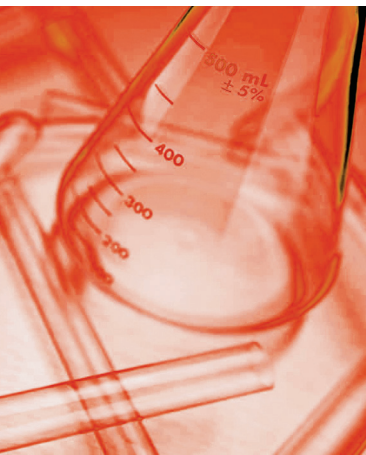


# Physicochemical Testing and the GLPs

Steven S. Kuwahara



ROBERT GEORGE YOUNG/GETTY IMAGES

“GLP Forum” addresses topics of interest associated with good laboratory practices. We intend this column to be a useful resource for daily work applications. The key objective for the column: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Manuscripts or case studies submitted by readers are welcome. Please send your comments and suggestions to column coordinator Steven Kuwahara at [stevekuwahara@yahoo.com](mailto:stevekuwahara@yahoo.com) or to journal coordinating editor Susan Haigney at [shaigney@advanstar.com](mailto:shaigney@advanstar.com).

## KEY POINTS

The following key points are addressed in this article:

- This discussion addresses physicochemical (non-animal) testing in good laboratory (GLP) facilities
- US Food and Drug Administration GLP regulations do not address physicochemical testing
- Environmental Protection Agency GLP regulations do address physicochemical testing
- EPA GLP regulations delete certain regulations more applicable to typical GLP animal testing from the physicochemical testing
- Stability of the analyte in the test articles under the test conditions should be known as a matter of good practice in any test setting
- The deletions employed by the EPA GLP effectively reduce GLP costs
- It is reasonable to apply the EPA GLP modifications to the FDA GLP for situations where physicochemical tests are performed.

## THE PROBLEM

When working with the good laboratory practice (GLP) regulations (1), one of the more problematic areas deals with physicochemical testing that is conducted under “GLP rules.” This situation arises because many companies wish to avoid testing under the good manufacturing practice (GMP) regulations (2) sometimes for reasons that are difficult to decipher. Contract testing laboratories are often asked to conduct testing under the GLPs by clients who believe that GLP-based testing

is somehow less expensive than GMP-based testing (3). The problem is that the pharmaceutical GLP regulations really address testing that is conducted on animals, and physicochemical testing is not directly considered.

The US Food and Drug Administration has not issued many guidance documents covering GLP issues. This has been somewhat puzzling given the plethora of guidance documents covering even the minutest issues in the GMP regulations. As a result there is no clear guidance of how a testing laboratory should approach physicochemical tests conducted on various samples generated in the course of GLP studies.

### THE SOLUTION

The solution may be found in the GLP regulations issued by the Environmental Protection Agency (EPA). It has previously been noted (4) that the EPA GLPs (5, 6) are similar to the FDA GLP (1). These GLPs are the result of the Toxic Substances Control Act (TSCA)(7) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)(8) and they do consider the need for physicochemical testing.

Based on the parts of Title 21 of the Code of Federal Regulations in which they are found, the TSCA GLP will be designated as §792, the FIFRA GLP will be referenced herein as §160, and the FDA GLP as §58.

Both §792 and §160 contain a section 135 (21 CFR 792.135 and 21 CFR 160.135) with identical wording. Section 135 is titled: "Physical and chemical characterization studies," and it contains two parts. Part (a) states: "(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, photodegradation, and chemical degradation studies) of test, control, or reference substances" (5,6). Therefore the purpose of the testing will control the extent to which the GLP need to be applied.

The second part of section 135 (21 CFR 160.135(b), for example) reads (6): "(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:

- Sec. 160.31 (c), (d), and (g)
- Sec. 160.35 (b) and (c)
- Sec. 160.43
- Sec. 160.45
- Sec. 160.47
- Sec. 160.49
- Sec. 160.81(b) (1), (2), (6) through (9), and (12)
- Sec. 160.90
- Sec. 160.105 (a) through (d)
- Sec. 160.113
- Sec. 160.120(a) (5) through (12), and (15)
- Sec. 160.185(a) (5) through (8), (10), (12), and (14)
- Sec. 160.195 (c) and (d)."

