product chemistry experiments.

Response: The term "test system" is redefined to include any physical matrix, which may thus be applicable to product chemistry studies. However, note that a study designed solely for the determination of certain chemical or physical characteristics of a test substance are exempted from §160.120(a) (5), (7), (10), and (11) as described in §160.135. In addition, the word "of" prior to "frequency" should be "and." This was a typographical error noticed by one Commenter and has been corrected in this final rule.

iii. *Comment:* Guidance is needed in the final preamble for presenting addresses, as required by 0160.120(a)(3), of field and environmental locations used to conduct tests.

Response: The address of the testing facility is the address of the "person" (i.e. organizational unit or subunit) who ((34063)) actually conducts the study. Even if this organizational unit includes parts situated in different locations it may still be considered to have one address. The address should be a permanent address and would probably be synonymous with the address of the study director and/or testing facility's management.

iv. *Comment* "Address of sponsor" should be removed from this Part to maintain consistency with FDA GLP regulations.

Response: EPA maintains that the address of the sponsor is essential to its inspectional process, which differs from that of FDA.

v. *Comment* The requirement in §160.120(a)(4) to state proposed experimental start and termination dates poses problems for field studies where these dates cannot be predicted with certainty. Would this result in protocol deviations whenever these dates are not exactly met?

Response: The requirement to document the proposed experimental start and termination dates in the protocol does not suggest that a protocol deviation occurs when the date is not met. The term "proposed" signifies that this date is estimated. However, gross deviation from the proposed date may be a violation of the protocol, if there are date-critical aspects of the study that are identified as such.

vi. *Comment* Section 160.120(a)(5) is inappropriate because: (a) justification should be required only when more than one test system can be used in a study and not, for example, in residue chemistry studies where residue levels in specific target crops are the subject of a study; (b) Justification should only be required for those that deviate from, or fall outside the normal EPA guidelines and not where standard test systems (Pesticide Assessment Guidelines and Standard Evaluation Procedures) are used; © The retention of this requirement does not promote harmony between the EPA and FDA GLP regulations.

Response. Environmental studies are more diverse than health effects testing and are subject to details relevant to test system design that are more chemically dependent than is the case in health effects studies. Furthermore, this is not seen to impose a burden in the cases described in this *Comment*. In the case where only one test system can be used, that is the justification that

should be stated. The targeting of a specific crop may be part of the justification and so stated; it is still necessary to state that the test system (e.g., strain of crop, soil, location) used is justified for the purpose of the study. If a standard test system is used because it is the referenced system in EPA or Organization for Economic Cooperation and Development (OECD) guidelines, citing the use of such guidelines is sufficient justification. Thus, detailed discussions are required only in the relatively few cases where the study design requires deviation or special choices to be made in selection of the test system.

vii. *Comment*: EPA should add "range" to §160.120(a)(B) so it reads "* * * body weight range," since without specifying range, the protocol requirement could be misinterpreted to mean that all individual body weights of the test system should be included. This would not be possible since exact weights of test systems would not be known when the protocol is prepared.

Response: EPA did not intend a change here and retains the term "body weight range" as used in the 1983 rule.

viii. *Comment*: Section 160.120(a)(7) should be deleted since the test system will be identified and justification for its selection will be in the protocol.

Response: Identification of the test system is not covered in any of the other parts of §160.120. Identification is the specific description of which individual test system is used, not a general description of the kind of test system.

ix. *Comment*: The method for controlling bias is usually in the SOP, therefore inclusion of a reference in the protocol to the SOP should suffice.

Response: EPA agrees that this is allowed. The SOP may be referred to in the protocol in such cases.

x. *Comment*: The term "nutrients" should be added to the list for the description of the diet used in the study to cover the use of fertilizer in plant studies.

Response: EPA has incorporated this suggestion into the final rule.

xi. *Comment*: Section 160.120(a)(10) should be deleted, or amended with "if appropriate" because: (a) The reason for selecting the route of administration is the objective of the study; (b) route of administration and reason for its choice is not applicable to studies such as aqueous hydrolysis and anaerobic aquatic; © EPA Pesticide Assessment Guidelines require the use of certain routes.

Response: Unlike FDA, EPA requires many tests where a predefined route of exposure is not available. Multiple exposure routes may be possible for many test substances. It is appropriate to state that the route is mandated by guidelines or by the purpose of the study if either of these are the case.

xii. *Comment*: Section 160.120(a)(10) should be modified to read "*** route of administration and/or exposure ***" to encompass other types of protocols.

Response: EPA disagrees with the suggestion since the experimenter controls administration but does not have control of the route of exposure. Administration routes cover the potential of all exposure routes and hence is a more general, all-inclusive term in this case.

xiii. *Comment:* Section 160.120(a) should be reworded so that it reads: "The route or method of administration/ application and the reason for choice, if appropriate."

Response: EPA disagrees with the suggestion. The route of administration is not the same concept as method of application or administration. It would not be appropriate to introduce statements concerning methodology to this section.

xiv. *Comment:* In the case where the study director is part of a contract laboratory engaged for the study by the sponsor, it should be clarified that such signature as required under §160.120(a)(14) does not constitute review and approval of those parts of the protocol not related to the work done by the contract lab. For example, the study director for the chemical analysis of pesticide residues in plants may not be trained in the experimental design of the sponsor's overall study, although he or she may be qualified to conduct the subpart of the study contracted to the laboratory. Such a dilemma may similarly arise in §160.120(a)(5), (7), (10), and (15)

Response: EPA believes that the study director cannot, by definition, be an individual who is not trained or cognizant of the overall study. A study is not subdivided into multiple studies with multiple study directors. The definitions of "study" and "study director" preclude such a separation of responsibility.

xv. *Comment:* "Where applicable" should be added to §160.120(a)(15) since statistical methods are not used in field studies.

Response: Statistical methods are and should be used in field studies. However, where the use of statistics is limited this can be so stated. The phrase "to be used" should modify the term "statistical method" as in §160.120(a)(16) of the 1983 rule. This was a typographical error noted by one Commenter and has been corrected.

xvi. *Comment:* Section 160.120(a)(15) is redundant since all of §160.185(a)(3) requires statistical methods employed for analyzing the data.

Response: Section 160.185 describes reporting requirements after the study, ((34064)) while §160.120 describes protocol requirements before the study.

