ENFORCEMENT STRATEGY

GENERAL POLICY

1. What is the regulatory basis for conducting GLP inspections? It would seem that by making the GLPs regulations instead of guidelines, that the attorneys and accountants are managing the studies. How does that produce good science?

   The GLP regulations are process-oriented; they are designed to assure that the data collected in a nonclinical laboratory study are valid and accurately reflect the responses of the test system. The GLP inspections are necessary to assess the degree of compliance with the GLPs. The science of a study depends on the appropriateness of the design selected to answer the questions raised in the use of the test article as well as the soundness of the conclusions drawn from the data collected in the study. The assessment of the scientific merit of a study is made by scientists.

2. Does FDA have the authority to audit an ongoing study of a product for which an application for a research or marketing permit has not yet been submitted to FDA?

   A distinction needs to be made between an audit of a study and a GLP inspection. An audit involves a comparison of raw data with completed reports to identify errors and discrepancies. A GLP inspection involves an assessment of the procedures used to carry out the study and to record and store the data. FDA audits only studies, which have or are intended to be submitted to the Agency. The FDA will, however, look at on-going studies whether or not they involve FDA regulated products for purposes of documenting the laboratory's adherence to GLPs; such an inspection does not, however, constitute a data audit of the study rather it is an audit of the "process."

3. What happens when a laboratory refuses to permit an inspection of its facilities?

   If the laboratory is actively conducting studies on investigational new drugs, investigational new animal drugs, or investigational devices, refusal to permit inspection is a violation of section 301(e) or (f) of the Act and the Agency will take whatever action is required to compel inspection.

   Where the Agency has reason to believe that the laboratory is in fact conducting nonclinical laboratory studies, a letter will issue to the laboratory stating that FDA will not accept any future studies performed by that laboratory in support of a research or marketing application. If the laboratory has not, or is not testing an FDA regulated product, it is also advised to contact the local FDA district office to arrange for an inspection should they anticipate engaging in such safety testing.

4. What happens if in the course of an inspection of a contract laboratory, the sponsor of the study selected for GLP inspection refuses to permit access to the study records?

   The FDA investigator will select another study and proceed with the inspection. If the study originally selected for inspection involved an FDA regulated product, the Agency will pursue the matter directly with the sponsor.

5. If GLP regulations are not retroactive, will FDA audit pre-June 1979 studies? If so, will FDA investigators list non-conformance with GLPs on the FD-483 Notice of Observations associated with those studies?

   FDA will continue to audit pre-June 1979 studies for purposes of assessing not only the quality of a particular study, but also the general performance of the laboratory prior to the time when GLP regulations were first proposed in November 1976. This is necessary because many of the marketing applications pending before the Agency contain studies performed prior to 1976.

   While deviations from the GLPs will be noted in the FD-483 associated with these studies, the Agency will use this information only to make a judgment regarding the scientific acceptability of those studies and will not use the deviations to initiate regulatory action against the laboratory. After the June 1979 effective date, however, deviations from the GLPs could result in regulatory action against both the studies and the laboratories.

6. Will the GLPs apply to a study, which has been completed prior to the June 20, 1979, effective date for which a final report will not be prepared until after?

   The GLP regulations became effective June 20, 1979, and those portions of studies underway, as of that date, even if only the final report, became subject to the regulations at that time.

7. Will a laboratory engaged in testing an FDA-regulated product be subject to a GLP inspection if a research or marketing application has not been submitted to the Agency, e.g., a new company developing its first products?

   Generally speaking, FDA inspects only those laboratories, which have conducted studies submitted to the Agency. FDA strongly advises any laboratory which intends to engage in the safety testing of a regulated product, and which has not been previously inspected, to contact the local FDA district office and request a GLP inspection.

8. Will FDA accept data from a study not conducted in accordance with GLPs for regulatory purposes?

Even though a study has not been conducted totally in accordance with GLPs, FDA may accept the data from such a study if it can be demonstrated that the areas of non-compliance have not compromised the validity of that study. As a special corollary to this policy, FDA will take note of positive findings of toxicity in a study even though that study was not conducted in compliance with GLPs. While a technically bad study can never establish absence of a safety risk, it may establish the presence of an unsuspected hazard or untoward effect.

9. Where can the Inflationary Impact Assessment Report of the GLPs be obtained?

By writing to the: Hearing Clerk
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

10. How does FDA protect the confidentiality of valuable commercial or trade secret information given to an investigator during a GLP inspection?