### The Effect Of The Deletions

All of these sections and subparagraphs, except for §160.120(a)(15), Proposed Statistical Methods, are also found in §58 (FDA GLP). If these deletions were also applied to §58, the effect would be to remove the following sections:

- §58.31, Test Facility Management (c). Requirement for a quality assurance unit.
- §58.31(d). Assure testing of test and control articles or mixtures for identity, strength, etc.
- §58.31(g). Communication of deviations reported by the quality assurance unit.
- §58.35(b). Responsibilities of the quality assurance unit.
- §58.35(c). Responsibilities of the quality assurance unit shall be in writing.
- §58.43. Requirements for the animal care facilities.
- §58.45. Requirements for the animal supply facilities.
- §58.47. Facilities for handling the test and control articles.
- §58.49. Laboratory operation areas.
- §58.81(b), Standard operating procedures (SOPs) (1). Animal room preparation
- §58.81(b)(2). SOP for animal care.

- §58.81(b)(6). SOP for handling dead or moribund animals.
  - §58.81(b)(7). SOP for the necropsy of animals.
  - §58.81(b)(8). SOP for the collection and identification of specimens.
  - §58.81(b)(9). SOP for Histopathology.
  - §58.81(b)(12). SOP for the transfer, placement and identification of animals.
  - §58.90. Requirements for animal care.
  - §58.105. Test and control article characterization. In §58 the removal of paragraphs (a) through (d) has the effect of removing the whole section, but in §160 and §792 paragraph (e) remains. Paragraph §792.105(e) reads: “The stability of test, control, and reference substances under storage conditions at the test site shall be known for all studies.” Thus it may be inferred that there is no intent (on the part of the EPA) to remove the requirement to know the stability of the substances under GLP testing conditions.
  - §58.113. Mixtures of articles with carriers.
  - §58.120. Protocol (a)(5). Procedure for the identification of the test system.
  - §58.120(a)(6). Description of the experimental design.
  - §58.120(a)(7). Description and/or identification of the diet.
  - §58.120(a)(8). Description of the dosage levels.
  - §58.120(a)(9). Type and frequency of tests, analyses, and measurements.
  - §58.120(a)(10). The records to be maintained.
  - §58.120(a)(11). Dates of approval by the sponsor and the study director.
  - §58.120(a)(12). Statement of the proposed statistical methods to be used. The removal of this section accomplishes the same thing as the removal of subparagraph 120(a)(15) from §792 and §160.
  - §58.185. Reporting of nonclinical laboratory results (a)(5). Stability of test and control articles under conditions of administration. The effect of the removal of this subparagraph is negated by the use of 135(a) from §160 and §729 that requires the use of the full GLP for stability studies. AS §58.185 refers to the contents of the final report on the nonclinical laboratory study, the effect here is to remove the information about the stability study from the final report, but it does not say that the stability study should not be performed.
  - §58.185(a)(6). Description of the test methods used.
  - §58.185(a)(7). Description of the test system used. This section refers to the description, where applicable, of the animals employed.
  - §58.185(a)(8). Description of the dosage and route of administration.
  - §58.185(a)(10). Names of the study director and other scientists or professionals involved in the study.
  - §58.185(a)(12). Signed and dated reports from each of the scientists or professionals involved in the study.
  - §58.185(a)(14). The statement from the quality assurance unit.
  - §58.195. Retention of records (c) Wet specimens. This paragraph refers to the retention of wet specimens derived from the test system.
  - §58.195(d). The master schedule sheet, copies of protocols, and records of quality assurance inspections that are supposed to be maintained by the quality assurance unit.
- The effect of these deletions will be to remove the requirements for the quality assurance unit and the requirements related to the handling and care of animals used in nonclinical laboratory tests. These removals would seem to be reasonable for physicochemical studies as they are normally of short duration and may be performed according to well defined standard operating procedures. In addition, physicochemical studies do not employ animals as a part of the test system.
- There are several major subparts of §58 (FDA GLP) that are not affected by these deletions. Subpart A, General Provisions; subpart D, Equipment; and subpart K, Disqualification of Testing Facilities would not be affected if these deletions from the EPA GLP were applied to §58.