2. Physical and chemical characterization studies

I. *Comment:* Section 160.135 is confusing and needs to be read several times in order to understand it. EPA should clarify its intent by specifying those studies to be conducted under GLP standards, and by removing the double negatives currently presented in §160.135(a) and (b).

Response: EPA agrees with the *Comment*. The section is changed to eliminate the double negative and reworded for clarity while retaining the intent of the proposed changes.

ii. *Comment:* Should exemptions also apply to "assembly line" biological studies, such as the Ames test, acute lethality, eye irritation, etc?

Response: EPA does not intend to expand exemptions to biological tests previously covered by GLP standards, even when repetitive in nature. Section 160.135 applies only to physical and chemical characterization studies and is intended to ease the burden on many studies that will now come under GLP standards.

iii. *Comment:* The concept of what constitutes a study is blurred by this section. Partial deletion of protocol requirements implies that a protocol is still required for these "exempted measurements."

Response: EPA intends that a protocol still be required for the partially exempted studies. Some, but not all, of the full protocol requirements are eliminated.

iv. *Comment:* Areas for receipt and storage of test substances have been deleted in §160.47(a)(1), but corresponding SOPs are still required by § 160.81(b)(3).

Response: EPA maintains that SOPs for test, control and reference substance handling are still important, if not more important, when facilities for their handling are not specified.

v. *Comment:* Stability is to be known under conditions of the test under §160.105(e). but the requirement to report that information is deleted in | 160.185(a)(5)) and the requirement to determine stability is removed by deleting § 160.105(b).

Response: EPA agrees, but there is no contradiction. The requirements for determination and reporting of stability are relaxed although stability still needs to be known.

vi. *Comment:* A protocol is required even though certain specific elements have been deleted (§160.120(a)(5) through (12) and (15)), but the requirement for the quality assurance unit to retain the protocol is deleted (§160.195(d)),

Response: EPA agrees that this is true. The QAU record keeping requirements are relaxed although the protocol still needs to be written.

vii. *Comment:* A quality assurance unit is required by g 160.35(a), but by deleting §160.31© management will not have to assure the existence of a QAU.

Response: EPA eliminated §160.31© because it requires management to "assure that there is a quality assurance unit as described in §160.35." This would have contradicted the exclusion of certain portions of §160.35 as specified (i.e. §160.35(b) and (c)). That which is not excluded under §160.35 must comply with §160.35(a).

viii. *Comment:* A study director is required according to §§160.12 and 160.33, but does not have to be shown in the final report by the deletion of §160.185(a)(10).

Response: The study director is still required to sign the compliance statement submitted with the final report as required in §160.12 and is thus required to be named in the final report. A

number of individuals are listed in §160.185(a)(10) in addition to the study director. This section was exempted to reduce reporting requirements.

ix. *Comment:* Studies designed to determine stability, octanol water partition coefficient, volatility, and environmental persistence (biodegradation, photo degradation, or chemical degradation studies) should exclude §160.43(a)(1) through (e) and (f) through (h), 160.45, 160.81(b)(1), (2), (6), (7), and (9), and 160.90. Only the physical and chemical properties that are used to predict the environmental fate of a test substance should be developed in compliance with these regulations. Those properties which are not clearly used for this purpose should be excluded.

Response: EPA does not agree that the listed sections are irrelevant in their entirety to the listed studies. Those portions of the sections which are plainly not applicable to these studies (e.g. animal care facilities) do not place any burden on these studies.

x. *Comment:* The removal of physical and chemical characterization from the responsibilities of the QAU should not be accepted because it presents a major problem for the QAU personnel. The QAU should be responsible for every study within the laboratory with no exception.

Response: EPA disagrees with the conclusion that the QAU has no responsibilities in physical and chemical characterization studies. The exclusions reduce the responsibilities of the QAU, i.e. master schedule requirements, etc., but do not eliminate them.

xi. *Comment:* The QAU should be responsible for looking at the functional components of the laboratory (e.g., all melting points, all GC/MS analyses, etc.) rather than focusing on a particular study, such as with toxicology studies.

Response: EPA agrees and is modifying the inspectional requirements of the QAU under §160.35. This change specifies that the QAU conduct inspections and maintain records that are appropriate to particular studies. This gives latitude to the QAU with respect to how the information is gathered; i.e., as part of the standard review procedures of the laboratory, or as needed for the test. This change should reduce the burden in cases where it is appropriate to maintain central records regarding functional components that affect several studies rather than requiring such records to be maintained separately.

xii. *Comment:* If physical and chemical characteristics are to be covered by GLP standards, they should not be referred to as separate "characterization studies." These tests are listed in 40 CFR part 158 as physical and chemical characteristics and properties and are submitted to EPA in studies by Guideline series numbers, not necessarily as individual "characterization studies." Additionally, in product chemistry many of the characteristics listed in proposed §160.135(b) are part of Series 63 (i.e. stability, solubility, etc.), which is submitted as a single study. If these characteristics are to be covered by GLP standards, it should only be to the extent of the data requirements in 40 CFR 158, because it is not the purpose of the GLP standards to define

studies for registration.

Response: EPA disagrees with this *Comment*. GLP standards do not expand data requirements. The regulations only specify how the data are to be generated.

xiii. *Comment:* All product chemistry should be exempted from these regulations, except for those studies specifically noted in the preamble (i.e. stability, solubility, octanol water partition coefficient, volatility and persistence), which also affect the environmental hazard assessment and/or are required by other sections of the guidelines.

Response: EPA maintains that all data that are required to be submitted to EPA be collected according to GLP standards. While EPA believes that a portion of the requirements of the previous GLP standards can be reduced for some studies, the standards are still ((34065)) important to assure the quality and integrity of the data generated.

xiv. *Comment:* The series 60, 62, and 63 requirements are mainly process and method development type experiments, and are developed over a period of time with portions sometimes contributed from laboratories in plant locations, making it prohibitively expensive and unrealistic to have these portions under a GLP program.

Response: While there may be additional cost, the need to have the work performed under GLP standards overrides this concern. EPA does not agree that GLP requirements in this section entail unrealistic requirements on laboratories that perform these types of experiments.

xv. *Comment:* The data quality from the series 60, 61, 62 and 63 studies would not be compromised since the companies that are generating these data are usually doing so for their own economic benefit as well as for registration purposes.