FDA employees are required by statute to protect the confidentiality of any trade secret or confidential commercial information which they may acquire in the performance of their duties. Thus any trade secret information which an FDA investigator may receive from a laboratory being inspected is exempt from public disclosure. Whenever the FDA receives a Freedom of Information Act request for a copy of the laboratory inspection report, all information which falls under the definition of trade secret or confidential commercial information will be purged from the report before it's released.

From a practical standpoint, there is a "gray area." of information, which may or may not be privileged information. FDA personnel will make every effort to determine whether the rules of confidentiality apply in such cases. The final decision, however, will be FDA's.

11. Will FDA review non-GLP studies (range-finding, exploratory studies) in the course of conducting GLP inspections of studies intended to be submitted to the Agency? This is of particular concern in protecting proprietary research data. Will there be an opportunity for the inspected firm to do an FOI review before the final inspection report is written?

FDA may review on-going non-GLP studies as described in question 23 on Subpart A and question 11 under "Inspections."

The inspected firm may not review a draft inspection report for purposes of identifying what should not be released under FOI. Even if the Agency permitted this, which it does not, the fact that the report was made available to someone outside

the Agency would immediately make that draft document available for public disclosure under the provisions of the FOI regulations.

12. Will foreign laboratories be inspected to determine their compliance with GLPs?

    Foreign laboratories, which conduct studies submitted to the Agency, will be inspected and held accountable to the same GLP requirements as U.S. laboratories. While FDA has no authority to inspect foreign labs, the Agency has adopted the policy of not accepting data from any laboratory (domestic or foreign) which refuses to permit an inspection of its facilities.

13. What accords have been made with foreign countries regarding GLPs and inspections?

    FDA has signed a Memorandum of Understanding with Canada and Sweden, which commit both countries to establish GLPs and an inspection system. Discussions, which may lead to similar accords, have been held with Great Britain and Switzerland. Informal expressions of interest have been received from other countries. The long-range objective of these bilateral agreements is reciprocal recognition of each country's GLP program.

14. Has FDA inspected its own animal research facilities for compliance with GLPs? Other Federal laboratories?

    Yes. To date, FDA has completed GLP inspections of all its animal research facilities and is taking steps to bring all its laboratories into compliance. FDA has also established contacts with the NIH, DOD and USDA for purposes of scheduling inspections of laboratories performing safety studies intended to be submitted to the Agency.

15. Has FDA established liaisons with other Federal agencies regarding the GLP program?

    Yes, liaisons have also been established with CPSC, EPA, and OSHA for purposes of furthering the objectives of the GLP program, scheduling inspections of Federal laboratories and sharing information resulting from the FDA program.

INSPECTIONS

1. Is it possible that an FDA investigator may take exception to a firm's definition of regulated and nonregulated laboratory studies? If such a difference of classification arises for a given study, how would you resolve the conflict with the FDA?

   Yes, it is possible. The testing facility may appeal any differences it has with the investigator first to the FDA district office and, if this is not satisfactory to FDA headquarters.

2. What is the estimated number of laboratories being inspected by FDA?

   FDA's inventory of laboratories subject to GLPs includes approximately 380 domestic laboratories and 110 foreign laboratories. The laboratories include sponsor laboratories, commercial contract laboratories and university laboratories.

3. Will the inspectional training course at the National Center for Toxicological Research be open to industry and academia?

   No. The training of industry and academic personnel to enable them to properly perform their duties is the responsibility of their employers. However, FDA is prepared to participate in any training courses, which may be offered by industry associations or the academic community to the extent that resources will allow.

4. If the GLPs are Phase I of Bioresearch Monitoring, what other phases are anticipated by FDA?

   Other phases include new regulations on obligations of sponsors and monitors of clinical investigations, obligations of clinical investigators, and obligations of institutional review boards. Note that these regulations are directed towards efficacy data and the protection of human subjects whereas the GLPs are directed towards safety data.

5. Who makes the decision on whether or not a headquarters scientist participates in a GLP inspection? Why can't we have a headquarters scientist on each inspection?

   The scheduling bureau makes the decision. During the past two years, headquarters scientists have participated in about half of all GLP inspections and, with rare exception, the Bureau of Biologics assigns a headquarters scientist to each GLP inspection. Resources do not permit more extensive participation.