## Stability Characterization

It should be noted that while some of the deletions, when applied to §58, appear to remove the need to understand the stability of the test and control articles. The EPA GLP, however, in section 135(a) of §792 and §160 retains the requirements to apply the full GLP to stability studies on the test and control articles. For this reason the need to characterize the stability properties of the test and control articles should be retained in §58. In any event, the stability of the analyte in the test articles under the test conditions should be known as a matter of good practice in any test setting.

## FINAL THOUGHTS

It has been noted previously (3) that the activities of the quality assurance unit and some of the administrative requirements of the GLP result in additional costs when tests are conducted under GLP rather than GMP rules. The deletions employed by the EPA GLP have the effect of reducing or removing some of these additional costs.

When the reduced costs are considered in conjunction with the fact that many of the requirements of the §58 are really not applicable to physicochemical tests, it would seem to be reasonable to propose that the modifications shown in section 135 of §160 and §792 should be applied to §58 for situations where physicochemical tests are performed.

## REFERENCES

1. 21 CFR 58, "Part 58—Good Laboratory Practice for Non-clinical Laboratory Studies," Code of Federal Regulations, Title 21, Volume 1, Chapter 1, (21 CFR 58), *Federal Register*, Volume 43, pp. 60013, December 22, 1978, and subsequent changes.
2. 21 CFR 210 & 211, "Parts 210 & 211—Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General. & Current Good Manufacturing Practice for Finished Pharmaceuticals," Code of Federal Regulations, Title 21, Volume 1, Chapter 1 (21 CFR 210 & 211), *Federal Register*, Volume 43, pp. 45076, September 29, 1978, and subsequent changes.
3. Kuwahara, SS, "GLP and GMP in Contract Testing of Drugs and Biologics— What's the Difference?", *Journal of GXP Compliance*, Vol 13, No. 2, Spring 2009.
4. Kuwahara, SS, "GLP Forum: The Other GLPs—The Environmental Protection Agency," *Journal of GXP Compliance*, Vol. 13, No. 4, Autumn 2009.
5. 40 CFR 792, "Part 792 – Good Laboratory Practice Standards." Code of Federal Regulations, Title 40, Volume 31, Chapter 1, (40 CFR 792), *Federal Register*, Volume 54, pp. 34043, August 17, 1989.
6. 40 CFR 160, "Part 160 – Good Laboratory Practice Standards." Code of Federal Regulations, Title 40, Volume 23, Chapter 1, (40 CFR 160), *Federal Register*, Volume 54, pp. 34067, August 17, 1989.
7. Toxic Substances Control Act, United States Code, Title 15, Section 2603 et seq.
8. Federal Insecticide, Fungicide, and Rodenticide Act, United States Code, Title 7, Section 136a, 136c, 136d, 136f, 136j, 136t, 136v, 136w; United States Code, Title 21, Section 346a, 348, 371. **GXP**

## ARTICLE ACRONYM LISTING

<b>EPA</b>	Environmental Protection Agency
<b>FDA</b>	US Food and Drug Administration
<b>FIFRA</b>	Federal Insecticide, Fungicide, and Rodenticide Act
<b>GLP</b>	Good Laboratory Practice
<b>GMP</b>	Good Manufacturing Practice
<b>SOPs</b>	Standard Operating Procedures
<b>TSCA</b>	Toxic Substances Control Act

## ABOUT THE AUTHOR

Steven S. Kuwahara, Ph.D., is principal consultant at GXP BioTechnology LLC ([www.gxpbiotech.org](http://www.gxpbiotech.org)) in Sunnyvale, CA. Steve has more than 30 years of experience supervising quality control departments dealing with drugs, biologics, HCT/P, and nutraceuticals. He has supervised animal facilities and testing laboratories that operated under GLP rules and also those operating under GMP and ISO standards. He may be reached by e-mail at [kuwahara@gxpbiotech.org](mailto:kuwahara@gxpbiotech.org) or [stevekuwahara@yahoo.com](mailto:stevekuwahara@yahoo.com) and by phone at 408.530.9338.