0273–2289/86/1303–0241$02.00

REVIEW

FDA Inspection of an Academic Laboratory

LEONA MARX AND BRUCE F. MACKLER*

Mackler, Cooper, and Marx, 1220 L. St., NW Suite 615, Washington, DC

Received and Accepted January 21, 1986

Academic researchers who perform nonclinical (toxicology) testing for sponsors interested in clinical testing or marketing of a product (food or color additives, human and animal drugs, medical devices for human use, biological products, and electronic products) within the authority of the Food and Drug Administration must conform to the FDA regulation for good laboratory practices (GLP) for nonclinical laboratory studies (21 C.F.R. § 58.1 et seq.). This regulation sets standards for acceptable safety testing, including what must be included in a protocol, adequate quality assurance program, adequate record keeping, and other aspects of toxicology laboratory operations. The regulation is intended to assure the quality and integrity of safety data filed in support of a clinical testing or marketing application† (21 C.F.R. § 58.1). A testing laboratory's reputation and success may depend upon complying with the GLP regulations because the FDA can reject an application for clinical testing or marketing if the reliability of the safety data was undermined by failure to meet GLP standards. Because of the growth in the use of academic facilities for safety testing of intended commercial products, more and more academic researchers will be encountering GLP inspections.

The FDA is inspecting about 100 nonclinical laboratories per year.‡

*Author to whom all correspondence and reprint requests should be addressed.

†In October 1984, FDA announced proposed revisions of the current regulation to reduce some of the burdens imposed on testing facilities. 49 FR 43530 (Oct. 29, 1984). The public comment period on the proposed revised regulation has ended, but FDA has not yet issued a final version.

‡Information obtained from the prepared remarks dated Oct. 16, 1985 of Dr. Lepore, Bioresearch Program Coordinator, Office of Regulatory Affairs, FDA, hereinafter referred to as "Lepore remarks," presented before the 1985 Annual Meeting of the Society of Quality Assurance.

In its October 1984 announcement of proposed revisions in the GLP regulations, the FDA explained that of 425 domestic laboratories, 165 were sponsor-run laboratories, 174 contractor laboratories, 72 university laboratories, and 14 government laboratories (49 FR 43530).

To enforce the Federal Food, Drug, and Cosmetic Act, the FDA maintains district offices distributed throughout the 50 states. Within the supervision of the district offices are regional offices from which investigators conduct inspections of facilities within the authority of the FDA.† Although the FDA often refers to its inspectors as "investigators," to avoid confusion with the laboratory researchers, the FDA examiners will be called "inspectors" and the researchers "investigators." The FDA is authorized to perform inspections at a reasonable time, in a reasonable manner, and to complete them with reasonable promptness [21 C.F.R. § 58.15(a)]. Of course, total compliance with all the particulars of the GLP regulations should be the goal for every researcher. Yet, at times, less than perfrect conditions may arise, and it is under these circumstances that an FDA inspection presents extra worries for the investigator. The following guidance is offered for academic researchers yet to encounter an FDA inspection.

In 1984, the FDA conducted 104 inspections of laboratories of all types doing safety testing.‡ Most of these laboratories were randomly selected within their region and come within the FDA's biennial "bioresearch monitoring" or "surveillance" program, although some of the inspections were limited to "data audits" or follow-up inspections. Another type of inspection, a "directed inspection" is undertaken to examine the facility and records relating to a particular study under agency review, either because the agency is seeking to verify the reliability of the nonclinical data prior to allowing clinical trials or before granting marketing approvals or in response to a complaint or an inconsistency FDA has found in a report. An investigator will therefore have more cause for concern in a directed inspection.

Regardless of the type of inspection, one will surely take place sometime in the course of an investigator's work, and it will probably occur years after the completion of the study. In light of the difficulties of collecting and filling in old or inadequate records, academic investigators should maintain their records in anticipation of eventual inspection. Good data reporting will lead to minimal anguish during an FDA inspection and help ensure the acceptability of the data submitted to the FDA.

The FDA usually notifies the investigator by letter of a planned academic facility inspection. After receipt of a request for inspection, an investigator should promptly arrange a mutually convenient time for the inspection. The principal investigator should handle all communication

†A nonclinical laboratory facility, including an academic facility, may be subject to EPA, USDA, OSHA, and National Toxicological program inspections and audits as well as FDA inspections. The EPA has its own GLP regulations (40 C.F.R. § 792 and § 160). Usually, EPA inspections are performed with an FDA inspector present.

‡"Lepore remarks" slide 1.

with the FDA and he/she should find out, in advance of the inspection date, the scope of the inspection, how many people will handle the inspection, who they are in terms of the FDA hierarchy, and what type of inspection it will be (routine monitoring, data audit, or directed). For an academic facility inspection, a headquarter's scientist usually accompanies a field inspector.

