

Frequently Asked Questions

GLP Amendments, Deviations, & Unforeseen Circumstances

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Excursions from GLP procedures, such as protocols, standard operating procedures, and test methods, can be problematic and impact the integrity of the GLP study. Simple strategies can be easily implemented to avoid procedure pitfalls by preventing or minimizing the potential for excursions to occur in the first place. Because of the nature of GLP studies, procedural excursions inevitably do and will occur. When they do occur, proper documentation of amendments, deviations, unforeseen circumstances and unusual events is crucial to the reconstructibility of a GLP study and the quality and compliance of the study report. Below are responses to ten frequently-asked questions related to excursions which occur in the real world of GLP.

1. Q. What is the difference between a protocol amendment and a deviation?

A. An amendment is a permanent change to a GLP protocol. A deviation is an excursion from a procedure (e.g. protocol, SOP, test method) or from a regulatory requirement or guideline. A deviation is usually a one-time occurrence or special case change that is not representative of the entire study. In some cases an excursion from a procedure will initially be a deviation and should be documented as such and then a protocol amendment will be written to permanently modify the protocol to include the change.

2. Q. Can you give an example of the difference between an amendment and a deviation?

A. Example of a deviation: The protocol states that the bioanalysis of the concentration of the test article in the plasma is to be conducted using a 0.5-mL aliquot of plasma. One vial of plasma from one test system contains less than 0.5 mL of plasma. The analyst makes a decision to run the sample using a 0.3-mL aliquot for that one sample only. This is a deviation to the protocol and is documented in the study file as such. The test results will be calculated based on an aliquot of 0.3 mL for this one sample. All other study samples are analyzed using an aliquot size of 0.5-mL so no protocol amendment should be written. The PI and study director must be notified and the impact on the integrity of the study must be assessed and documented.

Example of a protocol amendment: The protocol states that the bioanalytical method is to be conducted using a 0.5-mL aliquot of urine for the analysis. During the study it is determined

that the study sample concentrations are below the range of the calibration standard curve so a larger aliquot must be used for the assay to gain the sensitivity to allow quantification of the study samples. The volume used in the bioassay is therefore changed from 0.5-mL to 1-mL and a partial re-validation is conducted to assure the method is appropriate using the larger aliquot volume. The study samples are assayed based on an aliquot volume of 1-mL. The study director must generate an official written amendment to modify the protocol.

3. Q. Why is documentation of deviations and unforeseen circumstances so important?

A. As with all GLP study record-keeping, documentation of deviations and unforeseen circumstances is important. Documentation describing the deviations and events is a useful tool which may be critical in explaining “anomalies” in data and results and most importantly in supporting reconstructibility of GLP study.

4. Q. How can the negative stigma of deviations be overcome?

A. First, deviations have to be dissociated from job performance. While some deviations are indeed the result of poor job performance or neglect, that is more the exception than the norm. GLP deviations and unforeseen circumstances are generally the result of the “real life” nature of preclinical studies; after all this is a life science. Some deviations and unforeseen circumstances are the results of human error which again we must accept as a phenomenon that happens occasionally in “real life”. By accepting that deviations do occur, we can reduce the barriers that distract us from objectively handling these issues, and thereby focus on ways to prevent or minimize the potential for occurrence and effectively handle the inevitable deviation or incident. This message must be conveyed to all persons involved in GLP studies (study personnel, study director/PI, management, QA, sponsors).

5. Q. Amendments and deviations are supposed to be documented “promptly”. What is “promptly”?

A. FDA has issued 483 findings for lack of promptly written protocol amendments. While the regulations do not define “promptly” the FDA will issue findings for untimely issuance of amendments. Do not wait until the study report is being written to “catch up” on the writing and issuance of protocol amendments. This defeats the principle of the amendment. All individuals involved in the GLP conduct and monitoring must have access to the study protocol and therefore must have timely access to any modification to the study protocol (i.e. protocol amendments) in order to assure the study is conducted in accordance with the approved protocol. The study protocol is a summation of the original protocol document plus all subsequent

amendments. Your interpretation off “promptly”, therefore must be justifiably sufficient (pardon the use of another ambiguous term) for the circumstance at hand. It is recommended that protocol amendments be finalized within a few days/ less than two weeks of the modification. If the issue is urgent, a memo notification of the modification should be sent by the study director to all involved individuals and maintained in the study file. (Sometimes it takes longer to complain about why we don’t have time to promptly write a protocol amendment then to actually sit down and write one.)

