参考資料３－３

Guidance for Industry

Good Laboratory Practice Regulations Management Briefings

Post Conference Report

U.S. Department of Health and Human Services
Food and Drug Administration
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MANAGEMENT BRIEFINGS
ON THE GOOD LABORATORY PRACTICE REGULATIONS
POST CONFERENCE REPORT

On May 1, 2 and 3, 1979, FDA conducted half-day briefing sessions in Washington, Chicago and San Francisco on the Good Laboratory Practice Regulations. The purpose of the sessions was to provide the regulated industry with information to understand and comply with the regulations. The program included speakers from FDA as well as representatives from the American Association for Accreditation of Laboratory Animal Care (Dr. J. W. Ward), the National Association of Life Science Industries (Mr. D. P. Neilsen and Dr. H. C. Brown, Jr.), and the Society of Toxicology (Dr. R. B. Forney). Attendance at the three sessions was estimated at 800 persons affiliated with some 149-sponsor laboratories, 68 contractor laboratories, 19 university laboratories and 10 government laboratories. Some three hundred questions were posed; many of which were answered by the panelists during the question and answer portion of the sessions. At the sessions, the agency announced its intention to make available to the registrants and other interested persons a post conference report which would include the substance of all the answers to the questions posed at the conferences, including those questions which were not responded to because of time limitations.

INTRODUCTION

The questions received pertained to general and specific issues concerning the provisions of the GLPs, inspectional procedures, and FDA's enforcement policies. Many of the questions and their answers have been consolidated to eliminate redundancy and to focus more sharply on the issues.

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QUESTIONS AND ANSWERS

THE GLP REGULATIONS - GENERAL

1. Do the GLPs require the establishment of Technical Operation Manuals?

   No.

2. If a laboratory is accredited by AAALAC (American Association for Accreditation of Laboratory Animal Care), does this serve as assurance of meeting the GLP requirements for animal care and facilities?

   AAALAC accreditation does not substitute for Agency inspection nor does it guarantee automatic compliance with the applicable GLP sections. It is of value, however, in that it demonstrates that the facility has favorably passed a peer group review.

3. Results of the quality assurance unit inspections are not routinely available to an Agency investigator. However, the conforming amendments require that GLP deviations are to be reported in detail with each submission to the FDA. Are we required to send the contents of the quality assurance unit inspection report to the FDA?

   No. The GLP compliance statement in the conforming amendments to the GLPs was included for several reasons:

   (a) to provide an orderly transition across the effective date of the regulations. It was understood that applications for research and marketing permits submitted to the Agency for some period of time after the GLP effective date of June 20, 1979, would contain final reports of nonclinical studies begun and completed prior to the effective date, begun prior to the effective date and completed thereafter, and begun and completed after the effective date. Studies begun and completed prior to the effective date are not required to comply with the GLPs and accordingly, the conforming amendments require that differences be noted. Similar considerations apply to studies begun prior to and completed after the effective date, although in these studies, those portions underway as of the effective date are required to comply.

   (b) to provide for the submission of final reports of studies, which were not required to comply with the GLPs but which otherwise, contribute to safety evaluation. The GLPs do not apply to safety studies conducted by independent investigators studying regulated products. Such studies are not sponsored by the product manufacturer, nor is there any intention to submit the results to the Agency. The study results are published in the open literature. The sponsor is required red to submit the study to the Agency but could in no way control the research. If the

sponsor wishes to use the data in support of the application, the conforming amendments provide a mechanism by which the sponsor can prove that the study was not compromised. A similar situation exists for preliminary exploratory safety studies done by the sponsor.

(c) to foster GLP compliance attitudes by management. The conforming amendment causes management to act responsively to all cases of GLP non-compliance and to take prompt corrective actions.

With these purposes in mind, the conforming amendments require a brief statement of overall GLP compliance and need not contain the Quality Assurance Unit findings. The Quality Assurance Unit findings should cover short-term GLP deviations, which are promptly corrected. The conforming amendments statement should cover those systematic GLP deviations which have occurred throughout the study.

4. Who provides the GLP compliance statement required by the conforming amendments?

   This statement is provided by the applicant for the research or marketing permit.

5. What is the degree of compliance with GLPs, which the FDA will require for INDs submitted after June 20, 1979, but which include toxicology studies initiated before June 20, 1979, and completed after June 20, 1979?

   Those portions of the studies underway as of the effective date will have to be done in accord with the applicable provisions of the GLPs.

6. Do nonclinical laboratory studies completed *prior to June 20, 1979 but submitted as part of an IND or NDA subsequent to that date fall under the conforming amendments?