After an investigator has received notice of the FDA's intent to inspect, the investigator should promptly inform the sponsor of the study in question. Often, the sponsor will help the investigator prepare for the inspection by assising in assembling all the pertinent documents and reviewing them for mistakes or omissions. Corrections should be made by the investigator before the inspection, but always indicating the date of the correction, by whom made, and the reason. Never back date a record or use white out or other obliteration on any lab notebook, data form, or other document. Always keep separate from the laboratory records all personal correspondence, financial records, and unessential documents. The FDA inspector may explain that refusal to allow inspection of requested documents may lead the FDA to reject the data related to the study in question. Therefore, always provide those records relating to the conduct of the study.

The investigator has the responsibility of maintaining "all raw data, documentation, protocols, specimens, and final reports" [21 C.F.R. § 58.190(a)]. An archives of raw data and other documentation should be under the responsibility of a designated person who shall assure that retrieval of needed material can be accomplished expediently [21 C.F.R. § 58.190(b)]. Generally, records need to be retained by the investigator for five years after approval by FDA of any research or marketing permit growing out of the nonclinical study [21 C.F.R. § 58.195(b) (2)]. If the study's results are not submitted to the FDA, records still need to be kept for two years following the end of the study [21 C.F.R. § 58.195(b) (3)]. Among the proposed changes in the GLP regulations is a modification of the record retention requirements to establish that records may be retained as originals or as microfilm, microfiche, photocopies, or other accurate reproductions of raw data [proposed § 58.195(g)].

Although it is necessary to provide those records relating to the conduct of the study under review, nonetheless, if an investigator feels sure an inspector is seeking documents beyond what he/she is entitled to examine, politely refuse to turn them over and explain that the matter will have to be handled through the institution's or sponsor's legal office.

It is wise not to volunteer information to the inspector. Although courtesy is urged at all times, keep your answers brief and directed only to the question asked. The FDA inspectors will not warn you in advance that you have the right to remain silent and anything you say might be used against you in the unlikely event of civil or criminal proceedings, but these are two facts to keep in mind. The inspectors are frequently familiar with medical terms, but are not scientists and do not make scientific judgments. They are fact finders and report their findings to re-

viewers who determine whether to recommend that the agency seek corrective action or institute other enforcement proceedings.

During the inspection, the examiner should be allowed to review documents in an office or work area cleared of all other papers. The chief investigator should be available to accompany the inspector through his/her tour of the facility. Preliminary housekeeping may save the investigator from unnecessary embarrassments. The inspector will most likely review the Laboratory Standard Operating Procedures (SOP) Manual to determine if the written procedures are adequate to ensure the integrity of the data [required by 21 C.F.R. § 58.81(a)]. The inspector may well take notes in his/her book of his/her observations of GLP compliance. If the examiner asks a question the principal investigator can not answer, he or she should ask for time to discuss the matter with the sponsor, other technical experts, such as the institution's building engineers, or the institution's legal office. Similarly, if an inspector wants to examine an area of the lab believed to be beyond his/her authority, the principal investigator should ask time to obtain outside guidance. Inspectors do not have authority to open drawers, closets, boxes, or containers or to question employees at their work. If an inspector does something the investigator believes to be improper, he/she should make a contemporaneous note of it, with the date it happened and the names of witnesses.

At the start of an inspection, the inspector will present to the principal investigator a Notice of Inspection (form FD 482). If an examiner fails to offer the form, the investigator should ask for it. Picture taking during an inspection should not be allowed. Likewise, it is appropriate to give the inspector photocopies of documents he/she has been given for inspection. If the documents are numerous, a reasonable copying charge can be assessed. Ask the inspector not to place any identification marks or initials on your documents. Always keep a duplicate set of all documents given to inspectors.

Often, a few days after completion of the inspection, the inspector will return to present a form 483 and have a postinspection interview. This form contains the inspector's statement of any significant conditions or practices that he/she thought were not in compliance with the GLP regulations. The investigator should ask the inspector to explain in detail the reasons for each recorded objectionable condition or practice. If corrective measures have already been taken, the inspector should be made aware of them. However, the investigator is advised not to acknowledge in writing or by verbal ascent his/her agreement with any uncorrected deficiencies noted by the inspector. In fiscal year 1984, 48% of the inspected nonclinical laboratories received 483s. During the five-year period in which the GLP regulations have been in effect, each year, about 20% of all inspected laboratories have received 483s.† In fiscal year 1984, 22% of the problems in GLP compliance were in the quality assurance

†"Lepore remarks" at 2 and slide 1.

unit, 40% involved protocol deviations, and 21% involved problems in the final reports†.

After the inspection and interview, the investigator should alert the sponsor the the deficiencies noted on form 483. The investigator should also prepare a letter for FDA headquarters addressing each of the specified problems and stating what corrective actions will be promptly begun. This letter should be reviewed by the institution's legal office and the sponsor before being sent to the FDA. The investigator's cooperative response to the inspector's findings may satisfy the FDA and prevent further problems with the agency.