Response: Data developed under manufacturer's demands for quality control information do not reflect the same constraints upon data integrity as required by EPA. During the manufacturing process, cost and time considerations may conflict with safety assessment data quality needs.

xvi. *Comment:* EPA should revise PR Notice 86-5 to ensure that the definition of study corresponds with the definition in the GLP regulations.

Response: The GLP regulations address the integrity of data generated during a study. PR Notice 86-5 addresses the reporting of the data, which is a separate concern.

xvii. *Comment:* The term "studies" in the title of §160.135 should be replaced with another term, such as "experiments," to avoid the misconception that these experiments must be carried out as separate "studies." As separate studies, they would require separate protocols, study directors, study reports, QAU audits, etc., when in fact these experiments are part of a larger study, which already has its own protocol covering all the various

experiments to be performed. It may be that this part should be deleted because these tests do not fit the basic definition of study and should not be included. in any way, under the scope of the GLP standards.

Response: EPA disagrees that these tests are not studies. The definition of study includes the phrase "to determine or help predict (the test substance's] effect *** and fate." Therefore the physical and chemical characterization parameters are included. EPA agrees that in some cases, the determinations will have been performed as part of a larger study (e.g. product chemistry) and consequently will have been performed under the protocol of the larger study. In other cases, however, each of these studies will require a separate protocol.

xviii. *Comment:* Are GLP requirements applicable when analyses are conducted by an outside laboratory, or are they exempted from the various sections outlined in §160.135(a)?

Response: The location where the analyses are performed does not affect the applicability of the GLP regulations.

xix. *Comment:* Section 160.135(a) in the proposed rule should be deleted because the regulation is far too complex to start applying parts of it to one study, but not to another. It is a major task to instruct personnel on the requirements in the GLP standards; and it would be an impossible task to instruct them on multiple versions of GLP standards.

Response: There should not be many cases where the same workers will need to be trained in both levels of GLP interpretation. There are not "multiple versions" of GLP standards, only a relaxation of some requirements for some studies. EPA does not consider this to be imposing an additional burden.

xx. *Comment:* Under §160.135(b), an unusual situation can occur with quality assurance because a QAU is required to exist by retention of §160.35(a) and is implied to have records of inspection by retention of §160.35(d), but has no duties by virtue of deleting §160.35 (b) and (c). Both §160.35 (a) and (d) should be added to the list of excluded provisions.

Response: EPA agrees that there are inconsistencies in eliminating §160.35 (b) and © since there are no inspectional responsibilities included in §160.35 (a) or (d). Consequently, EPA is expanding §160.35(a) to include inspectional responsibilities.

xxi. *Comment:* The repetitive inspection of the types of studies required in proposed §160.135(b) would consume large amounts of time for both study personnel and the QAU staff without contributing to the quality and integrity of the data. The periodic inspection of such operations would provide the necessary assurance that the data were of sufficient quality and integrity to meet all requirements under GLP standards.

Response: EPA disagrees with the *Comment* and expects that each study be inspected by the QAU at least once. Where these types of tests are repetitive or routine in nature it should be possible for the QAU inspectional process to be equally routine.

xxii. *Comment:* EPA should modify proposed §160.135(b) to make it perfectly clear that stability/solubility experiments carried out as part of a study are not excluded from the exemption provided

by §160.135(a). When the sole purpose of a study is to determine stability or solubility, GLP standards should apply, but where stability or solubility determinations are being made prior to the initiation of the actual experiment for which the study is being conducted, there is no reason to treat those determinations as a separate study. The study protocol will cover the need for, and method of, determining stability and solubility in situations where it is necessary to make those determinations in order to ensure the success of the study.

Response: EPA agrees that "sole purpose" stability/solubility studies are under GLP standards, but disagrees that these studies should be exempt when they are part of another GLP study. If they are a part of a larger study, they are within its protocol, and hence under GLP standards. If they are not within that protocol, then they are "sole studies" under GLP standards in their own right.

H. Records and Reports

1. Reporting of study results - I. Comment: Section 160.185 delineates the information to be included in the final report. Since the Office of Pesticide Programs (OPP) has already designed Data Reporting Guidelines (DRGs) as addenda to the Pesticide Assessment Guidelines and these are being used by applicants, this section appears to be unnecessary. Furthermore, there are a few issues where the GLP standards and DRGs are not compatible and illustrate a possible conflict in EPA requirements: (a) Section 160.185(a)(2) (protocol). The reviewer at OPP needs to know the study objectives, not necessarily what the objectives were in the protocol and what changes were made during the course of the study; (b) Section 160.185(a)(6) (methodology). A description of the methods used is required, but residue chemistry reports require a separate report for methodology; © Section 160.185© (report amendments). Information Services Branch has specific requirements in PR Notice 86-5 regarding the submission of amended reports. In cases such as these, which document has the superseding authority?

Response: DRGs are designed for presentation of data to EPA after the performance of the study, and GLP standards are designed to ensure data ((34066)) integrity during the performance of the study. GLP standards require additional information to be contained in the final report that are not required by the DRGs. This should not result in any issues of superseding authority.

ii. Comment: Section 160.185(a)(12) should be modified to require reports only when they are necessary to explain results that are highly subject to interpretational or critical to the final evaluation of the study. Otherwise this will result in an unusual reporting burden with little benefit during field residue studies.

Response: EPA does not agree that the requirement is impractical or unnecessary. This reporting requirement cannot be left entirely to the discretion of the study director.

iii. Comment: At the EPA's second data submitter's workshop on the implementation of PR Notice 86-5 on December 15, 1986, EPA

handed out the "Clarification of PR Notice 86-5 Requirements" pertaining to GLP considerations. EPA states in this clarification that reformatting final study reports to comply with the submission requirements of PR Notice 86-5 does not constitute a formal "correction or addition" to a final report that would otherwise require the signature of the study director under 40 CFR 100.185(c).

Response: EPA agrees and is incorporating the suggestion in the final rule so that modification to comply with EPA submission requirements does not constitute a correction, addition, or amendment. However, EPA advises that the process of reformatting final study reports does not alleviate the study director of accountability in signing the final report or the compliance statement.

2. *Storage and retrieval of records and data - I. Comment:* The phrase "beyond quality assurance" in §160.190(a) needs clarification since it could be ambiguously interpreted. Does it mean the date of the final approved report or does it mean beyond initial evaluation of the specimens, since that was the statement used in the corresponding preamble section?

