



Things We Don't Talk About... The GLP Preamble

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What is the GLP Preamble?

- ▶ In 1989 EPA amended the 1983 FIFRA GLPs to:
 - ▶ incorporate changes made by FDA to its revised GLP regulations;
 - ▶ expand the scope of the FIFRA GLP standards to include environmental testing provisions from TSCA GLPs;
 - ▶ extend the scope to cover all studies (previously only health effect studies) submitted to EPA to support a registration including product performance data (efficacy testing) as currently required to be submitted by 40 CFR 158.640.
- ▶ When EPA initially published the rule in the Federal Register for public comments they received 43 comments letters

What is the GLP Preamble?

- ▶ When EPA published the proposed rule in the Federal Register they received 43 comment letters
 - ▶ 24 pesticide manufacturers
 - ▶ 8 associations
 - ▶ 10 testing or consulting labs
 - ▶ 1 another government agency
- ▶ Comments that raised important policy questions, suggested modification to the essence of the proposed regulation, or required individual response are discussed in the Preamble to the 1989 GLPs.

Why is it Important?

- ▶ Some of the responses to the comments are clarification of the EPA interpretation of the GLPs.
- ▶ There are many editorial comments (e.g., re-wording, phrase changes, addition/deletion of words) where the responses explain the thought process regarding why certain terminology was chosen.

160.3 - Experimental Start/Termination Dates

- ▶ In response to a comment regarding the difficulty of predicting experimental start and termination dates which are required to be in the protocol, EPA indicated that:
 - ▶ Experimental start and termination dates specified in the protocol are proposed dates. Therefore if actual experimental start or termination date is different from proposed dates no protocol amendment shall be required.
 - ▶ The same difficulty was pointed out in a comment about section 160.120 and EPA indicated again that the dates are “proposed” but also that 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.

160.3 - Basic Exploratory Studies

- ▶ In response to a comment indicating that results of “basic exploratory studies” may be required to be GLP since they may be included in submissions that support of registrations, EPA indicated that:
 - ▶ EPA doesn't explicitly require GLP standards for such tests even if data are later submitted to EPA. However, if 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 context of a study that is **required to be submitted** to EPA in support of a research or marketing permit. When GLP standards were not followed for a study performed with original intent of exploratory testing, GLP compliance statement should indicate such.

160.3 - Study Definition/Separate Protocols

- ▶ In response to a comment stating that 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 so each would require separate protocols and QA inspections, EPA indicated that:
 - ▶ EPA intends that QAU inspections be conducted at intervals adequate to ensure integrity of 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 larger study's protocol or SOP.

160.3 – Test System for Product Chemistry

- ▶ In response to a comment regarding product chemistry testing not involving a test system so should not be considered a “study” and should not be in the scope of GLPs, EPA indicated that:
 - ▶ Studies designed to determine physical or chemical characteristics of a test substance are included within scope of GLPs. Therefore, EPA intends to include product chemistry experiments in the definition of "study." This change is consistent with definition of "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.**

160.3 – Test System

- ▶ In response to a comment regarding what constitutes a test system for pre-emergent herbicides, soil pesticides and product chemistry studies EPA indicated that:
 - ▶ Definition of "test system" includes 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.**

160.33 - Archiving

- ▶ In response to a comment requesting change of terminology to allow archiving of study records within a “reasonable period” after the study completion, EPA indicated that:
 - ▶ 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.

160.35 – Separate QA

- ▶ In response to a comment regarding financial burden and difficulty establishing a completely independent QA with qualified personnel, EPA indicated that:
 - ▶ EPA does not require QAU to be a fixed, permanently staffed unit whose only functions are to monitor quality of a study. EPA is only concerned that there be a **distinct separation of duties between those personnel involved with conduct or direction of a study and those personnel performing QA on study**. Therefore, 160.35(a) prohibits personnel from performing QA activities on their own study. Regulations allow a study director for a particular study to serve as a part of QAU or as QAU for a different study.

160.35(b) – QA Inspections

- ▶ In response to a comment regarding the requirement for inspection of each study regardless of duration being excessive, especially where studies are performed by highly standardized procedures and stating that random sampling procedures should be allowed, EPA indicated that:
 - ▶ EPA does not believe that random inspection would be an appropriate method of evaluating a study. Generally, random sampling provides an adequate means of QC where analysis involves repetition or identical procedures. However, any assumption that conduct of one phase of one study would be representative of another would be invalidated by differences among study personnel and 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).