About six weeks after the inspection, the investigator or his institution's legal office or the sponsor should request that the FDA send a copy of the Establishment Inspection Report (EIR). The EIR is a restatement of the findings noted in form 483 and is available upon request under the Freedom of Information Act. The request for the EIR should be addressed to the Freedom of Information Office, Food and Drug Administration, Room 12A-16, 5600 Fishers Lane, Rockville, MD 20857.

The FDA headquarters compliance personnel review the district offices' recommendations concerning any further agency action involving the investigator. The agency may choose to send the investigator only an Information Letter restating the observed deficiencies and suggesting areas for improvement. Information Letters are kept at the issuing FDA district office in a file relating to the study or investigator in question. An Information Letter may be reviewed by an inspector before making a follow-up inspection. In those situations in which the agency determines that more immediate corrective measures are necessary, a more sharply worded warning letter may be sent to the investigator or the principal investigator may be invited to meet informally with the FDA to discuss a program for bringing the facility into compliance.

If the FDA determines that a facility's conditions are even more drastically out of compliance with the GLP regulations, it may send the principal investigator a Notice of Adverse Findings Letter (NAFL). These letters relate the inspector's observations to particular provisions of the GLP regulations and usually ask that the investigator notify the FDA within 10–30 days of the corrective measures undertaken. Follow-up inspections are also arranged. In fiscal year 1984 only 19 such letters were sent to laboratory directors‡. For even more serious GLP deviations, the FDA might send a laboratory director a Regulatory Letter acknowledging the observed deficiencies and stating the possibility of rejection of an application relying upon the questionable data. Only one Regulatory Letter was sent by the FDA in 1984§.

Dr. Paul Lepore, Bio-Research Program Coordinator for the FDA's

†"Lepore remarks," at Slide 2.

‡"Lepore remarks," slide 1.

§"Lepore remarks," slide 2.

Office of Regulatory Affairs, recently stated that the key to improving GLP compliance "rests in the hands of management [academic laboratory director] and . . . the quality assurance unit. . . . Management should provide adequate facillities and equipment to carry out the studies."† In addition, according to Dr. Lepore, "management should periodically assess the effectiveness of the quality assurance unit" to determine whether there is proper staffing for production of a high quality final report.‡

The FDA efforts at obtaining compliance with the GLP regulations are strengthened by the underlying threat to the investigator that noncompliance might result in eventual rejection of the study's data as evidence of safety in an application for clinical testing or marketing approval. Each year since the GLP has been in effect, the FDA has taken this approach to some studies.§ An uncooperative laboratory director might, in extreme circumstances, find him/herself the subject of the formal administrative disqualification process through which the FDA seeks to bar an investigator or laboratory from submitting data for agency review. The agency would announce in the Federal Register its decisions to disqualify a laboratory or investigator from approved investigational work and might request other governmental agencies involved in reviewing its laboratory research to take similar action. In cases in which it appears that false statements were submitted to the FDA or there was fraud in reports prepared for the government, the FDA might recommend that the Justice Department institute proceedings to hold the investigator criminally culpable. This drastic measure has not been necessary. Likewise, the FDA has never needed to disqualify an academic laboratory because of failure to comply with its requirements.

The small number of FDA Notices of Adverse Findings and Regulatory Letters sent out in 1984 indicates that most of the laboratories inspected by the FDA met their regulatory obligations. Moreover, because the GLP regulations require a self-monitoring quality assurance system and the FDA provides a Program Guidance Manual (available through the FDA's Freedom of Information Office) for self-auditing, a well run laboratory should not have difficulties with an FDA inspection.

Leona Marx, J. D. is a partner with Mackler, Cooper, and Marx, a Washington DC law firm with expertise in Food and Drug (FDA) law, patents, product licenses, trademarks, and so on. Ms. Marx was formerly a staff attorney with the Office of the General Counsel, Food and Drug Administration, in private practice in criminal law, and an attorney with the US Commission on Civil Rights and Equal Employment Opportunity Commission.

Bruce F. Mackler, Ph.D., J. D., is a practicing attorney and immunologist. His law practice includes FDA, EPA, USDA, product safety, health care, and prod-

†"Lepore remarks" at 4.

‡"Lepore remarks" at 6.

§"Lepore remarks" at 2.

uct liability. He also has a part-time adjunct appointment at the University of Maryland Dental School. He publishes regularly in *Biotechniques, Medical Device and Diagnostic Industry,* is an associate editor of *Biotechnology Law Reporter,* and a columnist (ABC Dialog) in *Genetic Engineering News.* Dr. Mackler is a partner in the law firm of Mackler, Cooper, and Marx, Suite 615, 1220 L Street, NW, Washington, DC 20005, and General Counsel to the Association of Biotechnology Companies.