Response: EPA intends that the specimens be retained until the quality assurance unit assures that their discarding does not negatively impact the integrity of the study. The wording is being changed to "after quality assurance verification" to clarify this.

ii. *Comment:* Tissues and animal feeds collected from non-toxicology studies should also be discarded after quality assurance verification. If EPA does not intend for animal tissues to be retained from residue studies, "animal" not appearing after "plants" is an oversight.

Response: EPA did not include the term "animal" in the list since it would potentially include tissues and feeds from toxicology studies which must be kept. It is felt that the suggested wording would not provide sufficient breadth to cover non-residue samples. Therefore, EPA will require that all animal tissue samples, even from non-toxicology studies, be included in this Part.

iii. *Comment:* Retention time for ¹⁴C-labeled specimens needs to be addressed since a facility's license limit could be exceeded for storing radioactive material.

Response: The problem of licensing requirements is a facility responsibility under GLP standards. EPA does not agree that special consideration be given to sample storage based on the above reasoning

iv. *Comment:* This Part does not clearly define who must archive raw data or authenticated copies. If the test facility's portion of the study is small compared to the entire project, it does not make sense to archive at the test facility. The sponsor should be required to archive all raw data in support of a submission and provide that data to the test facility in the event of an audit. Archiving at the test facility will put an undue and

unnecessary hardship on small laboratory facilities. Another problem to be considered is whether the test facility is required to archive the final report submitted to EPA. It could find itself archiving analytical data generated by another facility. Furthermore, in the event that the sponsor may be involved in a lawsuit concerning the study, the contingent liability exposure for the test facility should be clarified.

Response: The test facility may contract with a commercial archives under §160.195 (b) and (8)- This implies flexibility in the physical location of the archives.

3. *Retention of records - I. Comment:* The appropriate endpoint for specimen retention in § 180.195 should be based on the integrity of the specimens and use by the study director, or other technical personnel, not based on when QAU personnel may perform a review.

Response: Quality assurance evaluation is needed to assure that the integrity of the data are not compromised by the decision to discard specimens. For consistency, EPA is changing the wording of §160.195© to concur with the wording of §180.190(a).

ii. *Comment:* EPA should explicitly state in §180.195(I) that when exact copies are substituted for original source as raw data, then the original may be discarded. In the past, EPA inspectors have required retention of original data sources even if exact copies existed. The burden imposed by some EPA auditors, that each copy must be signed and dated, is unrealistic. Verification of "batches" of reproduction copies is just as meaningful and would eliminate most of the unnecessary burden on personnel and time resources.

Response: Specific wording advising the discarding of raw data after copying is not necessary or useful. "True copies" will be acceptable as raw data by EPA inspectors under §180.190. Signing and dating each copy may be impractical and an acceptable alternative method may be devised and incorporated into standard operating procedures to ensure the integrity of the copies. Laboratories are cautioned that discarding originals places an additional burden on verification of the authenticity of the copies.

III. Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a rule is "major" and therefore subject to the requirement of a Regulatory Impact Analysis. EPA has determined that the amendments are not a major rule because they do not meet any of the criteria set forth and defined in section 1(b) of the Order. Compliance costs were estimated using data from a survey of laboratories potentially affected by the revised GLP standards and from data on pesticides testing demand, and costs taken from a 1980 study of the pesticides testing industry.

This rule was submitted to the Office of Management and Budget

(OMB) for review as required by Executive Order 12291. Any comments from OMB to EPA and any EPA Response to those comments are available for public inspection at Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St., SW., Washington, DC 20460; and at the Office of Management and Budget, Washington, DC 20503, with OMB requests marked "Attention: Desk Officer for EPA."

B. Regulatory Flexibility Act

This rule has been reviewed under the Regulatory Flexibility Act of 1980 (Pub. L. 96-354; 94 Stat. 1165 (5 U.S.C. 801 et. seq.)), and it has been determined that it will not have significant economic impact on a substantial number of small businesses, small governments, or small organization. It was found that the GLP revisions will not increase the costs of health effects testing and that non health effects testing costs will increase about 20 percent.((34067))

C. Paperwork Reduction Act

The information collection requirements in this rule will be submitted for approval to OMB under the Paperwork Reduction Act, 44 U.S.C. 3501 et seq. These requirements are not effective until OMB approves them and a technical amendment to that effect is published in the Federal Register.

Public reporting for this collection of information is estimated to average 15 hours per Response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St. SW. Washington, DC 20503.

List of Subjects in 40 CFR Part 180

Environmental protection, Good laboratory practice, Hazardous materials, Pesticides and pests, Reporting and record keeping requirements.

Dated: July 27, 1989 William K. Reilly, Administrator
Therefore, 40 CFR chapter I, part 160 is revised to read as follows:

PART 160 - GOOD LABORATORY PRACTICE STANDARDS

Subpart A - General Provisions

Sec.

- 160.1 Scope.
- 160.3 Definitions.
- 160.10 Applicability to studies performed under grants and contracts.
- 160.12 Statement of compliance or noncompliance.
- 160.15 Inspection of a testing facility.
- 160.17 Effects of non-compliance.

Subpart B - Organization and Personnel

- 160.29 Personnel.
- 160.31 Testing facility management.
- 160.33 Study director.
- 160.35 Quality assurance unit.

Subpart C - Facilities

- 160.41 General.
- 160.43 Test system care facilities.
- 160.45 Test system supply facilities.
- 160.47 Facilities for handling test, control and reference substances.
- 160.49 Laboratory operation areas.
- 160.51 Specimen and data storage facilities.

Subpart D - Equipment

- 160.61 Equipment design
- 180.63 Maintenance and calibration of equipment.

Subpart E - Testing Facilities Operation

- 160.81 Standard operating procedures.
- 160.83 Reagents and solutions.
- 160.90 Animal and other test system care.

Subpart F - Test, Control, and Reference Substances

- 160.105 Test, control, and reference substance characterization.
- 160.107 Test, control, and reference substance handling
- 160.113 Mixtures of substances with carriers.

Subpart G - Protocol for and Conduct of a Study

- 160.120 Protocol.
- 160.130 Conduct of a study.
- 160.135 Physical and chemical characterization studies.

Subpart H and I - [Reserved]

Subpart J - Records and Reports

- 160.185 Reporting of study results.
- 160.190 Storage and retrieval of records and data.
- 160.195 Retention of records.

