The Applicability of Good Laboratory Practice in Premarket Device Submissions: Questions & Answers

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Document issued on: August 28, 2013

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Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

This draft guidance answers commonly asked questions about the applicability of the Good Laboratory Practice (GLP) regulations for nonclinical laboratory studies conducted to support research and marketing applications for medical devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required..

For the purposes of this guidance, “you” refers to the device industry and “we” refers to FDA.

Background

The Good Laboratory Practice for Nonclinical Laboratory Studies (GLP) Regulations, 21 Code of Federal Regulations (CFR) Part 58, were first issued as a draft rule on November 19, 1976 (41 FR 51206), with the final rule issued on December 22, 1978 (43 FR 59986). Since then, the agency has received a number of inquiries regarding whether specific device premarket and research applications are subject to the GLP regulations. The agency has also received inquiries regarding whether specific nonclinical tests, e.g., animal studies, functional studies, or bench studies, are subject to the GLP regulations. The preamble to the

final rule issuing Part 58 generally discusses when Part 58 applies and also lists certain limitations regarding the scope, including the following: 1) GLP applies only to nonclinical laboratory studies submitted in support of a research or marketing application for a regulated product; 2) GLP does not apply to studies utilizing human subjects, human specimens, clinical studies, or field trials in animals; 3) the scope is limited to safety studies (functionality studies are excluded); and 4) the scope is confined to studies performed on animals, plants, microorganisms or subparts thereof (43 FR 59988, 12/22/78). The preamble does not distinguish between drug or device applications nor between premarket approval (PMA), humanitarian device exemption (HDE), premarket notification (510(k)), or investigational device exemption (IDE) submissions; rather, the preamble is careful not to create "exemptions based on broad categories of regulated products." The preamble states that "no compelling reasons have been presented that would support the contention that assurance of safety is less desirable for one class of regulated products than for another." (43 FR 59989) The specific purpose of this document is to provide guidance on the applicability of the GLP regulations for nonclinical laboratory studies submitted in support of premarket device applications and submissions.

Definitions

Q1: What is Good Laboratory Practice?

A1: The GLP regulations are found in 21 CFR Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies. FDA promulgated these regulations in response to public concerns that several important studies supporting the safety of FDA-regulated products were seriously flawed due to poor research practices and laboratory misconduct. The GLP regulations apply to nonclinical laboratory studies supporting research or marketing applications for FDA-regulated products (21 CFR 58.1). These regulations set forth the minimum basic requirements for study conduct, personnel, facilities, equipment, written protocols, operating procedures, study reports, and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated products.

Q2: What is a nonclinical laboratory study?

A2: A nonclinical laboratory study is an *in vivo* or *in vitro* experiment in which a test article is studied prospectively in a test system under laboratory conditions to determine its safety (21 CFR 58.3(d)). A test article is a medical device for human use, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (the Act) or under sections 351 and 354-360F of the Public Health Service Act (21 CFR 58.3(b)). A test system is any animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. A test system also includes appropriate groups or components of the system not treated with the test or control articles (21 CFR 58.3(i)). Examples of nonclinical laboratory studies include *in vitro* and *in vivo* biocompatibility testing and animal studies used to evaluate the potential for adverse responses to a medical device. Bench tests, such as chemical or physical testing, and any other studies that do not involve use of an animal, plant, or microorganism, are not included. Studies utilizing human subjects, human specimens, clinical studies, or field

trials in animals (e.g., wildlife studies) are not included, nor are basic exploratory studies carried out to determine whether a test article has any potential utility, or to determine physical or chemical characteristics of a test article.

Q3: Which device applications and submissions are subject to the GLP regulations?

A3: FDA promulgated the GLP regulation under section 701(a) of the Act, 21 U.S.C. §371, to assure the quality and integrity of safety data in support of FDA-regulated products. The scope of the GLP regulations (21 CFR 58.1(a)) includes nonclinical laboratory studies that support research or marketing applications across medical products, including devices marketed under section 510(k) of the Act, 21 U.S.C. § 360(k), PMAs and product development protocols under section 515 of the Act, 21 U.S.C. § 360e, and HDEs and IDEs under section 520 of the Act, 21 U.S.C. § 360j. See also 43 FR 59988.

Q4: Do the GLP regulations apply to human clinical studies?

A4: No. The GLP regulations do not apply to human clinical studies. FDA regulations governing human clinical trials are found in 21 CFR Parts 50, 54, 56, 312, and 812, among others.

Q5: Do the GLP regulations apply to nonclinical feasibility studies conducted in the early phases of product development or nonclinical effectiveness studies?

A5: No. The GLP regulations only apply to nonclinical laboratory studies that support research or marketing applications. Per 21 CFR 58.3(d), "nonclinical laboratory study" does not include "basic exploratory studies carried out to determine whether a test article has any potential utility . . . ." Therefore, basic exploratory studies carried out to determine whether a device has any potential utility, or to determine physical or chemical characteristics of a device, are not subject to the GLP regulations (21 CFR 58.3(d)). However, the design and implementation of such studies should be based on good science, and data collection should be such that the integrity and quality of the study remain robust.