160.35 – Master Schedule Indexing

- ▶ In response to a comment stating that the requirement to index the master schedule should be deleted, EPA indicated that:
 - ▶ Deleting requirement to index by test substance would be inappropriate, since master schedule is mechanism through which QAU can assure management that facilities are satisfactory and there are adequate numbers of competent personnel available to perform 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 and hamper the conduct of a critical management role.

160.35 – Master Schedule Content

- ▶ In response to a comment asking if all studies need to be listed on the master schedule, EPA indicated that:
 - ▶ The GLP standards specifically exempt many product chemistry studies as described in 160.135.
 - ▶ The master schedule need only list those studies that will be or will likely be submitted to EPA.

160.47 – Separation for Mixing

- ▶ In response to a comment asking if it is 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, EPA indicated that:
 - ▶ 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**. Same sink can be used for all work involving mixing provided that SOPs used are adequate to prevent contamination and mixups. Requirement does not mandate the use of separate rooms so areas could be in 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.

160.63 – Records for Rarely Used Equipment

- ▶ In response to a comment regarding the prohibitive requirement for routine inspection and maintenance/calibration logs for all equipment, even if rarely used (e.g., for field studies), EPA indicated that:
 - ▶ The requirement states that equipment shall be "adequately inspected, cleaned and maintained" and "adequately tested, calibrated, and/or standardized." There is latitude in defining in SOPs what is "adequate". 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.

160.63 – Equipment Calibration

- ▶ In response to comment stating that some equipment such as tractors, land preparation and land measuring devices should be exempt from calibration requirement, as should standard commercially available lab ware, such as graduated cylinders, beakers, flasks, etc. and that only equipment directly related to application of test substance, such as applicators should be listed as requiring calibration, EPA indicated that:
 - ▶ Calibration should be required for application phase of field studies. However, method and exact equipment to be calibrated, are not specified in GLPs, but methods and records should ensure quality and integrity of study. Some equipment, such as graduated cylinders and volumetric flasks are pre-calibrated and do not need to be recalibrated. Methods used to measure all parameters inherent in determination of application rates would have to be adequately calibrated in order to ensure quality and integrity of study.

160.81 – SOP Deviation Authorization

- ▶ In response to a comment about section 160.81 stating that **minor SOP** deviations should not need to be authorized by study director (SD), especially in field studies where SOP deviations may occur, based on standard agricultural practices, before field personnel can consult with SD, EPA indicated that:
 - ▶ EPA disagrees that some deviations do not require SD authorization. It is necessary for SD to authorize deviations from SOPs to ensure that deviations do not have an adverse impact on study. SOPs should be written with sufficient flexibility to accommodate field studies by anticipating conditions under which appropriate actions must be taken without need for authorization by SD. Standard agricultural practices can be referenced in SOPs as long as this does not lead to ambiguity concerning appropriate action to be taken in a given situation. If SOPs state constraints on action and a decision is made within these limits, there is no deviation.

160.105(c) – Storage Container Retention

- ▶ In response to a comment stating that liquids from large containers are often placed into smaller containers for use during study and that these containers need not be retained after they are empty, since their retention does not enhance the quality or integrity of the data collected, EPA indicated that:
 - ▶ EPA disagrees with the suggestion. The retention of containers is necessary to ensure integrity of study. This includes empty containers, which must be kept to verify disposition of test, control, and reference substance. Disposal of containers adversely affects accountability.

160.105(d) – “4 Weeks Duration” Definition

- ▶ In response to a comment asking how "studies of more than 4 weeks duration" are defined, EPA indicated that:
 - ▶ The term "4 weeks duration" is meant to apply to experimental start and experimental termination dates. 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.

160.105(e) – Stability for Short Studies

- ▶ In response to a comment stating that 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 and that adequate knowledge of stability may exist from chemical information about test substance, EPA indicated that:
 - ▶ If a substance is known to be stable for a few days, then its stability is known in terms of test requirements. If stability is not known, it must be determined, even for short term studies. Storage stability needs to be known even if material is used "immediately". If enough information is known about material to support its stability from other testing, its stability is known and requirement is met. However, **theoretical stability is not considered to be adequate.**

160.113 – Mixtures, Tank Mix Analysis

- ▶ In response to a comment asking whether determination of uniformity, stability, and solubility of mixtures requires analyses for each tank preparation for field studies, EPA indicated that:
 - ▶ Once preparation method has been proven valid for a particular mixture, it need not be reconfirmed each time mixture is prepared. For field trials, there will be data submitted to EPA that support uniformity, stability, and solubility of a substance in carrier when prepared by appropriate method, i.e. according to proposed use or label. In such cases it may not be necessary to test each batch that is prepared for field application. Where available data are inadequate to support uniformity, stability, and solubility in a particular case, then it is necessary for 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 GLP provisions.