Authority: 7 U.S.C 136a, 136c, 136d, 136f, 138j, 136t, 138v, 136w;
21 U.S.C 346a, 348, 371. Reorganization Plan No 3 of 1970.

SUBPART A - GENERAL PROVISIONS

§ 160.1 Scope.

(a) This part prescribes good laboratory practices for conducting studies that support or are intended to support applications for research or marketing permits for pesticide products regulated by the EPA. This part is intended to assure the quality and integrity of data submitted pursuant to sections 3, 4, 5, 8, 18 and 24© of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (7 U.S.C. 136a, 136c, 136f, 136g and 136v(c)) and sections 408 and 409 of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 346a, 348).

(b) This part applies to any study described by paragraph (a) of this section which any person conducts, initiates, or supports on or after October 16, 1989.

§160.3 Definitions.

As used in this part the following terms shall have the meanings specified:

Application for research or marketing permit includes:

- (1) An application for registration, amended registration, or re-registration of a pesticide product under FIFRA sections 3, 4 or 24(c).
- (2) An application for an experimental use permit under FIFRA section 5.
- (3) An application for an exemption under FIFRA section 18.

- (4) A petition or other request for establishment or modification of a tolerance, for an exemption for the need for a tolerance, or for other clearance under FFDCA section 408.
- (5) A petition or other request for establishment or modification of a food additive regulation or other clearance by EPA under FFDCA section 409.
- (6) A submission of data in response to a notice issued by EPA under FIFRA section 3(c)(2)(B).
- (7) Any other application, petition, or submission sent to EPA intended to persuade EPA to grant, modify, or leave unmodified a registration or other approval required as

a condition of sale or distribution of a pesticide.

Batch means a specific quantity or lot of a test, control, or reference substance that has been characterized according to § 160.105(a).

Carrier means any material, including but not limited to feed, water, soil, nutrient media, with which the test substance is combined for administration to a test system.

Control substance means any chemical substance or mixture, or any other material other than a test substance, feed, or water, that is administered to the test system in the course of a study for the purpose of establishing a basis for comparison with the test substance for known chemical or biological measurements.

EPA means the U.S. Environmental Protection Agency.

Experimental start date means the first date the test substance is applied to the test system. Experimental termination date means the last date on which data are collected directly from the study.

FDA means the U.S. Food and Drug Administration.

FFDCA means the Federal Food, Drug and Cosmetic Act, as amended (21 U.S.C. 321 et seq).

FIFRA means the Federal Insecticide, Fungicide and Rodenticide Act as amended (7 U.S.C. 136 et seq).

Person includes an individual, partnership, corporation, association, scientific or academic establishment, government agency, or organizational unit thereof, and any other legal entity.

Quality assurance unit means any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of the studies.

Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been ((34068)) transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data. "Raw data" may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

Reference substance means any chemical substance or mixture, or analytical standard, or material other than a test substance, feed, or water, that is administered to or used in analyzing the test system in the course of a study for the purposes of establishing a basis for comparison with the test substance for known chemical or biological measurements.

Specimens means any material derived from a test system for examination or analysis.

Sponsor means:

- (1) A person who initiates and supports, by provision of financial or other resources, a study;
- (2) A person who submits a study to the EPA in support of an application for a research or marketing permit; or
- (3) A testing facility, if it both initiates and actually conducts the study.

Study means any experiment at one or more test sites, in which a test substance is studied in a test system under laboratory conditions or in the environment to determine or help predict its effects, metabolism, product performance (efficacy studies only as required by 40 CFR 158.640), environmental and chemical fate, persistence and residue, or other characteristics in humans, other living organisms, or media. The term "study" does not include basic exploratory studies carried out to determine whether a test substance or a test method has any potential utility.

Study completion date means the date the final report is signed by the study director.

Study director means the individual responsible for the overall conduct of a study.

Study initiation date means the date the protocol is signed by the study director.

Test substance means a substance or mixture administered or added to a test system in a study, which substance or mixture:

- (1) Is the subject of an application for a research or marketing permit supported by the study, or is the contemplated subject of such an application; or
- (2) Is an ingredient, impurity, degradation product, metabolite, or radioactive isotope of a substance described by paragraph (1) of this definition, or some other substance related to a substance described by that paragraph, which is used in the study to assist in characterizing the toxicity, metabolism, or other characteristics of a substance described by that paragraph.

Test system means any animal, plant, microorganism, chemical or physical matrix, including but not limited to soil or water, or subparts thereof, to which the test, control, or reference substance is administered or added for study. "Test system" also includes appropriate groups or components of the system not treated with the test, control, or reference substance.

Testing facility means a person who actually conducts a study, i.e., actually uses the test substance in a test system. "Testing Facility" encompasses only those operational units that are being or have been used to conduct studies.

Vehicle means any agent which facilitates the mixture, dispersion, or solubilization of a test substance with a

carrier.

§160.10 Applicability to studies performed under grants and contracts.

When a sponsor or other person utilizes the services of a consulting laboratory, contractor, or grantee to perform all or a part of a study to which this part applies, it shall notify the consulting laboratory, contractor, or grantee that the service is, or is part of, a study that must be conducted in compliance with the provisions of this part.

§160.12 Statement of compliance or non-compliance.

Any person who submits to EPA an application for a research or marketing permit and who, in connection with the application, submits data from a study to which this part applies shall include in the application a true and correct statement, signed by the applicant, the sponsor, and the study director, of one of the following types:

- (a) A statement that the study was conducted in accordance with this part; or
- (b) A statement describing in detail all differences between the practices used in the study and those required by this part; or
- © 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 this part.

§160.15 Inspection of a testing facility.

- (a) A testing facility shall permit an authorized employee or duly designated representative of EPA or FDA, at reasonable times and in a reasonable manner, to inspect the facility and to inspect (and in the case of records also to copy) all records and specimens required to be maintained regarding studies to which this part applies. The records inspection and copying requirements should not apply to quality assurance unit records of findings and problems, or to actions recommended and taken, except that EPA may seek production of these records in litigation or formal adjudicatory hearings.
- (b) EPA will not consider reliable for purposes of supporting an application for a research or marketing permit any data developed by a testing facility or sponsor that refuses to permit inspection in accordance with this part. The determination that a study will not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any applicable statute or regulation to submit the results of the study to EPA.