6. How are laboratories selected for inspection?

   Laboratories are selected for inspection by bureaus within FDA. The criteria for selection are actual or potential involvement in studies associated with products

regulated by FDA. Inspections will involve a specific study submitted to a bureau or a study selected from the firm's master list which is of interest to FDA.

7. How often can a laboratory expect to be inspected?

   Routine surveillance inspections will occur at least once every two years or more frequently depending upon findings of previous inspections. However, more frequent inspections may occur when an audit of a specific study submitted to FDA or EPA in support of a marketing application is required.

   Either type of inspection can result in more frequent visits if serious adverse findings are reported. These latter visits are considered compliance or follow-up inspections and are carried out to determine if correction of previous violative conditions have been made.

8. Will laboratories be notified in advance of an inspection?

   Because of the comments received during the conferences and the experiences to date with this program, laboratories will generally be notified prior to inspection. However, compliance or special investigation inspections may not follow this procedure.

9. Can a laboratory postpone an inspection?

   A facility may at the time of initial FDA contact request a postponement. Such a postponement may occur when personnel responsible for the conduct of the study to be audited will be unavailable at the anticipated inspection date. FDA expects to be reasonable in arranging for an inspection date. Unreasonable delays in scheduling the inspection will however be viewed by FDA as a refusal to permit an inspection.

10. Can a laboratory request an inspection? How?

    A facility may request an inspection from either the local FDA district office or from FDA headquarters. However, an inspection will be initiated only with headquarters concurrence. Consideration will be given to the work schedules under which district management is operating.

11. If a laboratory is not performing a study on an FDA regulated product at the time the investigator arrives, will the inspection still be carried out?

    Routinely, GLP inspections are not scheduled unless the Agency has received a final report on a regulated product or has received submitted protocols, interim study reports, or knows that a study on a regulated product is underway. In the case of a laboratory that is not currently performing a study on a regulated product the laboratory will be asked to consent to an inspection. The FDA investigator will

utilize an ongoing study, even though it is not associated with an FDA regulated product, to document the laboratory's compliance with GLPs. In such cases, the study will not be audited in terms of validating the raw data, and specifics of the study will not be included in the inspection report.

12. Will inspections cover other areas such as chemistry, physical testing, metallurgy, etc.?

    To the extent that the protocol of a nonclinical laboratory study requires tests in the field of metallurgy, clinical chemistry, etc., we will examine and evaluate adherence to test specifications or protocol requirements.

13. Are firms notified of specific studies to be audited? Will sufficient time be allowed to seek authorization from the sponsor of the study to disclose the data to the FDA investigator? What happens if the sponsor of the study refuses to authorize the laboratory to disclose the records?

    As stated with respect to prior notification of inspection, where FDA has an interest in auditing a study, ample time generally will be provided for the facility to seek authorization from the sponsor to disclose the data. In some cases, FDA investigators may begin inspecting the physical layout of the facilities while authorization to release the study records is being obtained. If the sponsor refuses to authorize disclosure of the records to the investigator, FDA will pursue the matter directly with the sponsor.

14. Can FDA investigators ask for records to which they are not legally entitled; can they engage in "fishing expeditions?"

    It is not FDA policy to request documents during an inspection to which the Agency is not legally entitled. On occasion, the Agency may request such documents when pursuing an audit trail of a possible violation. Under these circumstances, it is the laboratory's prerogative to cooperate or refuse without fear of reprisal. The requests should be specific and pertinent to the inspection. The Agency discourages investigators from making vague requests to see documents with no specific purpose in mind.

15. Should the Form-FD-483, Notice of Observations issued by the FDA investigator reflect current practices only; and should it include practices that were corrected during the course of the inspection?

    The FD-483 can include historical practices, which may have affected the scientific validity of the nonclinical study in question even though subsequent correction may have occurred. Any corrective action taken by the facility will be noted by the investigator in the establishment inspection report.

16. What should a laboratory do when there is disagreement between the laboratory and the FDA investigator regarding the findings reflected in the FD-483 Notice of Observations?

    At time of the observation, the management should discuss any differing opinions and attempt to clarify the investigator's perceptions or observations. The management may also, at the conclusion of the inspection, offer to explain what the management considers to be erroneous 483 observations. Should the matter in question remain unresolved, a written objection should be sent to the local FDA district director or a meeting with district personnel should be requested to attempt to resolve the issue.