   These studies would not have to have been conducted under the GLPs but the conforming amendment statement of compliance is required.

7. How many members of the National Association of Life Science Industries (NALSI) come under the GLPs? How can the membership list be obtained?

   The Agency has not compiled such a list. A membership list is available from NALSI, 1747 Pennsylvania Avenue, NW, Suite 300, Washington, D.C. 20006. All members who conduct nonclinical laboratory studies are subject to the GLPs.

8. Should a contract laboratory ask a sponsor if the article they are testing is subject to FDA regulations? Should these studies then be listed as a separate master list of studies to comply with the GLP regulations?

Contract laboratories should ask sponsors to identify studies which are associated with FDA regulated products, although the GLPs place this responsibility on the sponsor. A separate listing of such studies, apart from the firm's master list of all studies undertaken by the firm will satisfy the requirements of the GLPs.

9. What impact have the GLP regulations had on the cost of performing toxicology studies?

The president of a large contracting laboratory has stated that three years ago a chronic rat study could be done for about $80,000; and that the current cost is closer $250,000. He estimated that half of the increased cost is due to GLPs, 30% to larger numbers of test animals per study on present day protocols and 20% to inflation. The Agency has not developed cost estimates.

SUBPART A
GENERAL PROVISIONS

58.1 SCOPE
58.3 DEFINITIONSAPPLICABILITY TO STUDIES PERFORMED UNDER GRANTS AND CONTRACTS
58.15 INSPECTION OF A TESTING FACILITY

1. Are short-term microbiological screening tests and microbiological preservative stability research and development covered by the GLPs?

   Microbiological preservative stability research, development and quality control tests are not covered by the GLPs. However, microbiological tests conducted to establish the toxicological profile of an article are covered.

2. Does the Agency intend to audit analytical data collected on a test article?

   Yes, insofar as it contributes to the evaluation of a nonclinical laboratory study.

3. Does the Agency intend to audit draft final protocols and draft final reports?

   The regulations do not require that such materials be retained, however, if draft reports are available, they may be audited in order to help the Agency follow the process from raw data to final report.

4. Explain why the GLPs apply to "microorganisms or subparts thereof." How are microorganisms currently used by FDA in assessment of safety?

   For certain products, FDA does request that microbial tests be done for the purpose of obtaining information on potential neoplastic and mutagenic activity. Likewise, microsomal preparations (subparts thereof) are used as activating systems for certain in vitro tests. When this happens, the tests should be done in accord with the GLPs.

5. Do the GLPs apply to engineering/electronic testing laboratories that perform functionality tests on medical devices?

   No.

6. Is a licensed manufacturer of human biological products subject to continuing GLP inspection?

   The GLPs apply to safety studies submitted to the Agency in order to obtain the license. They do not apply to such studies conducted for the purpose of obtaining batch release of licensed biologicals.

7. Will nonclinical studies in support of medical devices which do not come in contact with man (e.g., stopcocks, a gas machine, a urine bag) be subject to the GLP regulations?

   If the medical device application for a research or marketing permit does not require the submission of safety data for approval, then the GLPs do not apply.

8. If a test article is produced by microbial fermentation, are tests run on the bacteria, such as pathogenicity or virulence covered by the GLPs?

   No.

9. Are studies performed for label purposes as required by the Federal Hazardous Substances Act considered to be nonclinical laboratory studies under the GLPs?

   No.

10. When an application for Premarket Approval for a Class III Device is scrutinized, would a GLP audit by FDA become a criterion for premarket approval?

    Safety data are required for Class III Devices and such data are to be collected under the GLPs, but an FDA audit will not automatically become part of the premarket approval mechanisms.

11. Are Class I, II and III Devices regulated products within the meaning of the GLPs?

    Yes.

12. Are data contained in a 510(k) notification subject to the GLPs?

    No.

13. How do the GLPs apply to the testing of electromechanical medical devices (non-animal work)?

    It is presumed that the question refers to engineering tests and in vitro tests of such devices conducted to assess functionality. In these cases, the GLPs do not apply.

14. Please elaborate on the preamble statement (43 FR 59989) that studies involving "diagnostic products" and "medical devices, which do not come in contact with or are implanted in man" are not within the scope of the GLPs.

    Failure of diagnostic products or medical devices, which do not come in contact with man or are not implanted does pose a safety hazard. This is also true for implantable devices. Tests to establish the reliability of these articles are functionality tests, not

safety tests. The GLPs cover implantable devices, which may cause adverse tissue reactions or may have components, which leach into the tissues and cause a toxic response.