§160.17 Effects of non-compliance.

- (a) EPA may refuse to consider reliable for purposes of supporting an application for a research or marketing permit any data from a study which was not conducted in accordance with this part.
- (b) Submission of a statement required by § 160.12 which is false may form the basis for cancellation, suspension, or modification of the research or marketing permit, or denial or disapproval of an application for such a permit, under FIFRA section 3, 5, 6, 18, or 24 or FFDCA section 406 or 409, or for criminal prosecution under 18 U.S.C. 2 or 1001 or FIFRA section 14, or for imposition of civil penalties under FIFRA section 14.

SUBPART B-ORGANIZATION AND PERSONNEL

§160.29 Personnel.

- (a) Each individual engaged in the conduct of or responsible for the supervision of a study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.
- (b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a study.
- © There shall be a sufficient number of personnel for the timely and proper conduct of the study according to the protocol.
- (d) **((34069))** Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test, control, and reference substances and test systems.
- (e) Personnel engaged in a study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test, control, and reference substances.
- (f) Any individual found at any time to have an illness that may adversely affect the quality and integrity of the study shall be excluded from direct contact with test systems, and test, control, and reference substances, and any other operation or function that may adversely affect the study until the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a study.

§160.31 Testing facility management.

For each study, testing facility management shall:

- (a) Designate a study director as described in §160.33 before

- the study is initiated.
- (b) Replace the study director promptly if it becomes necessary to do so during the conduct of a study.
 - © Assure that there is a quality assurance unit as described in §160.35.
 - (d) Assure that test, control, and reference substances or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.
 - (e) Assure that personnel, resources, facilities, equipment, materials and methodologies are available as scheduled.
 - (f) Assure that personnel clearly understand the functions they are to perform.
 - (g) Assure that any deviations from these regulations reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

§160.33 Study director.

For each study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. 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 of study control. The study director shall assure that:

- (a) The protocol, including any change, is approved as provided by §160.120 and is followed.
- (b) All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified.
- © Unforeseen circumstances that may affect the quality and integrity of the study are noted when they occur, and corrective action is taken and documented.
- (d) Test systems are as specified in the protocol.
- (e) All applicable good laboratory practice regulations are followed.
- (f) All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

§160.35 Quality Assurance Unit.

(a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study. The quality assurance unit shall conduct inspections and maintain records appropriate to the study.

(b) The quality assurance unit shall:

- (1) Maintain a copy of a master schedule sheet of all studies conducted at the testing facility indexed by test substance, and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director.
 - (2) Maintain copies of all protocols pertaining to all studies for which the unit is responsible.
 - (3) Inspect each study at intervals adequate to ensure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems which are likely to affect study integrity found during the course of an inspection shall be brought to the attention of the study director and management immediately.
 - (4) Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.
 - (5) Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.
 - (6) Review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study.
 - (7) Prepare and sign a statement to be included with the final study report which shall specify the dates inspections were made and findings reported to management and to the study director.
- © The responsibilities and procedures applicable to the quality assurance unit, the records maintained by the quality assurance unit, and the method of indexing such records shall be in writing and shall be maintained. These items including inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection shall be made available for inspection to authorized employees or duly designated representatives of EPA or FDA.
- (d) An authorized employee or a duly designated representative of EPA or FDA shall have access to the written procedures established for the inspection and may request testing facility management to certify that inspections are being implemented, performed, documented, and followed up in accordance with this paragraph.

SUBPART C - FACILITIES

§160.41 General.

Each testing facility shall be of suitable size and

construction to facilitate the proper conduct of studies. Testing facilities which are not located within an indoor controlled environment shall be of suitable location to facilitate the proper conduct of studies. Testing facilities shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

§160.43 Test system care facilities.

- (a) A testing facility shall have a sufficient number of animal rooms or other test system areas, as needed, to ensure: proper separation of species or test systems, isolation of individual projects, quarantine or isolation of animals or other test systems, and routine or specialized housing of animals or other test systems. ((34070))
 - (1) In tests with plants or aquatic animals, proper separation of species can be accomplished within a room or area by housing them separately in different chambers or aquaria. Separation of species is unnecessary where the protocol specifies the simultaneous exposure of two or more species in the same chamber, aquarium, or housing unit.
 - (2) Aquatic toxicity tests for individual projects shall be isolated to the extent necessary to prevent cross-contamination of different chemicals used in different tests.
- (b) A testing facility shall have a number of animal rooms or other test system areas separate from those described in paragraph (a) of this section to ensure isolation of studies being done with test systems or test, control, and reference substances known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.
- © Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory test system diseases. These areas shall provide effective isolation for the housing of test systems either known or suspected of being diseased, or of being carriers of disease, from other test systems.
- (d) Facilities shall have proper provisions for collection and disposal of contaminated water, soil, or other spent materials. When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.
- (e) Facilities shall have provisions to regulate environmental conditions (e.g., temperature, humidity, photoperiod) as specified in the protocol.
- (f) For marine test organisms, an adequate supply of clean sea water or artificial sea water (prepared from deionized or distilled water and sea salt mixture) shall be available. The

- ranges of composition shall be as specified in the protocol.
- (g) For freshwater organisms, an adequate supply of clean water of the appropriate hardness, pH, and temperature, and which is free of contaminants capable of interfering with the study, shall be available as specified in the protocol.
 - (h) For plants, an adequate supply of soil of the appropriate composition, as specified in the protocol, shall be available as needed.

§160.45 Test system supply facilities.

- (a) There shall be storage areas, as needed, for feed, nutrients, soils, bedding, supplies, and equipment. Storage areas for feed nutrients, soils, and bedding shall be separated from areas where the test systems are located and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.
- (b) When appropriate, plant supply facilities shall be provided. As specified in the protocol, these include:
 - (1) Facilities for holding, culturing, and maintaining algae and aquatic plants.
 - (2) Facilities for plant growth, including, but not limited to greenhouses, growth chambers, light banks, and fields.
 - © When appropriate, facilities for aquatic animal tests shall be provided. These include, but are not limited to, aquaria, holding tanks, ponds, and ancillary equipment, as specified in the protocol.

§160.47 Facilities for handling test, control, and reference substances.