Applicability of GLP Requirements and Device Submissions

Q6: Is a certification form to demonstrate compliance with GLPs required to be submitted?

A6: No, a certification form is not required. Facilities conducting studies in accordance with the GLP regulations are required to have a Quality Assurance (QA) Unit to monitor each study to assure conformance with the regulation (21 CFR 58.35). The final study report should include a signed statement from the QA Unit with the dates the study was inspected and findings reported. In support of research and marketing approval applications for medical devices, the applicant must include a statement that such studies

have been conducted in compliance with Part 58, or, if a study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance must be included in the submission (21 CFR 812.27(b)(3) and 21 CFR 814.20(b)(6)(i)). Similar statements indicating compliance with applicable requirements or providing the reason for any noncompliance should also be included with any nonclinical study reports provided in a 510(k) submission in which the purpose of the report is to provide information regarding the safety of the device.

Q7: What types of information should be provided if data from a study that is not in compliance with the GLP regulations is included in a research or marketing submission?

A7: The submission should contain a statement explaining the reasons why the study was not in compliance with GLP regulations and describe in detail all deviations from the regulations. The statement should include information that will help FDA reconstruct the study, explain any confounding variables, and demonstrate that authentic and complete test data have been collected and reported. Finally, if the study was not in compliance for lack of a QA Unit, the statement should indicate how the sponsor limited study bias and how they ensured the validity and integrity of the data without an independent QA Unit.

Additionally, the following information is helpful to FDA when evaluating the results of a noncompliant study. Such information helps to assure FDA that the test facility is operating under adequate controls, and includes:

- Statements that the test facility complied with the USDA regulations (9 CFR, Chapter 1, Subchapter A, Parts 1, 2, and 3) promulgated under the Animal Welfare Act (7 U.S.C. §§ 2131 et. seq.),
- USDA animal use policy statements,
- The US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training promulgated under P.L. 99-158, "Animals in Research," and
- Whether the test facility has an Assurance Statement on file with the Office of Laboratory Animal Welfare at the National Institutes of Health which administers the Public Health Service Policy on Humane Care and Use of Laboratory Animals and/or is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International.

Q8: What is the best way to address the impact of GLP non-compliance in a submission?

A8: We recommend that the submission systematically address key elements of 21 CFR Part 58, and include a statement addressing how bias was minimized and how the reporting of the results is objective. Another option is to provide a contract audit or peer-reviewed evaluation of the study director's report by experts who can demonstrate that they are separate from and independent of the personnel engaged in the direction and conduct of the study.

Q9: Is financial burden an appropriate consideration for accepting data not in compliance with the GLP regulations?

A9: No. 21 CFR Part 58 does not include a provision for accepting data not in compliance with the GLP regulations due to the financial burden incurred by the sponsor or applicant.

Q10: Are nonclinical laboratory studies conducted outside the U.S. (OUS) that support a U.S. marketing or research submission subject to the GLP regulations?

A10: Yes, as discussed in question 3, the GLP regulations govern nonclinical laboratory studies conducted in support of FDA research and marketing applications for medical devices, regardless of where the testing is conducted.

Q11: Is OUS marketing approval an appropriate consideration for accepting data not in compliance with the GLP regulations?

A11: No. There is no provision to accept data not in compliance with the GLP regulations for a device that has been approved for marketing OUS. However, adequate data collected to support approval for foreign markets may satisfy data requirements for US studies that otherwise would require animal or other nonclinical data. We recommend you discuss with FDA how foreign clinical data or experience with a device may be used to satisfy premarket requirements.

Q12: Do the GLP regulations (21 CFR Part 58) apply to *in vitro* diagnostic (IVD) devices?

A12: The GLP regulations only apply to nonclinical laboratory studies, which are defined as: "*in vivo* or *in vitro* experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety." (21 CFR 58.3(d)) Studies intended to evaluate the performance of IVD devices to determine their safety typically utilize human subjects or specimens derived from human subjects and are therefore not subject to the GLP regulation.

Q13: Are nonclinical laboratory studies subject to audit and inspection for compliance with the GLP regulations?

A13: Yes. Testing facilities are required under 21 CFR 58.15 to permit an authorized employee of the FDA to inspect the facility and inspect all records and specimens required to be maintained regarding studies within the scope of Part 58. The FDA will not consider a nonclinical laboratory study in support of a research or marketing application if the testing facility refuses to permit the inspection (21 CFR 58.15(b)).

References

1. "Good Laboratory Practice for Nonclinical Laboratory Studies," Title 21 Code of Federal Regulations Pt. 58. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=58

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    - ”Definition of Terms,” Title 9 Code of Federal Regulations, Pt. 1: http://www.access.gpo.gov/nara/cfr/waisidx_03/9cfr1_03.html
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5. Public Law 99-158 “Animals in Research” Health Research Extension Act of 1985 November 20, 1985. http://grants.nih.gov/grants/olaw/references/phspol.htm#HealthResearchExtensionActof1985

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