17. What is the procedure for correcting errors in the FDA investigator's inspection report? Such errors can be damaging to the laboratories since the reports are ultimately available through FOI.

    If in fact an error is made in an investigator's report, the matter should be immediately brought to the attention of FDA district management. If district management agrees with the complaint, the report will be amended and amended reports will be sent to all outside persons who may have received the erroneous report. It should be stressed, however, that the time to change what a facility believes is an erroneous conclusion is when the FD-483 is discussed with laboratory management because as soon as the FD-483 is presented to management, it becomes available for public disclosure.

18. Does refusal to allow the FDA investigator access to certain information, which the laboratory sincerely believes is not subject to FDA jurisdiction, constitute a refusal of inspection? How can a disagreement of this kind be resolved?

    Refusal to permit access to records which are associated with a study being audited or which preclude a judgement being made regarding compliance with GLPs, is considered a refusal of inspection with certain ensuing consequences. However, a facility may legitimately question FDA authority to review certain documents. Such objections and the reasons therefore, should be presented in writing or by telephone to the FDA district office management where the investigator is based. Each case will be individually reviewed both in the field and, if necessary at headquarters and a decision will be communicated to the inspected facility.

19. Will inspections and audits of foreign laboratories be carried out? Who pays for these inspections?

    Inspections are being conducted of foreign facilities, which have engaged in nonclinical studies, which have been submitted to FDA in support of a marketing permit. FDA pays for travel and other expenses associated with such inspections.

20. In order for foreign laboratories to comply with the GLPs, do protocols, standard operating procedures, records, etc. have to be in English? Do FDA investigators bring interpreters with them to review records and data?

    Submissions to FDA in support of a marketing application for a FDA regulated product must be in English. Review of source documents at the site of the foreign facility may necessitate review of documents written in the language of the country of origin. FDA does not employ interpreters to accompany investigators on foreign inspections. It has been our experience that persons associated with the laboratory are normally fluent in the English language.

21. What kind of training does an FDA investigator have which qualifies him/her to conduct a GLP inspection or data audit? Does the investigator draw conclusions from his observations regarding the competence of the laboratory or quality of the studies?

    Along with education in one of the natural or physical sciences, the individuals selected to conduct GLP inspections generally have had considerable experience inspecting facilities involved in drug manufacturing, biologics production, medical device assembly, food processing, and a range of other operations on products regulated by the Agency. In addition, the investigators conducting nonclinical laboratory inspections (GLPs) have undergone intensive training in the normal operating procedures of nonclinical testing facilities. This training which includes a full review of the Agency's policies and of the GLP regulations National Center for Toxicological Research accomplished at FDA's National located in Pine Bluff, Arkansas. Field investigators are encouraged to contact any resource within the Agency, i.e., scientists and other personnel of the various bureaus to resolve scientific questions that may arise during an inspection. Bureau scientists and not the investigators, draw conclusions regarding the competence of the laboratory of the quality of the study

22. Does a laboratory manager have the right to ask for the FDA investigator's educational and experience qualifications prior to a GLP inspection?

    Yes, questions regarding the formal training, educational experience, and on-the-job training of an individual investigator may be addressed to the investigator prior to a GLP inspection.

23. What can a laboratory manager do when he encounters an FDA investigator who is overly antagonistic or uncertain as to what he is looking for?

    The Agency makes every effort to promote a professional attitude in its investigators including special training and selection of investigators for this program. However, if in the judgement of the laboratory manager there is a question as to the qualifications

or attitude of the investigator, the local FDA district office director should be contacted.

24. What assurance does a firm have that confidential or trade secret information given to the FDA investigator will be safeguarded by the Agency? What happens when an FOI request for the inspection report is received by FDA?

    Section 301(j) of the Food, Drug, and Cosmetic Act prohibits any employee from revealing for his/her advantage any information obtained in the course of carrying out his/her duties. Trade secrets and confidential commercial information are deleted from documents before they are released under FOI. Inspected firms may help by identifying information, which they consider to be confidential when it is given to the investigator. FDA will however, exercise its own judgment, in accordance with its FOI regulations as to whether such information may properly be classified as confidential.

25. How can copies of inspection reports be obtained under FOI?

    Inspection reports may be obtained by making a request under FOI to:
    Freedom of Information Staff, HFI-35
    U.S. Food and Drug Administration
    5600 Fishers Lane
    Rockville, Maryland 20857