- (a) As necessary to prevent contamination or mixups, there shall be separate areas for:
 - (1) Receipt and storage of the test, control, and reference substances.
 - (2) Mixing of the test, control, and reference substances with a carrier, e.g., feed.
 - (3) Storage of the test, control, and reference substance mixtures.
- (b) Storage areas for test, control, and/or reference substance and for test, control, and/or reference mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the substances and mixtures.

§160.49 Laboratory operation areas.

Separate laboratory space and other space shall be provided, as needed, for the performance of the routine and specialized procedures required by studies.

§160.51 Specimen and data storage facilities.

Space shall be provided for archives, limited to access by

authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

SUBPART D - EQUIPMENT

§160.61 Equipment design.

Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control 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.

§160.63 Maintenance and calibration of equipment.

- (a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standardized.
- (b) The written standard operating procedures required under §160.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation.
- © Written records shall be maintained of all inspection, maintenance, testing, calibrating, and/or standardizing operations. These records, containing the dates of the operations, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of non-routine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

SUBPART E - TESTING FACILITIES OPERATION

§160.81 Standard operating procedures.

- (a) A testing facility shall have standard operating procedures in writing setting forth study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be ((34071)) properly authorized in writing by management.

- (b) Standard operating procedures shall be established for, but not limited to, the following:
 - (1) Test system area preparation.
 - (2) Test system care.
 - (3) Receipt, identification, storage, handling, mixing, and method of sampling of the test, control, and reference substances.
 - (4) Test system observations.
 - (5) Laboratory or other tests.
 - (6) Handling of test systems found moribund or dead during study.
 - (7) Necropsy of test systems or postmortem examination of test systems.
 - (8) Collection and identification of specimens.
 - (9) Histopathology.
 - (10) Data handling, storage and retrieval.
 - (11) Maintenance and calibration of equipment.
 - (12) Transfer, proper placement, and identification of test systems.
- © Each laboratory or other study area shall have immediately available manuals and standard operating procedures relative to the laboratory or field procedures being performed. Published literature may be used as a supplement to standard operating procedures.
- (d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

§160.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

§160.90 Animal and other test system care.

- (a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals and other test systems.
- (b) All newly received test systems from outside sources shall be isolated and their health status or appropriateness for the study shall be evaluated. This evaluation shall be in accordance with acceptable veterinary medical practice or scientific methods.
- © At the initiation of a study, test systems shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If during the course of the study, the test systems contract such a disease or condition, the diseased test systems should be isolated, if necessary. These test systems may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorization of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

- (d) Warm-blooded animals, adult reptiles, and adult terrestrial amphibians used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require these test systems to be removed from and returned to their test system-housing units for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification (e.g., tattoo, color code, ear tag, ear punch, etc.). All information needed to specifically identify each test system within the test system-housing unit shall appear on the outside of that unit. Suckling mammals and juvenile birds are excluded from the requirement of individual identification unless otherwise specified in the protocol.
- (e) Except as specified in paragraph (e)(1) of this section, test systems of different species shall be housed in separate rooms when necessary. Test systems of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to test, control, or reference substances or test system mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.
 - (1) Plants, invertebrate animals, aquatic vertebrate animals, and organisms that may be used in multispecies tests need not be housed in separate rooms, provided that they are adequately segregated to avoid mixup and cross contamination.
 - (2) [Reserved]
- (f) Cages, racks, pens, enclosures, aquaria, holding tanks, ponds, growth chambers, and other holding, rearing and breeding areas, and accessory equipment, shall be cleaned and sanitized at appropriate intervals.
- (g) Feed, soil, and water used for the test systems shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed, soil, or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.
- (h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.
- (I) If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.
- (j) All plant and animal test systems shall be acclimatized to the environmental conditions of the test, prior to their use in a study.

SUBPART F - TEST, CONTROL, AND REFERENCE SUBSTANCES

§160.105 Test, control, and reference substance characterization.

- (a) The identity, strength, purity, and composition, or other characteristics which will appropriately define the test, control, or reference substance shall be determined for each batch and shall be documented before its use in a study.

Methods of synthesis, fabrication, or derivation of the test, control, or reference substance shall be documented by the sponsor or the testing facility, and the location of such documentation shall be specified.

- (b) When relevant to the conduct of the study the solubility of each test, control, or reference substance shall be determined by the testing facility or the sponsor before the experimental start date. The stability of the test, control, or reference substance shall be determined before the experimental start date or concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.
- © Each storage container for a test, control, or reference substance shall be labeled by name, chemical abstracts service number (CAS) or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test, control, or reference substance. Storage containers shall be assigned to a particular test substance for the duration of the study.
- (d) For studies of more than 4 weeks experimental duration, reserve samples from each batch of test, control, and reference substances shall be retained for the period of time provided by § 160.195.
- (e) The stability of test, control, and reference substances under storage conditions at the test site shall be known for all studies.

§160.107 Test, control, and reference substance handling.

Procedures shall be established for a system for the handling of the test, control, and reference substances to ensure that:

- (a) There is proper storage. ((34072))
- (b) Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.
- © Proper identification is maintained throughout the distribution process.
- (d) The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

§160.113 Mixtures of substances with carriers.

- (a) For each test, control, or reference substance that is mixed with a carrier, tests by appropriate analytical methods shall be conducted:
 - (1) To determine the uniformity of the mixture and to determine, periodically, the concentration of the test, control, or reference substance in the mixture.
 - (2) When relevant to the conduct of the study, to determine the solubility of each test, control, or reference substance in the mixture by the testing facility or the sponsor before the experimental start date.
 - (3) To determine the stability of the test, control, or reference substance in the mixture before the

experimental start date or concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

- (b) Where any of the components of the test, control, or reference substance carrier mixture has an expiration date, that date shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.
- © If a vehicle is used to facilitate the mixing of a test substance with a carrier, assurance shall be provided that the vehicle does not interfere with the integrity of the test.

SUBPART G - PROTOCOL FOR AND CONDUCT OF A STUDY

§160.120 Protocol.