15. Is an in vitro study to quantitate the amounts of residual proteolytic enzyme on a soft contact lens (the enzyme is used to clean the lens) a safety study which is covered by the GLPs?

    No, the enzyme is part of the lens manufacturing process and its analysis would be covered by the GMPs and not the GLPs. If, however, the proteolytic enzyme is sold as a means of cleaning lenses after purchase by a person, the enzyme is an accessory to a medical device and the safety studies supporting the use of the enzyme would be subject to the GLPs.

16. Do engineering laboratory tests done on components of implantable medical devices fall under the GLPs?

    No.

17. Are safety tests conducted on biological products exempt from the GLPs?

    Two kinds of safety tests are performed on human biological products. Those which are performed by the manufacturer prior to licensing, and those performed post licensing. The tests performed prior to licensing establish the basic safety profile of the product and they are covered by the GLPs. The safety tests performed post licensing are part of the required quality control assays, which permit the release of each batch of product. These tests are not covered by the GLPs. Safety testing of interstate biological products for use in animals is not covered by the GLPs since these products are not regulated by FDA.

18. Do the GLPs apply to veterinary drug and biological manufacturers even when the end products are strictly for veterinary use?

    The GLPs apply to animal drugs used on a prescription basis but they do not apply to interstate veterinary biologicals since these products are regulated by USDA. Intrastate veterinary biologicals, which are considered to be new animal drugs, are also covered by the GLPs.

19. If an organization has separate divisions for basic research and for toxicological safety testing, will the basic research division be subject to inspection under the GLPs?

    No, as long as the basic research division is not providing any service function for the safety-testing unit.

20. Do the GLP requirements apply to an equal degree to acute, medium-term, and long-term studies?

    The GLPs apply equally to all nonclinical laboratory studies. It should be recognized, however, that short-term (less than 6 months) studies need not be inspected as frequently as long term (more than 6 months) studies by the quality assurance unit.

21. Are preliminary protocol development or design studies that employ laboratory animals covered by the GLPs?

    No, these are preliminary exploratory studies.

22. If an acute oral toxicity study, a 90-day oral toxicity study, and a two-year chronic study are done, is only the two-year study required to be done under the GLPs?

    No. Each study, regardless of its duration or complexity should be considered in terms of its purpose. A study, which is conducted for the purpose of estimating the safety of a product in, humans or animals and which will be submitted to FDA, is covered under the GLPs. This includes acute oral toxicity studies as well as 90-day oral toxicity studies and two-year chronic studies. In early phases of research, acute studies are often used to select the most promising product from a group of candidate products. In this sense acute studies are exploratory or screening in nature and would be exempted from the GLPs. There are also special situations where a 90-day oral toxicity study or even a chronic oral toxicity study may be exempted from GLPs. For example, a multinational company may want to develop Product A for a very specific foreign market. The company has no intention of ever applying to FDA for an investigational or marketing permit for Product A. Long-term safety studies with Product A for the purpose of foreign registration would be exempted from GLPs.

23. Will you please ease define a range-finding study and will such studies be inspected?

    A range-finding study is conducted to gather information such as dose range or toxicological end point to permit the more proper design of a subsequent nonclinical laboratory study. Such studies, which are usually short-term, are preliminary exploratory studies, which are exempt from the GLPs if properly labeled as "range-finding" or "preliminary pilot study" or similar designation. These studies will usually not serve as the basis of inspection, but may be reviewed to determine whether the operation of a facility is in compliance with the GLPs. Although the studies are exempt from the GLPs, they must still be submitted to the Agency as part of the respective application for a research or marketing permit.

24. Does the Agency agree that the GLPs are applicable to safety studies intended for submission to the Agency in support of the approval of a regulated product and that

they are not applicable to preliminary exploratory studies, screening studies, and range-finding studies whose purpose is to develop or improve the experimental design of a planned nonclinical laboratory study?

Yes.

25. Many toxicological studies are conducted on products or formulations, which are comprised entirely of materials which are known to be safe. Such studies are intended to be a quality control measure to determine lack of product integrity or to detect adulteration. Do the GLPs apply to such studies?

No. The Agency considers such studies to be quality control studies, which are not subject to the GLPs.

26. Does a food manufacturer's laboratory, which conducts only microbiological screening studies, have to comply with the GLPs?

Generally no. The GLPs apply to safety studies intended for submission to the Agency in support of product approval. Food microbiology studies are quality control studies not subject to the regulations.

27. Do the GLPs apply to laboratories, which perform routine sterility analyses on marketable medical devices, which have been treated with gas for the purpose of sterilization?

No.