160.113 - Characterization

- ▶ In response to a comment stating that 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.
 - ▶ GLP standards do not require characterization for each study. 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.

160.120 – Exact Analyses in Protocol

- ▶ In response to a comment indicating that regulations state that a protocol must exist prior to study conduct, yet it would be almost impossible to specify exact analyses that would be performed on biological samples collected in the field until samples were collected, EPA indicated that:
 - ▶ Protocol requirement is not too restrictive to allow for situations where exact analyses performed may not be known in advance. Type or nature of analysis still needs to be specified in protocol. 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 protocol.

160.120(a)(7) – Test System Identification

- ▶ In response to a comment stating that “procedure for identification of test system” should be deleted since test system will be identified and justification for its selection will be in protocol, EPA indicated that:
 - ▶ Identification of test system is not covered in any 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.

160.120(a)(14) – Study Director Signature

- ▶ In response to a comment stating that when study director is part of a contract lab engaged for study by sponsor, it should be clarified that such required signature does not constitute review and approval of those parts of the protocol not related to the work done by the contract lab, EPA indicated that:
 - ▶ 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 definition of "study" and "study director" preclude such a separation of responsibility.

160.120(a)(15) - Statistics

- ▶ In response to a comment stating that “where applicable” should be added because statistics are not used in field studies, EPA indicated that:
 - ▶ Statistical methods are and should be used in field studies. However, where the use of statistics is limited this can be so stated.

160.135 – Product Chemistry Studies

- ▶ In response to a comment stating that all product chemistry should be exempted from GLP regulations, except for those studies specifically noted in 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, EPA indicated that:
 - ▶ 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 important to assure the quality and integrity of the data generated.

160.135 – Product Chemistry Studies

- ▶ In response to a comment regarding confusion about whether a protocol is required for “exempted” physical characterization studies, EPA indicated that:
 - ▶ EPA intends that a protocol still be required for partially exempted studies. Some, but not all, of the full protocol requirements are eliminated.
 - ▶ Sections 160.120(a)(1) through (4), (13), (14) are applicable for partially exempted study types.

160.135 –Product Chemistry QA

- ▶ In response to a comment stating that removal of physical and chemical characterization from responsibilities of QAU should not be accepted because it presents a major problem for QAU personnel and that QAU should be responsible for every study within the lab with no exception, EPA indicated that:
 - ▶ EPA disagrees with conclusion that QAU has no responsibilities in physical and chemical characterization studies. Exclusions reduce responsibilities of QAU, i.e. master schedule requirements, etc., but do not eliminate them.

Note: 160.35(a) which requires monitoring each study and conducting inspections applies to partially exempted product chemistry studies.

160.135 –Product Chemistry QA

- ▶ In response to a comment stating that QAU should be responsible for looking at functional components of lab (e.g., all melting points, all GC/MS analyses, etc.) rather than focusing on a particular study, such as with toxicology studies, EPA indicated that:
 - ▶ EPA agrees and is modifying inspection requirements of QAU under 160.35. This change specifies that QAU conduct inspections and maintain records that are appropriate to particular studies. This gives latitude to the QAU with respect to how information is gathered; i.e., **as part of standard review procedures of lab, or as needed for test**. This change should reduce 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.

160.135(b) - Product Chemistry QA

- ▶ In response to a comment stating that repetitive inspection of types of studies required in proposed 160.135(b) would consume large amounts of time for both study personnel and QAU staff without contributing to quality and integrity of data and that periodic inspection of such operations would provide necessary assurance that data were of sufficient quality and integrity to meet all requirements under GLP standards, EPA indicated that:
 - ▶ 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.

160.190(a) – Specimen Retention

- ▶ In response to a comment regarding clarification of retaining specimens “beyond quality assurance”, EPA indicated that:
 - ▶ 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.

160.195(i) – Exact Copies

- ▶ In response to a comment stating that EPA should explicitly state that when exact copies are substituted for original source as raw data, then original may be discarded and that in the past, EPA inspectors have required retention of original data even if exact copies existed and that some EPA auditors insisted that each copy be signed and dated, EPA indicated that:
 - ▶ Specific wording advising discarding of raw data after copying is not necessary or useful. "True copies" will be acceptable as raw data by EPA inspectors under 160.190. Signing and dating each copy may be impractical and an acceptable alternative method may be devised and incorporated into SOPs to ensure integrity of copies. Laboratories are cautioned that discarding originals places an additional burden on verification of authenticity of copies.

Link to Preamble

- ▶ A copy of the preamble can be found on the NAICCC website at:

<https://naiccc.org/wp/wp-content/uploads/epa-glp-preamble-1989.pdf>

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