- (a) Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain but shall not necessarily be limited to the following information:
 - (1) A descriptive title and statement of the purpose of the study.
 - (2) Identification of the test, control, and reference substance by name, chemical abstracts service (CAS) number or code number.
 - (3) The name and address of the sponsor and the name and address of the testing facility at which the study is being conducted.
 - (4) The proposed experimental start and termination dates.
 - (5) Justification for selection of the test system.
 - (6) Where applicable, the number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.
 - (7) The procedure for identification of the test system.
 - (8) A description of the experimental design, including methods for the control of bias.
 - (9) Where applicable, a description and/or identification of the diet used in the study as well as solvents, emulsifiers and/or other materials used to solubilize or suspend the test, control, or reference substances before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.
 - (10) The route of administration and the reason for its choice.
 - (11) Each dosage level, expressed in milligrams per kilogram of body or test system weight or other appropriate units, of the test, control, or reference substance to be administered and the method and frequency of administration.
 - (12) The type and frequency of tests, analyses, and

measurements to be made.

(13) The records to be maintained.

(14) The date of approval of the protocol by the sponsor and the dated signature of the study director.

(15) A statement of the proposed statistical method to be used.

(b) All changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol.

§160.130 Conduct of a study.

(a) The study shall be conducted in accordance with the protocol.

(b) The test systems shall be monitored in conformity with the protocol.

© Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.

(d) In animal studies where histopathology is required, records of gross findings for a specimen from postmortem observations shall be available to a pathologist when examining that specimen histopathologically.

(e) All data generated during the conduct of a study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

§160.135 Physical and chemical characterization studies.

(a) All provisions of the GLP standards shall apply to physical and chemical characterization studies designed to determine stability, solubility, octanol water partition coefficient, volatility, and persistence (such as biodegradation, photo degradation, and chemical degradation studies) of test, control, or reference substances.

(b) The following GLP standards shall not apply to studies, other than those designated in paragraph (a) of this section, designed to determine physical and chemical characteristics of a test, control, or reference substance:

§160.31 (c), (d), and (g)

§160.35 (b) and ©
§160.43
§160.45
§160.47
§160.49
§160.81(b) (1), (2), (6) through (9), and (12)
§160.90
§160.105 (a) through (d)
§160.113
§160.120(a) (5) through (12), and (15)
§160.185(a) (5) through (8), (10), (12), and (14)
§160.195 © and (d)

SUBPARTS H-I [RESERVED]

SUBPART J-RECORDS AND REPORTS

§160.185 Reporting of study results.

- (a) A final report shall be prepared for each study and shall include, but not necessarily be limited to, the following:
- (1) Name and address of the facility performing the study and the dates on which the study was initiated and was completed, terminated, or discontinued. ((34073))
 - (2) Objectives and procedures stated in the approved protocol, including any changes in the original protocol.
 - (3) Statistical methods employed for analyzing the data.
 - (4) The test, control, and reference substances identified by name, chemical abstracts service (CAS) number or code number, strength, purity, and composition, or other appropriate characteristics.
 - (5) Stability and, when relevant to the conduct of the study the solubility of the test, control, and reference substances under the conditions of administration.
 - (6) A description of the methods used.
 - (7) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.
 - (8) A description of the dosage, dosage regimen, route of administration, and duration.
 - (9) A description of all circumstances that may have affected the quality or integrity of the data.
 - (10) The name of the study director, the names of other scientists or professionals and the names of all supervisory personnel, involved in the study.
 - (11) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
 - (12) The signed and dated reports of each of the individual scientists or other professionals involved in the study, including each person who, at the request or direction of

the testing facility or sponsor, conducted an analysis or evaluation of data or specimens from the study after data generation was completed.

- (13) The locations where all specimens, raw data, and the final report are to be stored.
- (14) The statement prepared and signed by the quality assurance unit as described in § 160.35(b)(7).
- (b) The final report shall be signed and dated by the study director.
- © Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible. Modification of a final report to comply with the submission requirements of EPA does not constitute a correction, addition, or amendment to a final report.
- (d) A copy of the final report and of any amendment to it shall be maintained by the sponsor and the test facility.

§160.190 Storage and retrieval of records and data.

- (a) All raw data, documentation, records, protocols, specimens, and final reports generated as a result of a study shall be retained. Specimens obtained from mutagenicity tests, specimens of soil, water, and plants, and wet specimens of blood, urine, feces, and biological fluids, do not need to be retained after quality assurance verification. Correspondence and other documents relating to interpretation and evaluation of data, other than those documents contained in the final report, also shall be retained.
- (b) There shall be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents of specimens. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens maybe retained elsewhere provided that the archives have specific reference to those other locations.
- © An individual shall be identified as responsible for the archives.
- (d) Only authorized personnel shall enter the archives.
- (e) Material retained or referred to in the archives shall be indexed to permit expedient retrieval.

§160.195 Retention of records.

- (a) Record retention requirements set forth in this section do not supersede the record retention requirements of any other regulations in this subchapter.
- (b) Except as provided in paragraph © of this section,

documentation records, raw data, and specimens pertaining to a study and required to be retained by this part shall be retained in the archive(s) for whichever of the following periods is longest:

- (1) In the case of any study used to support an application for a research or marketing permit approved by EPA, the period during which the sponsor holds any research or marketing permit to which the study is pertinent.
 - (2) A period of at least 5 years following the date on which the results of the study are submitted to the EPA in support of an application for a research or marketing permit.
 - (3) In other situations (e.g., where the study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.
- © Wet specimens, samples of test, control, or reference substances, and specially prepared material which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation. Specimens obtained from mutagenicity tests, specimens of soil, water, and plants, and wet specimens of blood, urine, feces, and biological fluids, do not need to be retained after quality assurance verification. In no case shall retention be required for longer periods than those set forth in paragraph (b) of this section.
- (d) The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by § 160.35© shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraph (b) of this section.
 - (e) Summaries of training and experience and job descriptions required to be maintained by § 160.29(b) may be retained along with all other testing facility employment records for the length of time specified in paragraph (b) of this section.
 - (f) Records and reports of the maintenance and calibration and inspection of equipment, as required by § 160.63 (b) and (c), shall be retained for the length of time specified in paragraph (b) of this section.
 - (g) If a facility conducting testing or an archive contracting facility goes out of business, all raw data, documentation, and other material specified in this section shall be transferred to the archives of the sponsor of the study. The EPA shall be notified in writing of such a transfer.
 - (h) Specimens, samples, or other non-documentary materials need not be retained after EPA has notified in writing the sponsor or testing facility holding the materials that retention is no longer required by EPA. Such notification normally will be furnished upon request after EPA or FDA has completed an audit of the particular study to which the materials relate and EPA has concluded that the study was conducted in accordance with

this part. ((34074))

- (I) Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records.