28. Are studies of approved drugs or devices undertaken for physician education, advertising or pharmaceutical marketing purposes subject to the GLPs?

No.

29. Do the GLPs apply to safety substantiation studies conducted on over-the-counter drugs, which are covered by a final monograph?

No.

30. It is not clear whether a laboratory involved solely in chemical analysis support of a nonclinical laboratory study would be required to comply with the GLPs. Can this be clarified?

Yes. Analytical laboratories must comply with the GLPs to the extent that they provide data, which support the nonclinical laboratory study. Only those portions of the laboratory, those procedures and those personnel involved are required to be in compliance with the GLPs.

31. What is FDA's position regarding the testing of "medical foods" according to GLP requirements?

    By "medical foods," it is assumed that you mean either diets, which complement human therapy, or dietary products used for nutritional purposes. Such products usually do not require an application for a research or marketing permit and therefore they do not fall under the scope of the GLPs. If an application is required, the safety tests would be within the scope.

32. How do previous GLP inspections prior to these new regulations affect our being accredited by AAALAC?

    Not at all. AAALAC accreditation deals with animal care practices and is a process, which is independent from FDA's GLP inspections.

33. What about the special problems university laboratories have with complying to the GLPs? Are these laboratories expected to comply to the same degree as industry laboratories?

    In crafting the final order, the Agency was cognizant of the problems of university laboratories and certain changes were made which would simplify compliance for all laboratories without frustrating the intent of the GLPs. All laboratories are expected to comply to the same degree since product safety decisions are of equal importance regardless of the size or of the organizational structure of the laboratory doing the study.

34. Are analytical laboratories, which perform support characterization of a substance subject to GLP inspection? If so when and under what circumstances?

    Yes, the laboratories are subject to inspection at the request of the headquarters bureau, which is evaluating the nonclinical laboratory studies on that substance. The kind of inspection will be a data audit which will include only those records, personnel and portions of the laboratory which collected the data on that substance.

35. Does the definition of nonclinical laboratory study include electrical safety of medical devices or evaluation of "safe" operation of equipment, i.e., fail-safe studies for a critical device?

    No, functionality studies do not fall within the scope of the GLPs.

36. Do metabolism studies come under the scope of the GLPs?

    For drugs and feed additives used in food producing animals, metabolism studies come under the GLPs. In these cases, the studies are intended to define the tissue

residues of toxicological concern as well as to estimate tissue depletion. Such studies on other regulated products are usually conducted as part of the pharmacological evaluation and would not be covered. However, metabolism studies on food additives are covered.

37. Does the FDA have a list of laboratories, which do and do not comply with the GLPs?

No, but the Agency maintains a list of the laboratories which have been inspected. Copies of individual inspection reports may be obtained as a Freedom of Information request.

38. Does the term "nonclinical laboratory study" include animal laboratory studies, which are designed for the explicit purpose of determining whether a test article has reasonable promise of clinical effectiveness, and in which observations bearing on clinical safety are only incidental or fragmentary, or at most, clearly secondary?

No.

39. With regard to the Submission of foreign toxicity data to the Agency, must a sponsor monitor and inspect the foreign laboratories and audit the final study report?

Not necessarily. The foreign laboratory would be considered a contract laboratory and the sponsor's responsibilities would be as set forth in question 40 (below).

40. If a sponsor company utilizes a contract laboratory, who is responsible for the GLP compliance of the contract laboratory? Should a sponsor have its own quality assurance unit to monitor contracted studies? If a contract laboratory has its own quality assurance unit, is it necessary for the sponsor to audit these studies also? How does a sponsor validate a report of a study performed at a contract lab?

The ultimate responsibility for assuring the quality and integrity of a nonclinical laboratory study rests with the person (sponsor) who submits the application for a research or marketing permit to the Agency. This responsibility can be discharged as follows:

Case 1. The contract laboratory has a fully functional quality assurance unit and is operating in conformance with the GLPs. In this case, the sponsor should assure itself that the contract facility has adequate personnel, facilities, equipment and standard operating procedures to perform the study properly. Likewise, the sponsor should examine the procedures used by the contract facility's quality assurance unit and make a determination that such procedures are adequate to obtain GLP compliance. Finally, the sponsor should review the final report (not audit since this has already been done by the contract facility) for consistency and accuracy.

Case II. The contract laboratory does not have a quality assurance unit and may or may not be operating in conformance with the other provisions of the GLPs. In this case, the sponsor must perform all quality assurance functions and take whatever steps are required to promote the GLP compliance of the contract facility. The final report will have to be audited since this has not been done by the contractor.