As with all study raw data, the original documentation of a deviation must be recorded at the time of occurrence. The only exception is when a deviation is not discovered at the time it occurred, but at a later time (e.g. when study file is reviewed) in which case it should be documented when the deviation is identified and then brought to the attention of the study director.

6. Q. Can you give an example of how to avoid “protocol pitfalls” and minimize occurrence of protocol deviations?

- A. When writing a protocol, be specific enough to be useful (not ambiguous or open for interpretation), flexible enough to allow for decisions during conduct, and clear about details (which elements are flexible, how decisions/activities will be documented, and who makes the decisions). Compare the two excerpts below. Example 2, demonstrates the value of writing specific, flexible and clear protocols that can minimize deviations.

Example 1: Stability samples will be analyzed at time (t) = 0, 8, 24, and 48 hrs.

Example 2: Stability samples will be analyzed within ± 2 hours of target time points (t) = 0, 8, 24, and 48 hrs. Additional time points may be added as needed, with approval from the study director, and will be documented in the study file and final report. Backup samples will be prepared and stored in the event additional time points are needed, or as replacements for broken vials.

7. Q. Is a formalized system for the documentation of SOP deviations necessary?

- A. The important thing to remember is that your organization’s practice for documenting deviations should be established in a written SOP and performed consistently. Documentation can be in the format of free text recorded in the study file raw data, controlled forms used to document the deviation and investigation, or a corrective and preventative action (CAPA) system or database.

If your organization has a formal system set up for tracking deviations using controlled deviation forms or a database system, then deviations related to specific SOPs can be reviewed during the SOP review process. Examination of the SOP deviations which have occurred in the past may shed some light on beneficial revisions to the SOP which may reduce or eliminate the occurrence of deviations in the future.

8. Q. Who must be notified when a deviation occurs?

- A. Per the GLP regulations, the study director is the “single point of study control”. FDA GLPs 21 CFR Part 58 Sec. 58.33 Study director (EPA GLPs 40 CFR 160.33, 40 CFR 792.33) states that the study director shall assure that the protocol, including any change, is approved and followed; all experimental data, including observations of unanticipated responses are accurately recorded and verified; and unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented. Therefore the study director must be notified of all deviations which occur during a GLP study. It is then the study director’s responsibility to assure that the deviation is properly documented in the study file and all individuals involved in the study are informed as needed to assure the overall quality of the study.

For multi-site studies, the principal investigator (PI) must acknowledge all deviations which occur within the delegated phase of the study. The PI must also assure that the study director is notified of any such deviations and the study director, with the assistance of the PI, must assure the deviation is properly documented in the study file and assess the impact on study integrity.

9. Q. What deviations need to be reported in the final report?

- A. All deviations which occur during a GLP study must be documented in the study file. The final report must include a description of all protocol deviations and include a description of all circumstances and other deviations (e.g. SOP deviations) that may have affected the quality or integrity of the data. For example, if a protocol states that daily observations of the test systems will occur at time, 0, 1, 2 and 4 hours after dosing and a deviation occurs whereby the 4-hr observation time point is missed then this would need to be addressed in the final report. If an SOP states that the animal cage boards are to be changed 3 times a week and the technician missed one cage board change during the study, the deviation would require assessment by the study director and documentation in the study file but would most likely not affect the quality of the study or integrity of the data and would not need to be included in the final report.

10. Q. How should non-study-specific deviations be documented?

- A. Sometimes deviations occur that are not specific to any GLP study, for example, a facility inspection which is conducted after an 18-month interval instead of a 12-month interval as stated in an SOP or an analytical balance or pipette that was not calibrated by the calibration due date. In some cases, these deviations may occur when no GLP studies are being conducted and the deviation issue may have been resolved before a GLP study is started (e.g. the facility inspection has been completed or the calibration has successfully demonstrated that the equipment is still fit for use).

These non-study-specific deviations can be documented in several ways; there is no one best answer. Deviations related to equipment may best be documented in the corresponding equipment file/equipment logbook dedicated to that instrument so that all future users of that equipment will have access to the maintenance history and suitability of the equipment. Deviations pertaining to facility procedures such as inspections, training records, etc may be documented in a format that links the deviation with the relevant information (e.g. within the facility inspection or in the training file etc.)

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